ANZCA

AUSTRALIAN AND NEW ZEALAND
COLLEGE OF ANAESTHETISTS

AUSTRALASIAN ANAESTHESIA 2017

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Invited papers and selected continuing education lectures

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Published in 2017 by:

Australian and New Zealand
College of Anaesthetists
630 St Kilda Road
Melbourne, Victoria 3004
Australia

ISBN 978-0-9945075-5-6

Printed by:
Ellikon
384 George Street
Fitzroy, Victoria 3065
Australia

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Preface

Welcome to the 2017 edition of *Australasian Anaesthesia*.

I continue to be surprised at the depth and breadth of talent in our fields. Although there is some emphasis in several topics, it is always gratifying that we are able to produce a wide range of areas that reflects the diversity of practice in anaesthesia and pain medicine. Airway management, regional anaesthesia, coagulation and cardiac function will always be topical. Articles on education and management also feature to make this edition well-rounded and deserving of your attention.

In this edition we also welcome the inclusion of several chapters focusing on intensive care medicine. I hope that you will be similarly impressed to read about some of these developments that our ICU colleagues are leading. Further, a chapter on outcomes following decompressive craniectomy for severe traumatic brain injury is timely and thought-provoking. Having a family member undergo such an operation years ago made it especially poignant.

Several years back a keynote speaker at an international simulation in healthcare meeting described the reluctance of many senior clinicians to ask for feedback on their own clinical and teaching practices. As a practicing surgeon, and clinical educator, he decided to embrace the principles of adult education and began to seek feedback from his surgical trainees. Thus, at the completion of each day's operating, he now asks the trainee, "How'd I do today?" It was a little confronting at first but it became part of his embedded practice and he now welcomes it. The speaker exhorted us to follow his example and seek feedback from our juniors; irrespective of their level of training. He suggested that we might be surprised at the feedback.

To follow on this theme, I can let you know that I typically receive one complaint and one to two compliments for each edition of *Australasian Anaesthesia*, but this is hardly enough. Thus, if you have bouquets or brickbats about the "Blue Book", I would encourage you to give us feedback. An email address below is provided to facilitate this.

Finally, I wish to thank the authors, the regional editors and ANZCA's Publications Manager Liane Reynolds for their work and support in producing this edition. Please take the opportunity to thank our authors personally when you can and also consider writing yourself for a future edition.

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Airway

Awake videolaryngoscopy

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Dr Douglas is a Consultant Anaesthetist at Royal Perth Hospital (RPH) in Perth, Western Australia. His interests include difficult airway management, airway management education, airway surgery, apnoeic oxygenation and obstetric anaesthesia, and he is the Director of Audit at RPH. He regularly teaches “Cannot Intubate Cannot Oxygenate” rescue techniques, is an Advanced Life Support and Effective Management of Anaesthetic Crisis (EMAC) instructor, and is co-author of the new EMAC Airway chapter.

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Following his graduation from Belgrade Medical School, Dr Hodzovic’s career took him to the United Kingdom where he became a Fellow of the Royal College of Anaesthetists and Senior Lecturer at Cardiff University. His main clinical interests are major otolaryngological cancer surgery and anaesthesia for gastrointestinal surgery. He has published in the field of difficult airway management and is an invited reviewer for national and international peer reviewed anaesthesia journals. He chairs the All Wales Airway Group and is a member of the Innovation Committee of the Aneurin Bevan University Health Board.

INTRODUCTION

Awake direct laryngoscopy has historically been used in patients with compromised airways, in whom asleep airway management was anticipated to be difficult. The technique may be tolerated by a moribund patient without topicalisation or sedation, but the stimulation may still induce airway reflexes making intubation difficult, if not impossible, and cause undesirable autonomic sequelae. Patients with a preserved level of consciousness are generally unable to tolerate unmedicated awake direct laryngoscopy.

The key advantages of performing awake intubation are the maintenance of upper airway tone and spontaneous respiration. When anaesthesia is induced, apnoea frequently occurs and airway obstruction may worsen. The Royal College of Anaesthetists Fourth National Audit Project highlighted inexperience as the main reason for underuse of awake intubation techniques in the United Kingdom[1,2].

Effective topical local anaesthetic (LA) and sedation strategies, along with recent technological advances in airway equipment, has renewed interest in awake laryngoscopy. The introduction of videolaryngoscopes, particularly those with hyper-angulated blades, has reduced the degree of stimulation required to perform awake laryngoscopy.

Video laryngoscopy (VL) is now firmly embedded within the anaesthetic airway management armamentarium. This is reflected by the inclusion of the technique in “Plan A” of the 2015 Difficult Airway Society (DAS) guidelines flowchart for the management of unanticipated difficult tracheal intubation in adults[3]. Similarities between indirect VL and conventional laryngoscopy have led to faster attainment of proficiency in the skill by novices[4,5] and experienced operators demonstrated no difference in technical difficulty, patient discomfort and time to orotracheal intubation between Awake Video Laryngoscopy (AVL) and Awake Flexible Bronchoscopic Intubation (AFBI) in patients with an anticipated difficult airway[6]. AFBI is the preferred term of the authors as many intubating bronchoscopes are either hybrids of fibreoptic and digital technology or have no fibreoptics at all. VL’s ease and usability has had the desirable secondary effect of multi-disciplinary familiarity with the technique and the advent of AVL as an alternative strategy for awake intubation.

The authors of this paper recognise that AVL is an evolving technique and those finessing it encounter many pitfalls and challenges. We do not claim to be in any way experts in the field of AVL, but we recognise, and in this article will consider, its evolving role in contemporary airway management practice.

IS THERE A NEED FOR AVL?

A key objective of airway management is to predict difficulties and thereby prevent adverse clinical outcomes. In the face of an anticipated difficult intubation, it is widely acknowledged that techniques which maintain spontaneous breathing are the safest[1]. In cases where mouth opening is preserved and oral intubation is essential, there is an emerging interest in using AVL as an alternative to AFBI, the current “gold standard”, AVL may be perceived (rightly or wrongly) as being simpler and more familiar than AFBI, and in some institutions equipment for AVL may be more readily available. There is also a growing body of case reports which cite the successful use of AVL in preference to AFBI, or where AFBI has failed (table 1).

Airway oedema
Several case reports of AVL involve significant macroglossia and laryngeal inlet oedema. These patients presented in extremis with stridor. AFBI and nasendoscopy failed due to mucosal swelling. AVL displaced the oedematous tongue and provided glottic access with less base of tongue force (5-14 N) compared to conventional laryngoscopy. Use of a channelled VL was especially advantageous, as it negated the need for an introducer device, hence avoiding the "cork in bottle" effect[7,8,9].

An additional case report documents rescue AVL in a patient where successful awake insertion of a Flexible Intubating Bronchoscope (FIB) was followed by failure to pass the endotracheal tube (ETT). The FIB did not allow the glottis to be visualised during passage of the ETT and hence identification and rectification of hold-up was a peripherally blind process above the carina. AVL provided a widescreen view which allowed guidance of the ETT through the glottis without hold-up[10].

Fixed or immobilised cervical spine
AVL has facilitated timely intubation in patients with unstable cervical spines, without the need to remove immobilisation devices, and also for patients with a fixed neck deformity. The ability of hyperangulated VLs to provide laryngeal visualisation while maintaining anatomical alignment has been increasingly exploited in trauma scenarios[11,12].

Secretions
Airway secretions may impede the view of any device relying on a transmitted image. AVL may be more forgiving than AFBI in the presence of secretions in the airway, especially when using VLs with a designated suction channel or that permit the passage of large bore suction devices via the intubating channel[13].

Airway stenosis and obstruction
Rescue AVL was described in a morbidly obese patient with a massive multi-nodular goitre with pressure symptoms. Perioperative work up revealed a displaced trachea and a compressed airway with a diameter of 2 mm at the glottis. AFBI failed due to the size of the ETT being limited by the diameter of the FIB and extensive mucosal hypertrophy, which prevented the FIB advancement. AVL provided a Cormack-Lehane grade two glottic view on screen and allowed a Frova airway intubation catheter (Cook Medical) to be inserted into the trachea[14].

AFBI was considered of limited appeal in managing a case of laser excision of a ball-valving laryngeal mass. Potential further obstruction was possible from inadvertent trauma caused by the "blind" advancement of the ETT over the FIB in the presence of pathologically friable tissue. AVL was considered advantageous, allowing continuous visualisation of the airway and guidance of the ETT past the friable mass. Importantly, with the entire team able to follow events, immediate expert advice was provided in real time[15].

Morbid obesity
AVL has been successfully used to intubate tracheas in morbidly obese patients presenting with a potentially difficult airway. It was found to be comparable in this group to AFBI in terms of time to awake tracheal intubation, number of intubation attempts and glottic view achieved[16,17].

Table 1. Case reports where AVL was used preferentially over AFBI

Airway oedema/swelling	7,8,9,10
Immobilised neck and fixed neck deformities	11,12
Airway stenosis and obstruction	14,15
Morbid obesity	16,17

Cost
Although the exact values will vary by location and device, the cost of single use VL blades and sterilising reusable VL blades is usually significantly cheaper than the cost of single use FIBs or sterilising reusable FIBs.

NOVEL TECHNIQUES

The Combination Technique
AVL can be used in combination with AFBI. This technique aims to limit the individual disadvantages of the FIB and VL. Two operators are required to monitor the entire process of intubation. The VL is inserted first and the best possible screen view is obtained. If Cormack-Lehane grade one or two views are obtained on the VL, the FIB is used like a stylet with a controlled flexible tip. If grade three or four views are obtained the VL is used to open the oropharynx and guide (or act as a conduit, if a channelled scope) the FIB to the point where the glottis can be visualised by the FIB operator. Appropriate views are then maintained on the VL and FIB monitors, independently, by both operators. This technique offers a wider field of view and a reduced need for ETT manipulation. It can also be used in the presence of oedema to displace tissue[18,19].

The Tomahawk Technique
Awake intubation in the face-to-face upright position can mitigate some of the disadvantages associated with the traditional laryngoscopy position, especially in those with a threatened airway. Upright AVL is best performed with a hyperangulated blade, inserted handle down in the "tomahawk" position. This method has been found to produce Cormack-Lehane grade one or two views in less than 30 seconds. Optimisation of those glottic views was then achieved with only minor adjustments to the patient's sitting position. Note that if a non-channelled scope is employed, the hyperangulated blade necessitates the use of a preformed introducer[20,21].

WHAT ARE THE LIMITATIONS OF AVL?

Not all VLs are equal and it is important to acknowledge their limitations.

Incorrect size/shape to match airway anatomy
Any laryngoscope blade with a fixed length and curvature, video or otherwise, will not suit all mouth to larynx distances and shapes at the extremes of anatomical variability.

Difficult insertion
Insufficient mouth opening
Although the exact amount varies, for any particular VL there will be a minimum mouth opening distance required to insert and manipulate the VL, and (if the VL is unchanneled) insert and manipulate an ETT separately from the VL. Extremely limited mouth opening may necessitate AFBI via the nasal approach.

Difficult/impossible insertion due to neck/chest wall relationship
In those with fixed flexion deformities or prominent breast tissue, obstruction due to the chest wall may make it impossible to insert the VL. Introducing the blade with 90 degrees of rotation before returning to the normal alignment may overcome this problem. For VLs with blades and handles that can be detached from one another, introducing the blade alone without the handle attached may also be of assistance[11].

Traumatic insertion
During VL the operator's visual attention is directed toward the screen, which can result in damage to soft tissues or ETT cuff. It is essential that the VL blade is inserted into the mouth under direct observation and not while looking at the screen. Experienced VL operators have similar minor complication (bleeding and sore throat) rates to FIB intubation. However, there are reports of VL related palatopharyngeal arch injury requiring surgical repair in patients with abnormal upper airway anatomy, prior airway surgery and/or previous radiotherapy[22].

Channelled or unchannelled?
Channelled VLs eliminate the need for an ETT introducer, avoiding the "cork in a bottle" phenomenon, reducing the risk of trauma during insertion of the ETT, simplifying the technique, and creating a protected conduit for the ETT, however they usually require a greater degree of mouth opening. Unchannelled VLs may require less mouth opening, but do require an ETT introducer. This is important, as the smallest internal diameter of an ETT that can be used with a preformed GlideRite® stylet is 5 mm[15].

Pharyngeal hyperreflexia
AVL is not simply a skill hybrid of AFBI and VL. Exaggerated gag responses are the most commonly cited reason for failure of AVL. This can be understood after consideration of the physical differences between the techniques. VLs have evolved from the Macintosh blade. The pressure of the blade on the tongue and in the vallecular provokes discomfort and the gag reflex in otherwise well-topicalised airways that are likely to have tolerated AFBI.

The intermittent failure to tolerate AVL has contributed to the use of the "awake look" technique. If a Cormack-Lehane grade of one or two is transiently seen during AVL, conversion to a GA technique occurs. Extreme caution is recommended with this approach, as grade of laryngoscopy may deteriorate with loss of muscle tone, and a clear laryngoscopy does not guarantee a straight forward intubation!

SUPPRESSION OF THE GAG REFLEX

Within our specialty there is a belief that dense airway topicalisation alone, particularly of the mucosal surfaces supplied by the glossopharyngeal nerve, can improve AVL outcomes.

It is hypothesised that those with a persistent gag reflex have deeper submucosal pressure receptors less amenable to a topicalisation. Therefore, some authors advocate bilateral glossopharyngeal nerve blocks. They are performed using a spinal needle to inject lidocaine at the bases of the palatoglossal folds. Patient refusal or disease burden may render this technique inappropriate[23].

There is considerable evidence to demonstrate multifactorial aetiology underlying the gag response. Those pursuing a completely sedation-free AVL technique are now turning their interest towards alternative management strategies. These include patient selection, behavioural, pharmacological and complimentary therapies[24].

Patient selection
The gag reflex is well recognised within the dental community, where an exaggerated response results in some patients self-limiting their treatment. The Gagging Severity Index was developed as a predictive scoring system which takes no more than five minutes to complete and score. This may help anaesthetists minimise negative AVL experiences for patients most at risk[25].

Pharmacological adjuncts
The benefits of conscious sedation during awake intubation were recognised as early as 1975. However, an ideal elixir for conscious sedation remains elusive[26].

Drugs commonly used for sedation are either anxiolytic or analgesic. Appropriate levels of "sedation" for safe awake intubation are difficult to standardise, especially as the pharmacodynamics of sedation using opioids and hypnotics are not directly comparable. Operator preferences tend to lack a firm evidence base. The authors of this paper would advocate the use of easily reversible drugs, and strongly suggest having their antagonists readily available.

The relative requirements of anxiolysis and analgesia will vary with the anatomical and physiological condition of patients and also with the urgency of the situation. The use of sedation is often employed by anaesthetists who are also mindful to avoid significant morbidity or mortality that over sedation can bring[1,27].

Midazolam
Midazolam is a benzodiazepine sedative agent with a rapid onset and short duration of action. It is most commonly used in combination with an opioid. It is usually administered as intermittent boluses of 0.5-1 mg IV, with a recommended maximum limit of 0.05 mg/kg^{-1}. The technique is often favoured by anaesthetists because of their widespread familiarity with the drug.

The main benefits for the patients are its anterograde amnesia and acute reversibility with flumazenil. Disadvantages of the technique lie in the potential cumulative effect of multiple intermittent boluses resulting in unpredicted over-sedation[27].

Fentanyl
Fentanyl is a synthetic phenylpiperidine derivative opioid. It is primarily an analgesic with rapid onset and short duration of action. It is administered as 10-25 mcg intermittent boluses IV up to a maximum of 1.5 µg kg^{-1}. It is also associated with mild hypnosis and an antitussive effect. Airway instrumentation provokes an intense nociceptive response, especially during the passing of the tracheal tube, and fentanyl can help mitigate the effects of inadequate topicalisation. It is also acutely reversible with naloxone. The main risks of it use are respiratory depression, nausea, vomiting and, very rarely, chest wall rigidity[27].

Remifentanil
We advocate the use of remifentanil as an adjunct to topicalisation for awake intubation. It is an ultra-short-acting opioid with an elimination half-time of six minutes which is dependent only on hydrolysis by non-specific plasma and tissue esterases. Target-controlled infusion (TCI) administration allows a stable level of sedation to be titrated and maintained. Better tracheal tube tolerance during intubation has been attributed to the antitussive and analgesic properties of remifentanil. A testament to its effectiveness is the emergence and uptake of it as a sole agent, for a two-person AFBI technique.

As a single agent with no airway topicalisation, remifentanil is infused to achieve a predicted effect site concentration of 1 ng mL^{-1} and then titrated upwards in 0.5 ng mL^{-1} increments. Effect site concentrations of 6.3 (3.87 SD) ng mL^{-1} for nasal endoscopy and 8.06 (3.52 SD) ng mL^{-1} for tracheal intubation provided good conditions with no serious adverse events[28]. When used in combination with midazolam or propofol, a remifentanil effect site concentration of 3-5 ng mL^{-1} was considered sufficient[27]. Rosenstock et al found they gave a median remifentanil infusion of 0.13 mcg/kg^{-1} min^{-1} during AVL intubation, compared to 0.12 mcg/kg^{-1} min^{-1} for AFBI, in conjunction with airway topicalisation, including transtracheal injection, using a maximum dose of 3 mg/kg lidocaine[6].

Propofol
Propofol is an alkylphenol derivative hypnotic sedative and that can be administered as boluses, simple infusion, or as a TCI. Its relatively narrow therapeutic index for sedation makes its safe use demanding. TCI administration is more pharmacodynamically consistent and may allow for a more predictable level of sedation to be maintained. Current evidence would suggest that propofol only TCI is used with effect site concentrations ≤3 mcg/mL^{-1}[27], or ≤1 mcg/mL^{-1} when used in conjunction with benzodiazepines and/or opioids. Combining TCI propofol with other sedatives may help minimise the side effects and improve efficacy, though may also paradoxically increase the risk of excessive sedation.

Nitrous oxide
N_2O is commonly used in dental patients and has been shown to significantly increase tolerance of intrusive oropharyngeal stimulation. Other beneficial effects include reducing secretions and anxiolysis. Rapid onset and offset allows easy titration of the nitrous oxide to ensure patients remain fully conscious. It is contraindicated in patients with chronic lung disease pregnancy (first trimester), previous ear or eye surgery and previous bleomycin therapy (when co-administered with increased concentrations of oxygen)[29].

In dental practices, it is applied using a nasal mask. Patients are pre-oxygenated and nitrous oxide is introduced in 10 per cent increments. No more than a 50 per cent mix is administered, with an optimal effect noted to occur at between 30-40 per cent. It is reversed within two to three minutes with 100 per cent oxygen[29].

COMPLEMENTARY THERAPY

Acupressure and acupuncture
Acupressure and acupuncture are employed by dentists globally to control the gag reflex. In the UK, the British Dental Acupuncture Society offers courses for general practice dentists and dental care professionals. It has been shown to reduce the duration and intensity of the gag reflex on insertion of a Berman airway. Acupuncture uses needling to activate small myelinated nerve fibers in muscle, the midbrain and the pituitary hypothalamus via the spinal cord. Enkephalin, beta-endorphin, dynorphin, serotonin and noradrenaline are also all involved in this process[30,31].

The horizontal mento-labial groove approximately midway between chin and lower lip is used as an acupuncture and acupressure site. To control the gag reflex, an acupuncture needle is inserted 0.3-0.5 mm and rotated for five seconds, or sustained increasing digital pressure is applied for five minutes[24].

THE FUTURE ROLE OF AVL

It is the opinion of the authors that no single technique will always work and as such AVL is a useful technique to learn. AVL may also confer an advantage over AFBI, in specific situations, such as:

1. Unavailability of a FIB.
2. Unfamiliarity of the anaesthetist with AFBI.
3. Critically stenosed airways, to avoid the "cork in bottle" effect.
4. Friable supraglottic pathology, to provide a panoramic view for passing the ETT.
5. Supraglottic oedema, to displace tissue and form a path for passing of the ETT.

THE AUTHORS APPROACH TO AVL

Preparation for the procedure: Setup and equipment
AVL equipment should be ergonomically placed to ensure optimal viewing and working conditions. We recommend a semi-recumbent patient with their head in the neutral position. This allows the operator's eyes, the patient's opened mouth, and the video display to all be aligned in one line of sight.

Pre-procedural oxygenation can then commence and be maintained during the procedure via the buccal route or nasally[32]. Standard monitoring is applied as per ANZCA guidelines and topical anaesthesia (as described below) ± sedation are administered.

The intubator stands above the head of the patient holding the VL in their left hand. The semi-recumbent position ensures efficient performance of laryngoscopy, requiring only a movement of 30-60 degrees against the plane of gravity[33].

In addition to standard anaesthetic room equipment, nasal and oral Mucosal Atomisation Devices (MADs) [Teleflex Medical Europe Ltd. Ireland], 4 per cent lidocaine in 5 mL syringes and 2 per cent lidocaine in a 2 mL syringe should be prepared. Appropriately-sized ETTs should be selected, any flexometallic ETT should be placed in warm sterile saline or water to soften tube. The patient will need a kidney dish to expectorate into and also some tissues.

Oral anaesthesia
Lidocaine is the agent most commonly used for topicalisation of the airway. Published maximum doses for airway topicalisation range from 4-9 mg/kg^{-1}. The maximum dose should not be exceeded to avoid adverse effects such as arrhythmias and convulsions[34].

Sensory innervation of the oral and oropharyngeal mucosa is supplied by branches of the glossopharyngeal, vagus and facial nerves. Anaesthesia for AVL targets the glossopharyngeal and vagus nerves in particular (table 2). The rest of this section will focus on various methods this can be topically achieved.

Table 2. Sensory innervation of oropharyngeal mucosa

TOPICAL ANAESTHESIA TARGET SITE	SENSORY INNERVATION
Oropharynx, posterior tongue	Glossopharyngeal nerve
Larynx	Vagus nerve

Glossopharyngeal nerve
The glossopharyngeal nerve travels anteriorly along the lateral surface of the pharynx. It divides into three branches which provide the sensory innervation to the posterior third of the tongue, the vallecula, the anterior surface of the epiglottis, the tonsillar pillars,and the posterior and lateral walls of the pharynx. It also provides motor innervation to the stylopharyngeus muscle, involved in swallowing. Dense anaesthesia of the glossopharyngeal nerve is key to the success of AVL. This can be achieved using a combination of the following techniques.

Nebulisers
Four mL of four per cent lidocaine can be nebulised at flow rates of between 4-6 $Lmin^{-1}$. The patient then inhales the nebulised local anaesthetic for five to seven minutes. Mouth piece nebuliser kits can be used to reduce environmental losses.

Gargling
Gargling 2 mL of four per cent lidocaine provides dense anaesthesia and only 10 per cent of the dose need be included in the total dose calculation.

Aerosolisation
Ten mL of lidocaine can be administered via a McKenzie device (connect the oxygen tubing via a three-way tap to 20G cannula). With the oxygen flow set at 3 $Lmin^{-1}$, the patient then inhales the aerosolised local anaesthetic for five minutes, or the tongue and posterior pharynx are sprayed.

Targeted topicalisation with spray/direct application of LA
Provided there is sufficient mouth opening, the most superficial branches of the glossopharyngeal nerve can be targeted where they traverse the palatoglossal folds in the posterior tonsillar pillars. Standing contralateral to the side to be blocked, a tongue depressor held with the non-dominant hand is introduced into the mouth to sweep the tongue to the contralateral side, creating a gutter between the tongue and the teeth. Lidocaine 10 per cent spray or gauze swabs soaked with lidocaine 10 per cent can then be directed on to the posterior tonsillar pillars.

Vagus nerve
Blocking branches of the vagus nerve suppresses the gag reflex and the haemodynamic response to laryngoscopy. This can be achieved under (in)direct vision during VL. The MAD is used to spray 2 mL increments of 4 per cent lidocaine directly onto the vallecular, the vocal cord mucosa and through the vocal cords

To more precisely target the superficial laryngeal nerve, the pyriform fossa is identified during AVL lying lateral to the arytenoid cartilages, and medial to the lamina of the thyroid cartilage bilaterally. This area is then topicalised with the MAD and four per cent lidocaine.

STEP-BY-STEP GUIDE

The authors' technique for AVL is summarised below:

1. Equipment and skilled assistance are gathered and checked.
2. The patient is settled in a semi-recumbent position and the positions of the operator, patient, and screen are ergonomically optimised.
3. Standard monitoring is applied and intravenous access is obtained.
4. One to two sprays of 10 per cent lidocaine are applied intra-orally at each location indicated on figure 1 with tongue fully out and patient mouth breathing. Xylocaine® 10 per cent pump and nozzle will deliver a 10 mg dose per spray. LA is applied during the initial phase of deep inspiration. A further two sprays are directed into oropharynx keeping the tip of the nozzle centralised in the airway. The total number of sprays typically required is eight to 12.

Figure 1. Oropharyngeal sites for topicalisation

Next, the patient is asked to gargle and swallow 2 mL of four per cent lidocaine.

5. Shape an appropriate length MAD against the facial landmarks. Atomise 10 mL of one per cent lidocaine into the oropharynx. Two applications of 5 mL during the initial phase of deep inspiration will carry it toward the vallecula, epiglottis and glottic opening. Keep it close to the soft palate strictly in the midline (be aware of the tip rotation).
6. Test the gag reflex with the MAD. If suitably anaesthetised allow the patient to insert the VL blade into the oropharynx. Lubricate both sides of the blade of the scope using 10 per cent lidocaine prior to insertion. Wipe the camera eye of the video laryngoscope using a swab if needed.
7. Under direct vision with the video laryngoscope, use the MAD to spray increments of four per cent lidocaine directly onto the vallecular, the vocal cord mucosa and through the vocal cords.
8. If significant gagging still occurs after all the 4 per cent lidocaine has been applied, remove the VL and consider "top up" local application if safe dosing allows, addition of (further) sedation, or change to an alternate technique (e.g. AFBI).
9. If the patient has comfortably tolerated all of the above, proceed with intubation!
10. Confirm tracheal tube position via visualisation and capnography. Inflation of the cuff is very stimulating and in most cases can be safely done after induction of anaesthesia.
11. Induce anaesthesia and inflate the cuff.
12. The final check of tube position by auscultation is then performed.

TIPS AND TRICKS

- Apply LA during initial phase of inspiration; coughing is a sign of effective application.
- Ask the patient to hold in any LA applied to the mouth as long as possible and swallow it.
- Allowing the patient to insert the VL themselves may promote comfort, a feeling of control, and reduce the risk of triggering the gag reflex.
- Use of a preformed stylet is necessary if using an unchannelled VL.
- Ensure any LA aerosol device nozzles are positioned in the centre of the airway at all times (and not touching the mucosa).
- The four per cent lidocaine gargle is often better tolerated in an already partially anaesthetised pharynx.
- "Bring the trachea to the tube": If misalignment between the ETT and the glottis occurs, external laryngeal manipulation, head flexion, "relaxation" of the laryngoscope arm and bevel tip rotation may help.
- Inflating the cuff above the cords to push the ETT tip superiorly can help in presence of an anterior larynx.
- The duration of effective LA topicalisation is 20 to 30 minutes post application.

LEARNING AND TEACHING

In order to spread awareness and learn more about the technique, the first and third authors were faculty members on a pilot AVL familiarisation course (using only LA topicalisation) for a total of 10 senior registrars and consultants[35].

This hands-on method of teaching was found to be beneficial as it allowed colleagues to personally observe, perform and experience the procedure. Many have since found it helped them significantly during the AVL consent process and procedure.

The success rate in this group of motivated participants was 50 per cent. All failures were due to an exaggerated gag response. Once the reflex had been triggered we found it almost impossible to overcome with further topicalisation.

IS AVL A GAME CHANGER?

AVL is an evolving technique and should be considered an additional tool, rather than a replacement for AFBI or any other airway management technique. While AVL is not a panacea, the increasing number of case reports of its success where AFBI has failed, and the potentially superior performance over AFBI in certain clinical circumstances, support its ongoing learning and development.

A significant advantage is that the psychomotor skills for AVL are already embedded in the anaesthetic community and there is multidisciplinary familiarity with the practicalities of VL. The widespread availability of single use disposable blades for most VLs may have cost and patient safety advantages compared to reusable but very expensive equipment with infection control risks.

However, not all VLs are equal in their features and limitations, and further evidence is required to improve guidance on which is best for particular clinical scenarios. Lastly, there is a need for further investigation into identification of patients with a severe gag reflex and ensuring techniques to supress the gag reflex are safe, effective and appropriately targeted.

REFERENCES

1. Cook TM, Woodall N, Frerk C. 4th National Audit Project of the Royal College of Anaesthetists. UK: Royal College of Anaesthetists, 2011.
2. Goodwin M. Management of the anticipated difficult airway: without clinical upper airway obstruction. In: Popat M, editor. Difficult airway management. Oxford: Oxford University Press, 2009. pp.47–54.
3. Frerk C, Mitchell VS, McNarry AF, Mendonca C, Bhagrath R, Patel A, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth. 2015;115(6):827–848.
4. Ray DC, Billington C, Kearns PK, Kirkbride R, Mackintosh K, Reeve CS, et al. A comparison of McGrath and Macintosh laryngoscopes in novice users: a manikin study. Anaesthesia. 2009;64(11):1207–1210.
5. Heidegger T, Gerig HJ, Ulrich B, Schnider TW. Structure and process quality illustrated by fibreoptic intubation: analysis of 1612 cases. Anaesthesia. 2003;58(8): 734–739.
6. Rosenstock CV, Thøgersen B, Afshari A, Christensen A-L, Eriksen C, Gätke MR. Awake fiberoptic or awake video laryngoscopic tracheal intubation in patients with anticipated difficult airway management. Anesthesiology. 2012;116(6):1210–1216.
7. Sinofsky AH, Milo SP, Scher C. The awake GlideScope intubation: an additional alternative to the difficult intubation. Middle East J Anaesthesiol. 2010;20(5):743–746.
8. Bucx MJ, Scheck PA, Van Geel RT, Den Ouden AH, Niesing R. Measurement of forces during laryngoscopy. Anaesthesia. 1992;47(4):348–351.
9. McGuire BE. Use of the McGrath video laryngoscope in awake patients. Anaesthesia. 2009;64(8):912–914.
10. Asai T, Ito I, Kuremoto Y, Kawashima A. Tracheal intubation with Pentax AWS Airway Scope after failed fiberoptic intubation and failed insertion of the intubating laryngeal mask airway. [Japanese]. Masui. 2010;59(4):470–472.
11. Hughes CG, Mathews L, Easdown J, Pandharipande PP. The McGrath videolaryngoscope in unstable cervical spine surgery: a case series. J Clin Anesth. 2010;22(7):575–576.
12. Uslu B, Damgaard Nielsen R, Kristensen BB. McGrath videolaryngoscope for awake tracheal intubation in a patient with severe ankylosing spondylitis. Br J Anaesth. 2010;104(1):118–119.
13. Xue F-S, Cheng Y, Li R-P. Awake intubation with video laryngoscope and fiberoptic bronchoscope in difficult airway patients. Anesthesiology. 2013;118(2):460–471.
14. Jeyadoss J, Nanjappa N, Nemeth D. Awake intubation using Pentax AWS videolaryngoscope after failed fibreoptic intubation in a morbidly obese patient with a massive thyroid tumour and tracheal compression. Anaesth Intensive Care. 2011;39(2): 311–312.
15. Bruins BB, Mirza N, Gomez E, Atkins JH. Anaesthetic management for laser excision of ball-valving laryngeal masses. Case Rep Anesthesiol. 2015;875053:3.
16. Moore AR, Schricker T, Court O. Awake videolaryngoscopy-assisted tracheal intubation of the morbidly obese. Anaesthesia. 2012;67(3):232–235.
17. Abdellatif AA, Ali MA. GlideScope videolaryngoscope versus flexible fibreoptic bronchoscope for awake intubation of morbidly obese patient with predicted difficult intubation. Middle East J Anaesthesiol. 2014;22(4):385–392.
18. Sukernik MR, Bezinover DS, Stahlman B, Vaida S, Pott L. Combination of GlideScope with fiberoptic bronchoscope for the optimization of difficult endotracheal intubation. A case series of three patients. Anesthesia On-Line. 2009. From: http://www.priory.com/medicine/Glidescope_bronchoscope.htm. Accessed 17 September 2017.
19. El-Tahan MR, Doyle J, Khidr AM, Regal MA , El morsy AB, El Mahdy M. Awake tracheal intubation with combined use of King Vision™ videolaryngoscope and a fiberoptic bronchoscope in a patient with giant lymphocele. Middle East J Anaesthesiol. 2014;22(6):609–612.
20. Drenguis AS, Carlson JN. GlideoScope vs. C-MAC for awake upright laryngoscopy. J Emerg Med. 2015;49(3):361–368.
21. Lohse JA, Piepho T, Noppens RR. Awake video laryngoscopy – a revolution in the management of the difficult airway. Trends Anaesth Crit Care. 2016;6:37–42.
22. Dotson M. Awake video laryngoscope intubation: case report of a patient with a nasopharyngeal mass. AANA J. 2012;80(5):347–353.
23. Sanchez T, Morrison D. Preparation of the patient for awake intubation. In: Hagberg CA, editor. Handbook of difficult airway management. Philadelphia: Churchill Livingstone, 2000. pp. 49–82.
24. Shriprasad S, Shilpashree H. Gag reflex: no more a gag to a dentist the behavioral techniques, pharmacological techniques, acupressure and acupuncture in controlling the gag reflex – a review. Bangladesh J Med Sci. 2012;11(1):12–17.
25. Hearing C, Bind R, Tabacco M, Hallock R. A reliable and valid survey to predict a patients gagging intensity. J Oral Maxillofac Res. 2014;5(2):e3.
26. Kopman AF, Wallman SB, Ross K, Surks SN. Awake endotracheal intubation: a review of 267 cases. Anesth Analg. 1975;54(3):323–327.
27. Johnston KD, Rai MR. Conscious sedation for awake fibreoptic intubation: a review of the literature. Can J Anesth. 2013;60(6):584–599.
28. Vennila R, Hall A, Ali M, Bhuiyan N, Pirotta D, Raw DA. Remifentanil as single agent to facilitate awake fibreoptic intubation in the absence of premedication. Anaesthesia. 2011;66(5):368–372.
29. Kaufman E, Weinstein P, Somers EE, Soltero DJ. Experimental study of the control of the gag reflex with nitrous oxide. Anaesth Prog. 1988;35(4):155–157.

30. Mitchell J, Jeffrey S, Lochhead V. Use of acupuncture to reduce gagging during the insertion of an oral airway. Anaesthesia. 2008;63(12):1389–1390.
31. Rosted P, Bundgaard M, Fiske J, Pedersen AML. The use of acupuncture in controlling the gag reflex in patients requiring an upper alginate impression: an audit. Br Dent J. 2006;201:721–725.
32. Heard A, Toner AJ, Evans JR, Aranda Palacios AM, Lauer S. Apneic oxygenation during prolonged laryngoscopy in obese patients: a randomized, controlled trial of buccal RAE tube oxygen administration. Anesth Analg 2017;124(4):1162–1167.
33. Gupta D, Rusin K. Endotracheal intubation with GlideScope in semi-erect position in morbidly obese population. ASA Annual meeting abstracts, 2011.
34. Maheshi,P. Awake nasal intubation and topical anaesthesia: how and how much?. Anaesthesia. 2015;70(7):879.
35. The All Wales Airway Group. Awake video laryngoscopy course. 2016. From: https://allwalesairwaygroup.co.uk/event/view/51. Accessed 17 September 2017.

Airway management after cervical spine surgery: A review of the literature

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INTRODUCTION

The 2011 Difficult Airway Society (UK) extubation guidelines[1] have focused attention on the importance of postoperative airway management planning to ensure a safe extubation. The Fourth National Audit Project highlighted that a third of airway complications occur during emergence or recovery and that a common cause is airway obstruction[2]. Patients undergoing craniocervical surgery have up to six times higher risk of airway complications than the average surgical population owing to a combination of anaesthetic and surgical risk factors. However, the reported rate of postoperative airway compromise after cervical spine surgery (CSS) varies widely from 1.2 per cent to 30 per cent[3] and up to 6 per cent reintubation rate, depending on the type of cervical surgery performed. Despite this poor reporting in the anaesthetic literature, in a subset of patients, we believe it to be a significant and predictable event, while being poorly clinically recognised within the first 72 hours postoperatively. The complications can be catastrophic, leading to death or severe disability. In Australia, for the financial year 2015-2016, Medicare reported 4045 billable events (anaesthesia for spinal surgery; MBS item number 20600) or 17 services per 100,000 population. These figures probably represent about 45-50 per cent of the cases performed in Australia as they do not include public hospital cases, Department of Veteran Affairs cases or the more complex spine cases (MBS Item number 20670). So probably, the predicted magnitude of a serious post-operative airway complication would be between 97 to 2427 cases (1.2 per cent to 30 per cent)[3] for the 2015-2016 financial year, with up to an estimated 485 cases (6 per cent) requiring reintubation in the postoperative period. This has implications to any organisation in terms of planning the management and consenting of these patients to the potential risks.

Few studies have addressed this potentially life threatening complication in the anaesthetic literature, although several case reports describe the requirement of emergency re-intubation in the recovery room after complex, multilevel CSS[4-6]. An increasing awareness is developing about the extubation risks in the cervical spine patient,

leading some centres to develop protocols for managing these patients postoperatively. However, with a paucity of information in the anaesthetic literature, these guidelines are ad hoc and patchy in implementation. Anaesthetists should be aware of the risk factors, identify "high-risk" patients, and plan a safe extubation as part of the surgical team. We present a review of the literature and have included an extubation guideline for the safe management of these patients based on the current evidence.

LITERATURE REVIEW

Three retrospective case reviews were identified in the surgical literature[6-8]. All three reported a similar incidence of upper airway oedema (UAO) requiring postoperative re-intubation after anterior-approach CSS [1.9 per cent (n=6/311), 2.3 per cent (n=4/171), and 2.8 per cent (n= 7/174)]. Surgery at multiple cervical levels was associated with postoperative complications. Airway deaths occurred because of a failure to re-secure the postoperative airway in these reviews.

Terao and colleagues[3] reviewed postoperative airway management in 165 patients who underwent various types of CSS. The group (n=10) undergoing anterior and posterior combined CSS (APCS) had the highest rate (70 per cent) of emergency airway management, defined as re-intubation or delayed extubation. In comparison, only 1 per cent of the remaining 155 patients required emergent airway management. Six of 10 had life-threatening airway complications, with three requiring emergency airway intervention, two requiring awake fibreoptic re-intubation (difficult because of pharyngeal swelling/UAO), and one requiring a cricothyroidotomy. After the risk in this subpopulation of patients was identified, the next seven patients presenting for APCS remained intubated in the intensive care unit (ICU) and were extubated after fibreoptic evaluation of the airway. Interestingly, four of the seven patients could only be extubated between days five and 10 post-surgery.

The Terao findings contrast markedly with those of Epstein and colleagues[9], who reported a much lower complication rate of 6.9 per cent (n=4/58) for postoperative airway complications (re-intubation or tracheostomy) after APCS. The latter study included an airway protocol in which "high-risk" patients were kept intubated for the first night after surgery and the airway was assessed for swelling before extubation. These precautions may have influenced the reported complication rate. Three patients required tracheostomies on postoperative day seven, as the UAO was unresolved.

In anterior cervical surgery, the risk for UAO is less clear. Emery and colleagues[6] reviewed 133 patients undergoing anterior cervical surgery and identified seven who needed re-intubation. All seven patients had pre-existing myelopathy and underwent a multi-level corpectomy that had a prolonged operating time, with average duration of five hours.

More recently, Nandyala and colleagues[10] accessed the American College of Surgeons National Surgical Quality Improvement Program database and found that only 54 of 8648 patients undergoing CSS required prolonged intubation (0.62 per cent) and 56 (0.64 per cent) required postoperative re-intubation. Three-quarters of the procedures were anterior cervical discectomy and fusion, and none used a combined anterior and posterior approach. The authors found that the incidence of re-intubation was significantly higher among patients who underwent longer surgery or required blood transfusion.

Their findings concur with those of Sagi and colleagues[7], whose retrospective chart review of 311 patients indicated that operations lasting five hours or more and those in which more than 300mL of blood is lost have a significant correlation with airway complications. Also noted was the relationship with surgical level and outcome—surgery at or above the fourth cervical vertebra was associated with a higher risk for airway complications.

Wattenmaker and colleagues[11] reviewed 128 patients with rheumatoid arthritis who underwent CSS with a posterior approach. Rheumatoid arthritis can make intubation more difficult. The authors reported postoperative UAO in eight of 50 (14 per cent) patients who had been intubated directly but in only one of 70 (1.4 per cent) who had been intubated fibreoptically. However, another study by Manninen and colleagues[12] found no association between the method of intubation and postoperative airway complications.

Several studies have investigated the potential causes of UAO after CSS. Some have shown profound prevertebral tissue oedema leading to pharyngeal oedema and distortion of the upper airway to be a cause of UAO[3,13]. In sequential pre- and postoperative lateral neck x-ray films, Suk and colleagues[13] elegantly demonstrated maximal vertebral soft tissue swelling on postoperative day three. Andrew and Sidhu[14] examined vertebral swelling both before and after anterior cervical discectomy and fusion surgery by using lateral x-ray measurement between the anterior vertebral body and posterior border of the airway. The largest postoperative change was at the level of C2-C4, with an increase in anteroposterior length of up to 329 per cent (4.1 mm to 13.5 mm at C3).

DISCUSSION

The lack of strong evidence identifying high-risk patients makes it difficult to formulate a definitive evidence-based extubation protocol. We have reviewed both surgical and anaesthetic literature and believe that identification of key risk factors and safe extubation criteria can be formulated based upon current knowledge and reported experiences.

A review of the literature brought to light several factors that appear to increase the risk of postoperative airway obstruction and other complications (table 1):

1. Combined anterior and posterior cervical surgery.
2. Operative time more than five hours.
3. Surgery involving three vertebral levels, including one of C4 or above.
4. Surgery involving C2 fusion or C1 odontoid peg.
5. Blood loss greater than 300 mL.
6. Preoperative myelopathy.
7. Pre-existing pulmonary disease (asthma, chronic obstructive pulmonary disease, smoking, obstructive sleep apnoea).

Table 1. Risk factors for airway-related complications after cervical spine surgery

RISK FACTOR	REFERENCES
Combined anterior-posterior approach	Terao[3], Nandyala[10], Epstein[9]
Pre-existing myelopathy	Emery[6], Wattenmaker[11], Epstein[9]
Prolonged operative time (>5 hours)	Emery[6], Nandyala[10], Sagi[3], Epstein[9]
Estimated blood loss greater than 300 ml	Epstein[9], Sagi[3]
Multiple cervical levels involved (3+)	Sagi[7], Epstein[9]
C1 or C2 levels involved	Sagi[7], Epstein[9]
Pre-existing pulmonary disease	Emery[6], Epstein[9]

The combined anterior and posterior cervical surgery has repeatedly been identified as high risk for patients with UAO. Thus, a delayed extubation, or extubation followed by close monitoring, would be an important safety strategy for these patients and allow for postoperative swelling to resolve.

The aetiology of UAO differs from that of airway compromise seen after thyroid or carotid surgery. Haematoma formation and cerebrospinal fluid leak are potential complications of CSS that usually present early in the postoperative period, whereas upper airway obstruction most commonly develops in the late postoperative period (days rather than hours).

UAO occurs because of prevertebral tissue swelling that evolves late in the postoperative course. The danger is that the onset can be insidious in a ward environment, leading to late recognition and limited availability of practitioners with airway expertise[12]. Development of prevertebral oedema has been implicated in several near misses and deaths, which became the sentinel events that stimulated creation of departmental protocols to safely manage these patients postoperatively[9].

Surgical factors suggested in the aetiology for oedema are prolonged retraction time and manipulation of deep neck structures, which generate a local inflammatory response[6,7]. It is theorised that patients undergoing vertebral corpectomies have an increased risk, as they have a large surface area of bleeding cancellous bone that can lead to lymphatic obstruction, blood clot formation, and higher risk of oedema[6].

The combined anaesthetic-surgical literature offers very little information about the contribution of anaesthetic management to airway obstruction in patients undergoing CSS. A study by Manninen and colleagues[12] evaluated the choice of intubation technique in 327 patients with a variety of conditions who were undergoing cervical spine procedures by a mix of anterior and posterior approaches. They found no statistically significant association between the anaesthetic choice of preoperative airway management technique and postoperative airway obstruction.

Securing the airway with minimal pharyngeal trauma is particularly important in these patients, as multiple intubation attempts will add to the surgical prevertebral oedema. In the Manninen study, 71 per cent of the patients were intubated via fibreoptic intubation[12]. The presence of cervical myelopathy and decreased neck range of motion are risk factors for difficult intubation[15]. Therefore, practitioners should have a low threshold for using advanced airway techniques to reduce intubation attempts and thereby minimise pharyngeal trauma and risk to the cervical spine. The study of patients with rheumatoid arthritis by Wattenmaker and colleagues[11] supports the use of fibreoptic intubation to reduce postoperative airway complications.

Steroid administration is sometimes used in airway surgery to minimise oedema. However, the evidence in current literature that steroid prophylaxis is effective in preventing UAO is conflicting. In a small randomised trial of 66 patients, Emery and colleagues[16] found that the administration of dexamethasone (0.3 mg/kg before incision, 0.15 mg/kg at eight and 16 hours after incision) to patients undergoing two- or three-level anterior corpectomy procedures did not result in any significant reduction in airway oedema. A more recent study by Jeyamohan[17] showed a clinical significance in the severity of dysphagia postoperatively and a trend toward significance in reduction in postoperative airway management when steroids were given, at the expense of the six-month bone fusion rate. There was no difference in bone fusion rate at 12 months.

There should be consideration as to whether the institution is an appropriate place for the surgery to be performed and there is the 24-hour facility to manage re-intubation if necessary. In addition to the anaesthetic factors such as difficult laryngoscopy grade, the following factors should be considered when deciding to delay extubation:

1. Halo-thoracic brace in situ.
2. Obstructive sleep apnoea.
3. Pre-existing respiratory compromise:
   - Severe asthma.
   - Chronic obstructive pulmonary disease.
4. Gross facial oedema apparent at end of the case.

Identifying risk factors can be difficult due to the small number of studies, small patient numbers included in the studies, and lack of prospective data with comparison groups. One consistent factor based on reviews and case reports appears to be that surgery with the combined anterior-posterior approach is an identifiable high risk in the development of UAO.

Leak testing has been successfully used to determine safety for extubation on postoperative day one. Kwon and colleagues[18] employed a protocol wherein patients undergoing APCS remained intubated overnight postoperatively. Readiness for extubation was determined by the presence of cuff leak. In that study, risk factors for delayed extubation included prolonged operative time and higher administered volumes of crystalloid and blood products.

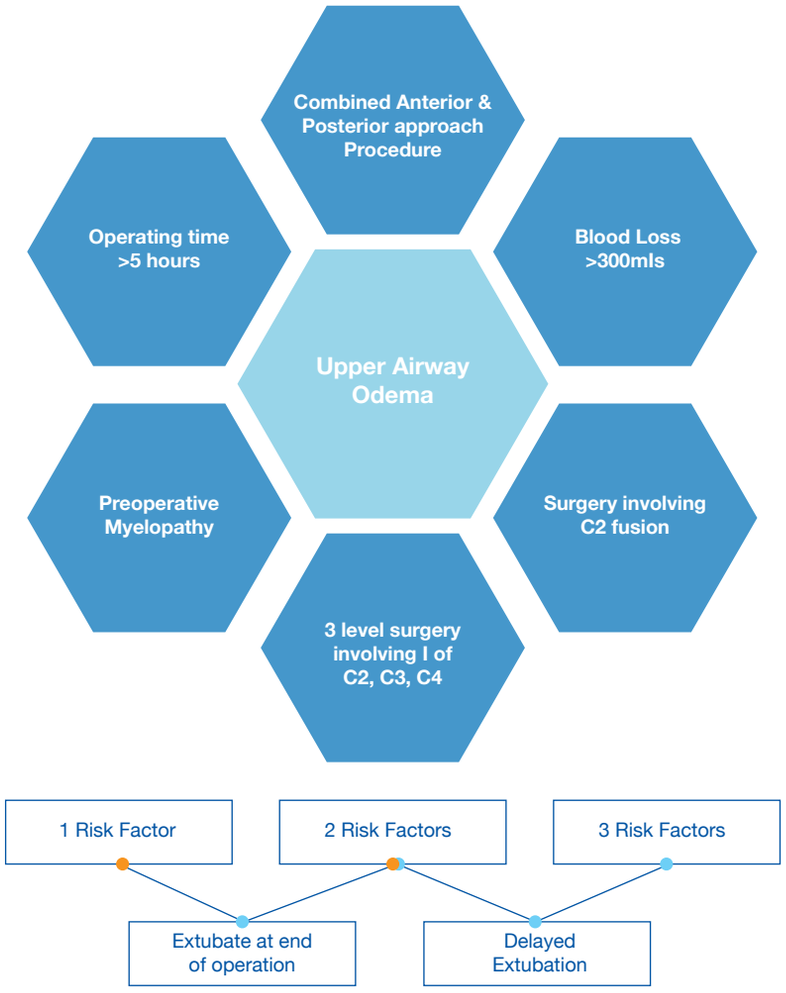
The absence of a leak around the endotracheal tube cuff should preclude extubation. Assessment and confirmation of a cuff leak before extubation ensures close monitoring of high-risk patients in the post-extubation period. Extubation over an exchange catheter is another technique that can be considered to minimise the risk of a failed re-intubation attempt. Extubation catheters can be placed through the in-situ tube before removal and used to re-intubate the patient if necessary[19].

A practice survey of extubation after CSS in Victoria showed that none of the centres questioned used a protocol and there was significant variation in awareness of all the potential surgical risk factors for the development of UAO[20]. Institutions that perform complex cervical surgery should formulate a protocol for the CSS patient to ensure that an efficient and safe process is in place, particularly when patients with two or more risk factors are encountered (table 1). The plan should include a safe extubation protocol as suggested by the Difficult Airway Society extubation guidelines, with modifications based on the unique challenges of cervical spine patients[1]. Increasing the rate of postoperative intubation in high-risk cervical spine patients may affect the availability of beds for other surgical patients however given the high risk of death from UOA in these patients it is likely to be justified. We recommend delayed extubation and careful post-extubation monitoring for patients who have undergone APCS and have two additional risk factors. Figure 1 illustrates an algorithm and figure 2 a cognitive aid that we have developed for patients undergoing CSS.

Figure 1. Recommended cervical spine surgery airway management protocol by the authors, Nicholson et al

CERVICAL SPINE SURGERY AIRWAY MANAGEMENT PROTOCOL	
Does the patient have	• Predictors of difficult intubation • Rheumatoid arthritis • Significant cervical myelopathy
If yes, consider	• Awake intubation • Fibreoptic intubation • Videolaryngoscopy
Are there two or more risk factors for post operative airway complications	• **Combined anterior posterior approach** • C1 or C2 levels involved • Difficult or traumatic intubation • Estimated Blood loss >300 mls • Pre existing myelopathy • Pre existing pulmonary disease • Prolonged operative time >5 hours • Surgery involving 3 vertebral levels including one C4 or above
If yes, consider	• Delayed extubation • Extubation with close monitoring in an ICU setting • Extubation over an airway exchange catheter
Post operative airway obstruction warning signs	• Agitation or restlessness • Difficult talking or altered voice • Difficult or painful swallowing • **Inspiratory stridor** • Respiratory distress or low oxygen saturations
If yes, consider	• Wound haematoma • CSF leak and accumulation • Upper airway oedema • Infection and abscess formation

Figure 2. Cervical Spine Extubation Cognitive Aid



CONCLUSION

The postoperative management of patients after CSS requires an experienced multidisciplinary team approach. Therefore, it is important for non-neurosurgical anaesthetists who provide postoperative care for these patients after hours and all members of the perioperative team (surgeons, anaesthetists, intensive care staff) to be aware of the airway risks associated with CSS and the possibility for UAO. Moreover, it is imperative that the teams coordinate a safe, appropriate postoperative plan for these patients. Anaesthetists also need to raise awareness among the nursing staff in the ICU and, more importantly, on the wards, about the potential for late development of oedema. Staff need to recognise the signs of UAO development (stridor, drooling, poor phonation, decreasing oxygen saturation), call for advanced airway help early, and readily transfer patents to an operating theatre environment, where experienced practitioners can secure what will be a challenging airway. However, we must emphasise that these patients should be transferred only if it is safe to do so. If the airway requires emergent management and it is unsafe to travel, the airway should be managed at the bedside. Ideally these patients should only have their surgery at centres with intensive care units that are experienced in managing them.

As awareness of CSS airway risk increases and institutions implement specific protocols based on our review and guidelines, anaesthetists will be able to identify patients early who are at high risk for post-CSS airway compromise, employ safe, appropriate management techniques, and potentially avoid significant airway-related complications. Ultimately, we would envisage an Australasian registry for cervical spine surgery be undertaken to provide further insight into postoperative airway complications and guide further recommendations to improve patient safety in those undergoing cervical surgery.

REFERENCES

1. Popat M, Mitchell V, Dravid R, Patel A, Swampillai C, Higgs A. Difficult Airway Society Guidelines for the management of tracheal extubation. Anaesthesia. 2012;67:318-340.
2. Cook TM, Woodall N, Frerk C. Fourth National Audit Project of the Royal College of Anaesthetists and Difficult Airway Society. Major complications of airway management in the United Kingdom. Report and Findings. March 2011. From: http://www.rcoa.ac.uk/system/files/CSQ-NAP4-Full.pdf. Accessed 10 December 2013.
3. Terao Y, Matsumoto S, Yamashita K, Takada M, Inadomi C, Fukusaki M, et al. Increased incidence of emergency airway management after combined anterior-posterior cervical spine surgery. J Neurosurg Anesthesiol. 2004;16:282-286.
4. Stefanutto TB, Gatt S. Cervical decompression and unexpected soft tissue oedema: case report. Anesth Pain Med. 2012;2:97-100.
5. Morita M, Nobuta M, Naruse H, Nakamura H. Prolonged airway obstruction after posterior occipitocervical fusion: a case report and literature review. Adv Orthop. 2011;2011:791923.
6. Emery SE, Smith MD, Bohlman HH. Upper-airway obstruction after multilevel cervical corpectomy for myelopathy. J Bone Joint Surg Am. 1991;73:544-551.
7. Sagi HC, Beutler W, Carroll E, Connolly PJ. Airway complications associated with surgery on the anterior cervical spine. Spine (Phila Pa 1976). 2002;27:949-953.
8. Fujiwara H, Nakayama H, Takahashi H, Shimizu M, Hanaoka K. [Postoperative respiratory disturbance after anterior cervical fusion]. Masui. 1998;47:475-478.
9. Epstein NE, Hollingsworth R, Nardi D, Singer J. Can airway complications following multilevel anterior cervical surgery be avoided? J Neurosurg. 2001;94:185-8.
10. Nandyala SV, Marquez-Lara A, Park DK, Hassanzadeh H, Sankaranarayanan S, Noureldin M, et al. Incidence, risk factors, and outcomes of postoperative airway management after cervical spine surgery. Spine (Phila Pa 1976). 2014;39:E557-E563.
11. Wattenmaker I, Concepcion M, Hibberd P, Lipson S. Upper-airway obstruction and perioperative management of the airway in patients managed with posterior operations on the cervical spine for rheumatoid arthritis. J Bone Joint Surg Am. 1994;76:360-365.
12. Manninen PH, Jose GB, Lukitto K, Venkatraghavan L, El Beheiry H. Management of the airway in patients undergoing cervical spine surgery. J Neurosurg Anesthesiol. 2007;19:190-194.
13. Suk KS, Kim KT, Lee SH, Park SW. Prevertebral soft tissue swelling after anterior cervical discectomy and fusion with plate fixation. Int Orthop. 2006;30:290-294.
14. Andrew SA, Sidhu KS. Airway changes after anterior cervical discectomy and fusion. J Spinal Disord Tech. 2007;20:577-581.
15. Mashour GA, Stallmer ML, Kheterpal S, Shanks A. Predictors of difficult intubation in patients with cervical spine limitations. J Neurosurg Anesthesiol. 2008;20:110-5.
16. Emery SE, Akhavan S, Miller P, Furey CG, Yoo JU, Rowbottom J, et al. Steroids and risk factors for airway compromise in multilevel cervical corpectomy patients: a prospective, randomized, double-blind study. Spine (Phila Pa 1976). 2009;34:229-232.
17. Jeyamohan S, Kenning T, Petronis K, Feustel PJ, Drazin D, DiRisio DJ. Effect of steriod use in anterior cervical discectomy and fusion: a randomized controlled trial. J Neurosurg Spine. 2015 23:137-143
18. Kwon B, Yoo JU, Furey CG, Rowbottom J, Emery SE. Risk factors for delayed extubation after single-stage, multi-level anterior cervical decompression and posterior fusion. J Spinal Disord Tech. 2006;19:389-393.
19. Mort TC. Continuous airway access for the difficult extubation: the efficacy of the airway exchange catheter. Anesth Analg. 2007;105:1357-1362.
20. Nicholson J, Bradley W, Stefanutto T, Downey G. When not to extubate after cervical spine surgery. ANZCA ASM 2014 Poster Presentation.

Tracheostomy crisis management

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INTRODUCTION

Surgical airways, such as tracheostomy, are infrequently encountered in most anaesthetic practice but represent a high proportion of airway litigation cases[1,2]. In New South Wales a catastrophic event involving a tracheostomy occurs at least every six weeks[3]. In surgical airway crises there is often not time to wait for treating teams to attend the ward, especially after hours. In most tracheostomy crises an anaesthetist is involved either in theatre or as part of a medical emergency team; as such it is imperative that these and other first responders are confident in the management of these challenging scenarios.

Surgical tracheotomies have been performed since ancient Egyptian times; however they have not always been popular. As US President George Washington died from epiglottitis, his physicians refused to perform a tracheostomy to maintain his airway, as the procedure was known to have unacceptable risks at that time[4]. Even with modern techniques, approximately 1 per cent of tracheostomy patients will die due to a complication of their surgical airway[5]. Half of all airway-related deaths or brain damage in critical care are a result of tracheostomy complications[6].

Complications of tracheostomy occur in 15 per cent of patients and 90 per cent occur greater than a week after the tracheostomy insertion[7]. The most common acute complications are listed in table 1 and include bleeding, dislodgement or obstruction[8]. Tracheal stenosis is one of the most common chronic complications, occurring in up to two per cent of tracheostomy patients[5].

Table 1. Tracheostomy complications[6-9]

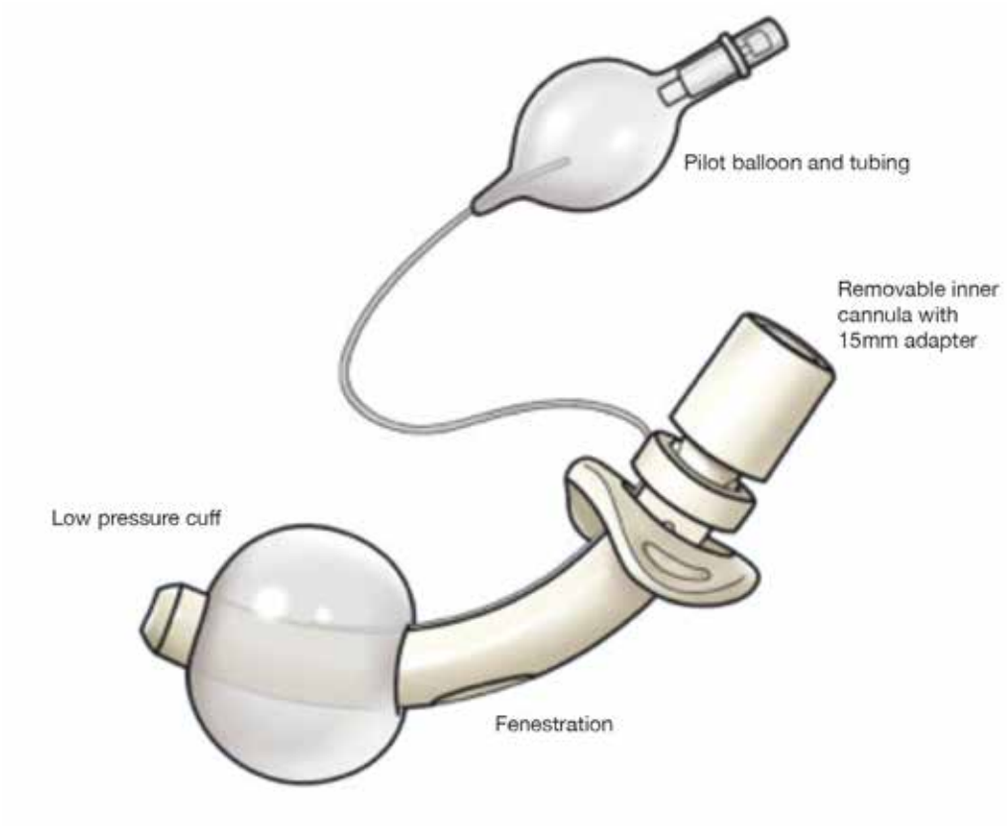
SHORT-TERM	LONG-TERM
Bleeding	Tracheo-innominate fistula
Dislodgement	Tracheoesophageal fistula
Obstruction	Tracheocutaneous fistula
Pneumothorax, pneumomediastinum	Tracheal stenosis
Infection	Tracheomalacia

ANATOMY OF A TRACHEOSTOMY TUBE

There are a few variations to the nature of tracheostomy tubes that can seem complex but after consideration are not too dissimilar to the variety of endotracheal tubes available (figure 1).

- Cuffed or uncuffed. Cuffed tubes are used for patients requiring ventilation or who are unable to protect their upper airways due to impaired laryngeal or cough function. The pilot balloon and tubing clearly indicate the presence of a cuff. Uncuffed tubes are mainly used in chronic upper airway obstruction.

Figure 1. Shiley-type cuffed tracheostomy tube with fenestration – adapted from J Fong[10]



- Inner cannula. All modern adult tracheostomy tubes have inner cannulae available. These are a major safety advance, functioning as the "sacrificial anode" in the event of obstruction of the tracheostomy. The inner tube can simply be removed, restoring patency and without removal of the tracheostomy. Shiley® tracheostomy tubes are in common use and require an inner cannula be inserted to allow physical connection to a breathing circuit or bag-valve resuscitator (figure 1).
- Fenestrations. Holes in the superior aspect of the tracheostomy tube are designed to permit speech during exhalation, as air is directed towards the larynx rather than out the tracheostomy. They are more common in chronic tracheostomy patients and can be complicated by growth of granulation tissue into the fenestration. Positive pressure ventilation may be possible if a non-fenestrated inner cannula is placed inside a cuffed fenestrated tracheostomy tube.
- Adjustable flange. Obese patients often have a longer distance from skin to trachea; as such a tracheostomy tube with a longer anterior-posterior length is required. Adjustable flange tubes enable the length to be adjusted appropriate for the individual patient. If the locking mechanism releases, the tube can migrate, risking a dislodged tracheostomy.
- Caps and valves. A variety of caps and valves are sometimes used in weaning and to facilitate speech. In an airway emergency these can be removed to simplify the apparatus.

TRACHEOSTOMY CRISIS ALGORITHMS

In a threatened surgical airway, immediate interventions can reduce mortality. There is often not time to wait for a "tracheostomy expert", such as an ear, nose and throat (ENT) surgeon, to attend. As such all staff caring for tracheostomy patients must be able to perform safe, simple interventions to restore the airway. The most likely life threatening tracheostomy complications are bleeding, obstruction and dislodgement of the tube.

Life threatening bleeding greater than 72 hours post-tracheostomy may indicate a tracheo-innominate fistula which carries a 90 per cent risk of death. Loss of airway, rather than haemorrhagic shock, is thought to be the primary cause of arrest in these cases. As such, interventions focus on re-securing the airway as a primary aim followed by control of haemorrhage. Adjustable flange tracheostomy tubes may be adjusted so that the cuff sits at the level of the fistula, providing a secure airway and a method of tamponade. Large clots in the airway can be difficult to remove with airway suction catheters, necessitating larger calibre catheters such as those usually procured for rectal suction. Grant has described an algorithm for managing tracheo-innominate fistulas[11]. The first steps are cuff hyperinflation and direct pressure, followed by advanced interventions beyond the skill set expected of first responders.

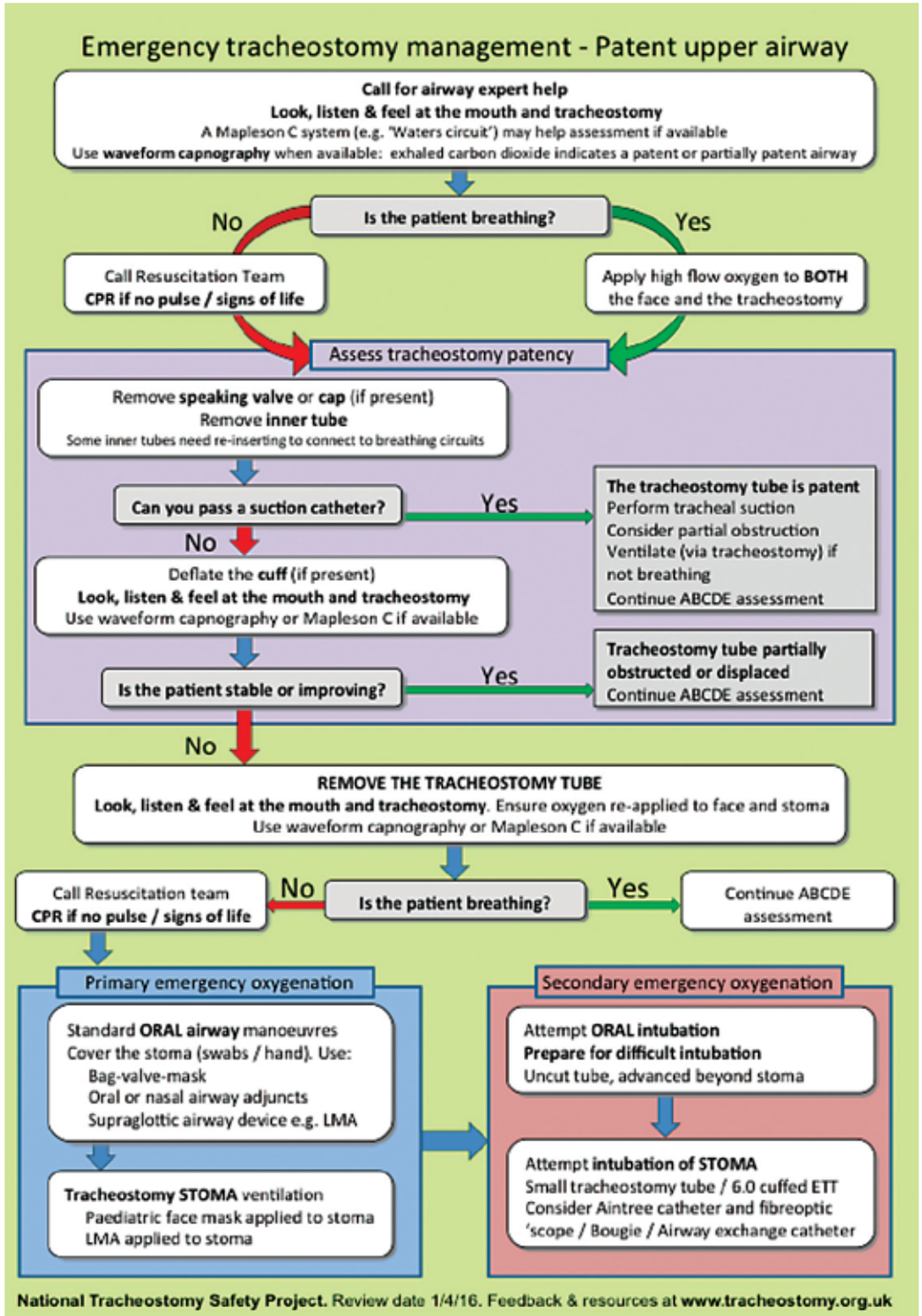
In the United Kingdom, the National Tracheostomy Safety Project[8] (NTSP) is a collaboration of intensive care, anaesthesia, maxillofacial, ENT, resuscitation, nursing and allied health societies. The NTSP algorithm focuses on blocked and dislodged tubes. The NTSP algorithm (figure 2) is designed to be followed by allied health, nursing and medical staff. Initial evaluation comprises assessment of whether the patient is breathing through the tracheostomy and/or mouth. Waveform capnography or movement of the Mapleson C circuit bag can assist in determining whether ventilation is occurring via either route. It is recommended that staff apply oxygen to the face and tracheostomy, as breathing may occur via either route in the case of a deflated cuff or dislodged tube.

Removal of any inner cannulae, valves and caps is a simple, safe and reversible intervention, which may restore the airway in an obstructed tracheostomy tube. A suction catheter is passed beyond the end of the tracheostomy tube as a "sound" to detect whether the tracheostomy tube is still in the trachea. If the suction catheter can be passed, then the tube must be in the trachea, and the clinician is prompted to assess other causes for the patient's condition. If the suction catheter cannot be passed beyond the end of the tracheostomy tube then the tube has become dislodged. Deflation of the cuff may restore upper airway or tracheostomy patency if the tube is partially dislodged. If cuff deflation does not restore an airway then the clinician has demonstrated that the tracheostomy tube is no longer providing an airway and may even be obstructing the airway. At this point the NTSP recommends removal of the tracheostomy tube, a confronting but potentially life-saving intervention.

Following removal of the tracheostomy tube, maintaining patency of the tracheal stoma with tracheostomy dilators may be possible in a breathing patient. If the patient is not breathing emphasis is placed on performing familiar (trans-oral) airway manoeuvres first, bearing in mind that this may not be possible if the patient has upper airway obstruction. While attempting ventilation via oral bag-valve-mask or laryngeal mask airway (LMA), one must obstruct the tracheal stoma with a gloved hand or other occlusive dressing. When orally intubating a patient with a tracheal stoma one must be mindful of not catching the endotracheal tube (ETT) on the anterior tracheal defect once the ETT is past the glottis.

In the event of a difficult or impossible upper airway, trans-stoma approaches should be attempted. In our faculty's experience, a size 3 "Classic" LMA placed over the stoma provides the best seal for bag-ventilation. The NTSP also suggests a paediatric mask, although the semi-rigid paediatric masks in our institution do not seal over a thin neck stoma. If the tracheal stoma needs to be intubated, the use of a flexible fibreoptic scope is advised to confirm correct placement and position of the airway device. ETTs should only be advanced into the stoma a short distance past the cuff, to avoid endobronchial intubation.

Figure 2: Reproduced from McGrath BA, Bates L, Atkinson D, Moore JA. Multidisciplinary guidelines for the management of tracheostomy and laryngectomy airway emergencies. Anaesthesia. 2012 Jun 26. doi: 10.1111/j.1365-2044.2012.07217, with permission from the Association of Anaesthetists of Great Britain & Ireland/Blackwell Publishing Ltd.



INSTITUTION READINESS FOR EMERGENCIES

In a tracheostomy crisis certain equipment is essential and urgently required. For example, if the blocked inner cannula of a Shiley® tracheostomy tube is removed, a fresh inner cannula of the correct size is required to enable connection to a breathing circuit. Most hospitals have a system in place which ensures that a "tracheostomy box" containing essential equipment (table 2) stays with tracheostomy inpatients at all times, including transfers.

Table 2. Example Tracheostomy Box Contents

- Suction catheters (10-14 Fr, 4x each) and rectal tube (40 cm, 40 Fr, 1x)
- Yankauer Sucker
- Tracheal Dilators
- Tracheostomy tubes:
  - 1x same size and model,
  - 1x same model, smaller size
  - spare inner cannulae (if not included in tracheostomy tube boxes).
- 10 mL syringe
- Crisis Algorithm

The algorithm discussed above (figure 2) is unlikely to be remembered in detail by staff. The presence of bed-head signs displaying the algorithm and indicating the nature of the surgical airway are advised for all tracheostomy patients[12].

TRAINING STAFF: TECHNICAL AND NON-TECHNICAL SKILLS

The NTSP recommends training staff in the use of the emergency algorithms and equipment[8]. There are many forms this can take. At our institution we have developed a multidisciplinary, one-day, tracheostomy crisis management course. Doctors, nurses and allied health staff attend the course. The day involves didactic lectures, hands-on equipment familiarisation and high fidelity simulation. The simulations are performed in a multidisciplinary team, attempting to replicate those who may attend in real crises.

To achieve a satisfactory (simulated) outcome, we have identified that it is not only the technical knowledge that needs to be taught. After analysing these multidisciplinary team simulations we have identified a number of human factors, which are barriers to progression through the algorithm. As more senior staff "arrive" to the simulated emergency we have seen progress in the algorithm stall and go back to the beginning. We observed scenarios where nursing or junior medical staff correctly identified a dislodged tracheostomy tube, yet they chose not to remove it, opting to wait for more senior staff to attend whilst hypoxia ensued. While it is not desirable to remove a tracheostomy unnecessarily, staff should be confident in their actions if they have followed the algorithm correctly. The algorithm in figure 2 may seem clear to the reader, however in a stressed simulated environment we witnessed senior anaesthetic team leaders who were cognitively overloaded and unable to progress in a timely manner. In simulations where a team member was allocated to read the algorithm, and prompt the leader, progress through the scenario was more successful.

There are differing views on the value of inter-professional education[13], however we feel that this topic works well with the mix of staff who would be present in real life. The course at our institution improves staff-reported confidence in managing surgical airway scenarios and we have anecdotal evidence of ward crises being resolved due to skills developed at the course.

CONCLUSIONS

Provision of bedside emergency equipment, training staff in the use of emergency algorithms and displaying NTSP bed-head signs has been shown to reduce the severity and frequency of tracheostomy clinical incidents in the UK[14], which is supported by our experience in Western Australia. We suggest that emergency management of tracheostomy crises become part of the ANZCA Curriculum and Australasian hospital staff training programs.

REFERENCES

1. Cook TM, Scott S, Mihai R. Litigation related to airway and respiratory complications of anaesthesia: an analysis of claims against the NHS in England 1995-2007. Anaesthesia. 2010;65(6):556-563.
2. Woodall NM, Cook TM. National census of airway management techniques used for anaesthesia in the UK: first phase of the fourth national audit project at the Royal College of Anaesthetists. Br J Anaesth. 2011;106(2):266-271.
3. Clinical Safety QaGB. Safety notice 018/09 reducing incidents involving tracheostomy tube care [Internet]. NSW Health, 2009; From: http://www.health.nsw.gov.au/sabs/Documents/2009-sn-018.pdf. Accessed 1 June 2017.
4. Morens DM. Death of a president. N Engl J Med. 1999;341(24):1845-1849.
5. Goldenberg D, Ari EG, Golz A, Danino J, Netzer A, Joachims HZ. Tracheotomy complications: a retrospective study of 1130 cases. Otolaryngol Head Neck Surg. 2000;123(4):495-500.

6. Cook TM, Woodall N, Harper J, Benger J, Fourth National Audit P. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. Br J Anaesth. 2011;106(5):632-642.
7. Das P, Zhu H, Shah RK, Roberson DW, Berry J, Skinner ML. Tracheotomy-related catastrophic events: results of a national survey. Laryngoscope. 2012;122(1):30-37.
8. McGrath D, Moore J, Bates L. National tracheostomy project [Internet]. 2014; From: http://www.tracheostomy.org.uk/Templates/Resources.html. Accessed 2017.
9. Schindler JS. Tracheotomy. In: Flint PW, editor. Cummings otolaryngology. 6 ed. Philadelphia: Elsevier, 2015. pp. 95-103.
10. Fong J. Fenestrated cuffed curved double lumen tube with unfenestrated inner tube [Internet]. The Chinese University of Hong Kong, 2008; From: https://www.aic.cuhk.edu.hk/web8/Tracheostomy%20tube.htm. Accessed 2017.
11. Grant CA, Dempsey G, Harrison J, Jones T. Tracheo-innominate artery fistula after percutaneous tracheostomy: three case reports and a clinical review. Br J Anaesth. 2006;96(1):127-131.
12. McGrath BA, Bates L, Atkinson D, Moore JA, National Tracheostomy Safety P. Multidisciplinary guidelines for the management of tracheostomy and laryngectomy airway emergencies. Anaesthesia. 2012;67(9):1025-1041.
13. Nicol P. Interprofessional education for health professionals in Western Australia: perspectives and activity. Sydney: University of Technology, 2013.
14. McGrath BA, Calder N, Laha S, Perks A, Chaudry I, Bates L, et al. Reduction in harm from tracheostomy-related patient safety incidents following introduction of the National Tracheostomy Safety Project: our experience from two hundred and eighty-seven incidents. Clin Otolaryngol. 2013;38(6):541-545.

Breathing / Ventilation

Perioperative lung protective ventilation

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INTRODUCTION

One of the most important developments in the use of mechanical ventilation is the recognition that, while it provides vital oxygenation to the body, it can adversely contribute to morbidity and mortality of the patient via a constellation of mechanisms collectively known as Ventilator Associated Lung Injury (VALI). These include, but are not limited to, barotrauma and volutrauma, caused by exposure to high inflation pressures for prolonged periods of time, and atelectrauma, sheer stress and strains caused by Repetitive Alveoli Collapse and Expansion (RACE), all of which results in biotrauma, the up-regulation of inflammatory mediators and cytokines leading to both a localised (via recruitment of neutrophils, increased alveolar-capillary permeability, pulmonary oedema, pulmonary fibrosis) and systemic responses and a significant contributor to multiple organ failure[1]. Significant biomarkers include vWF, IL6, IL8, PAI-1 and Protein C[1,2]. Macroscopically, damage to lung parenchyma was demonstrated with high driving pressures when Webb subjected rat lungs to either 14 cm or 45 cm of water, leading to significant oedema and haemorrhage[3]. Dreyfuss et al reproduced the experiment again in 1998 with similar results[4].

These observations lead to the notion of protecting the lungs from further injury not only by treating the underlying disease but also by optimising ventilator settings. Recognised as early as 1744 when John Fothergill, describing a case of mouth-to-mouth resuscitation by William Tossach of a coalminer, stated that "…a pair of bellows might possibly be applied with more advantage in these cases, than the blast of a man's mouth. [however] blowing…would seem preferable to the other [because] the lungs of one man may bear, without injury, as great force as those of another man can exert; which by the bellows cannot always be determine"[5]. Such observations were taken to the extremes in a demonstration by d'Etioles in 1834. By showing "the crude use of bellows as a mechanism of positive pressure ventilation resulted in pneumothoraces and eventual death", it led to the detrimental removal of mouth-to-mouth and positive pressure ventilation as a form of medical treatment by the Royal Humane Society in 1837[6].

ARDS

Acute Lung Injury (ALI) and its associated phase Acute Respiratory Syndrome (ARDS) was first used by Ashbaugh et al in a 1967 Lancet paper to describe a cohort of 12 critically ill patients suffering from acute respiratory failure[7]. Its diagnostic criteria has varied over the years, involving a combination of factors such as oxygenation, radiological changes and impaired respiratory mechanics (including but not limited to changes in pulmonary compliance and pulmonary capillary wedge pressure (PCWP))[8]. In 1994, Bernard et al definition of ALI was formally adopted by the American-European Consensus Conference (AECC) as having bilateral pulmonary infiltrates on chest radiography, a P_aO_2/FiO_2 ratio <300 for ALI and <200 for ARDS, and a PCWP <18 mmHg without left atrial hypertension[9]. While it had many limitations, it was the first step to objectivity and worldwide standardisation. The current Berlin Definition published in 2012 by a consensus panel of experts refined the definition of ARDS by eliminating the term ALI, to include a minimum amount of positive end expiratory pressure (PEEP) and to exclude the PCWP criteria and bilateral infiltrates that cannot be fully explained by cardiac causes[10]. This recent standard is endorsed by the European Society of Intensive Care Medicine, the American Thoracic Society and the Society of Critical Care Medicine.

Berlin Definition[10]: ARDS is an acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue…[with] hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space and decreased lung compliance. Meeting all the following criteria:

- Within one week of a known clinical insult or new or worsening respiratory status.
- Radiographically confirmed bilateral opacities.
- Not fully explained by effusions, lobar/lung collapse or of cardiac failure in nature.

The severity of ARDS can be classified into:

- Mild: PaO_2/FiO_2 200 to 300 mmHg (previous ALI).
- Moderate: PaO_2/FiO_2 100 to £200 mmHg.
- Severe PaO_2/FiO_2 £100 mmHg.

Importantly ARDS describes a syndrome with a multitude of different aetiologies including direct injury to the lung for example by trauma or infections as well as indirect organ involvement during sepsis, pancreatitis and many other conditions causing multi-organ failure. It is because of such diverse aetiology that any standardised treatment regime directed for ARDS needs to be validated against multiple patient populations. The 2016 the global LUNGSAFE trial[11] included more than 12,000 critically ill and mechanically ventilated patients and found that almost 25 per cent had ARDS according to the Berlin definition. The criteria were met typically during the first 48 hours of mechanical ventilation. However, it was only recognised by the treating physicians in 51 (mild) to 79 (severe) percent of the cases. The hospital mortality remained high and increased with severity (35, 40 and 46 per cent for mild, moderate and severe disease respectively). Pneumonia (60 per cent), extrapulmonary sepsis (16 per cent) and aspiration (14 per cent) were the most common risk factors.

STRATEGIES TO REDUCE VALI

Low tidal volume (TV)

The ARDSNET trial in 2000[12] showed that low tidal volume ventilation in ARDS has mortality benefit. It entails ventilating with TV of 6 ml/kg of predicted body weight and tolerating hypercapnoea (permissive hypercapnoea). This is mainly due to the fact that in ARDS there is loss of functional alveoli from the underlying disease process, leaving very few ventilatable alveoli. Gattinoni et al[13] coined the term “baby lung” as CT studies of lungs in ARDS showed normally ventilated lung dimensions of a five- to six-year-old.

Low plateau pressure (P_{plat})

Plateau pressure ventilation i.e. <30 cm H_2O is considered low P_{plat}. It is measured by an end inspiratory pause. High P_{plat} contributes to barotrauma and volutrauma of alveoli and worsens intrapulmonary inflammation[12].

Low driving pressures (ΔP)

Δ P can be calculated as (P_{plat} – PEEP). It may be a much better variable than tidal volume in ARDS as the lung compliance is poor. Amato[14] proposed that driving pressure is the key variable in optimisation of ventilation in ARDS. His analysis of previous nine RCTs has shown that low driving pressures has mortality benefit but further studies are needed to quantify low driving pressure.

PEEP (Positive End Expiratory Pressure)

In patients with ARDS, the lung comprises areas of aeration and areas of alveolar collapse, the latter producing intrapulmonary shunt and hypoxemia. Low lung volume ventilation can aggravate lung collapse and potentially produce lung injury through shear stress at the interface between aerated and collapsed lung and because of repetitive opening and closing of alveoli (atelectrauma).

PEEP prevents de-recruitment of alveoli at the end of each expiration thus maintaining functional residual capacity (FRC). Patients with ARDS often receive PEEP of 5 to 20 cm of water. Higher PEEP levels may improve oxygenation but may also cause circulatory depression and lung injury from over distention. Thus, optimal PEEP is that which prevents atelectrauma and at the same time prevents over distension of normal alveoli – it needs to be individualised to the patient’s respiratory mechanics. How to set “optimal PEEP” remains controversial. The following summarises some techniques suggested:

Above the lower inflection point

Setting PEEP above the lower inflection point (LIP) on the inflation static Pressure-Volume curve markedly improves PaO_2. However, this inflection point under static conditions is challenging to obtain in a clinical setting.

Titrating to trans-pulmonary pressure (TPP)

Oesophageal pressure (P_{oes}) is used to estimate pleural pressure, which is then used to estimate TPP. Because of reduced chest wall compliance, oedema or abdominal distension, P_{oes} is often elevated in patients with ARDS and the calculated TPP can be negative at end-expiration. This may indicate closed or compressed airways or atelectatic lung. Thus, PEEP could be increased until transpulmonary pressure becomes positive at end-expiration to keep the airways open. The usefulness of P_{oes} in guiding PEEP was shown in the EPVent study[15].

It did prove that individualising PEEP based on TPP at end of expiration (P_{Lexp}) improved oxygenation and lung compliance but further evidence is required before it can be widely adopted.

Lung volume measurement using N wash-out/wash-in technique

Direct measurement of lung volume allows the measurement of EELV (end expiratory lung volume) at each PEEP level and strain i.e. change in lung volume relative to FRC. Comparison of the measured lung volume with expected change in lung volume for the same change in pressure gives a reasonable estimate by the bedside of the amount of recruitment occurring when changing PEEP[16].

Lung ultrasound

Assessing Lung re-aeration in response to PEEP with lung ultrasound is an emerging technique. Bouhemad et al[17] have used a specific score based on the repeated examination of six lung regions in each lung, before and after increasing PEEP. More evidence needed to assess reproducibility and feasibility but its non-invasive nature makes this modality very attractive.

Oxygenation response to PEEP

A randomised controlled trial on titration of PEEP according to the oxygen concentration alone did not reveal a mortality benefit[18]. Since the degree of hypoxia is also determined by the presence of intracardiac and intrapulmonary shunt, haemodynamics and poorly recruitable lung areas, the oxygen concentration required at a given point in time will only give limited information on the “optimal PEEP”.

Prone ventilation

Prone ventilation was first described in 1976. Initial studies showed improved oxygenation without any outcome benefit. PROSEVA[19], a multicentre RCT conducted in France and Spain over five years showed mortality benefit, without an increase in adverse outcomes, from proning in early ARDS for about 16 hours a day.

Advantages:

1. Increasing end expiratory lung volume due to recruitment of dorsal lung.
2. Transpulmonary pressure along the ventral-to-dorsal axis is more homogeneously distributed in the prone position than in the supine position – thus recruiting collapsed dorsal lung and reducing the P_{plat} and PEEP[20].
3. Regional changes in ventilation associated with alterations in chest-wall mechanics.
4. Reduces overinflated lung areas while promoting alveolar recruitment and thus prevents VALI[21].

Disadvantages:

1. Trained staff needed to minimise complications – endotracheal tube (ETT) obstruction/dislodgement, drain dislodgement, and pressure injuries.
2. Difficult ETT suctioning.
3. Feed intolerance.
4. Difficult to perform procedures if needed.

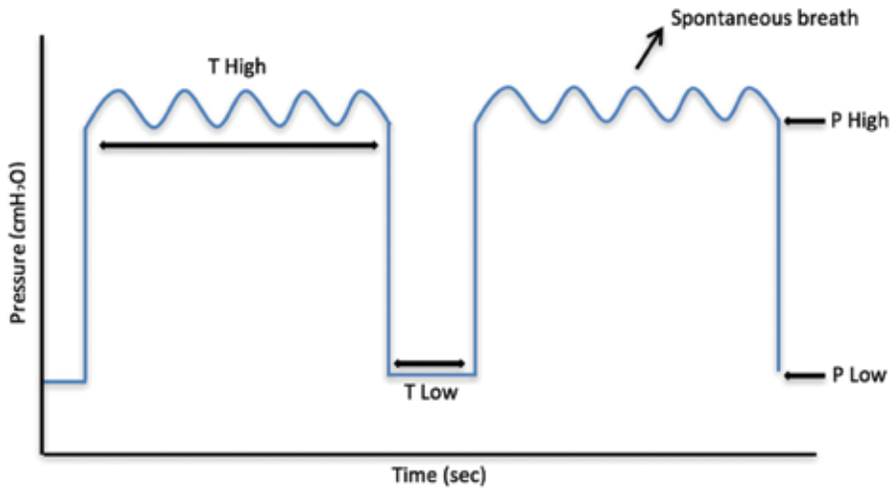
Recruitment manoeuvres

A recruitment manoeuvre is defined as the dynamic process of an intentional transient increase in transpulmonary pressure aimed at opening unstable airless alveoli. It is used as a third way of increasing the end-expiratory lung volume beyond what is possible to achieve with PEEP or prone ventilation. In general, lung units can be kept open by airway pressures that are lower than those required to open them leading to the concept of recruitment using periodic higher pressure manoeuvres with moderate levels of PEEP to maintain alveolar patency. Nature and extent of the lung injury affect the success rate and it is generally agreed that not all inflamed lung areas can be recruited while overdistention can damage relatively normal areas in the process. Many techniques have been described to achieve alveolar recruitment but no clinically relevant benefits have been demonstrated in large clinical trials so far.

APRV (airway pressure release ventilation)

In APRV (also called bi-level) is a newer mode of ventilation where spontaneous breathing is possible in addition to time-triggered and cycled biphasic pressure levels (high and low CPAP). Conventional time cycling provides prolonged inspiratory pressure aimed at recruiting slow time constant air spaces while minute ventilation and CO_2 clearance are augmented by brief (1-1.5 seconds) periodic cycling to lower level of CPAP (figure 1).

Figure 1. Pressure-time curve in APRV-ventilation



Potential advantages may include:

1. Improved oxygenation at similar or lower airway pressures compared to conventional ventilation.
2. Improve V/Q matching due to better dependent aeration.
3. Less need of sedation and helps promotes spontaneous ventilation.
4. Less haemodynamic compromise.

An ongoing large multicentre RCT (ClinicalTrials.gov: NCT01862016) will examine the efficacy and safety of early spontaneous breathing in ARDS while on APRV.

HFOV (High-frequency oscillatory ventilation)
Lungs are held inflated to maintain oxygenation, and carbon dioxide is cleared by small volumes of gas moved in and out of the respiratory system at 3-15 Hz. This action is thought to minimise the repeated process of opening and collapsing of lung units that causes the secondary lung damage during mechanical ventilation.

Recent evidence from OSCAR[22] and OSCILLATE[23] trials show no outcome benefit and potential harm in ARDS from HFOV compared to conventional ventilation.

Controlled versus spontaneous mechanical ventilation
Complete inactivity of the diaphragm results in disuse atrophy and muscle weakness, referred to as ventilator-induced diaphragmatic dysfunction (VIDD), after as little as 18-24 hours of mechanical ventilation. This can contribute to weaning difficulty and poorer prognosis. Spontaneous ventilation has a role only in mild-moderate ARDS based on animal studies. Further evidence is required to assess its safety and effect on outcome. Contrary to this, in severe ARDS muscle relaxants are beneficial. The ACURASYS study[24] demonstrated that the early administration of cisatracurium for the first 48 hours of ARDS reduced adjusted 90-day mortality and barotrauma, and also increased ventilator free days without increasing muscle weakness. Proposed mechanisms include minimising VALI by minimising the transpulmonary pressure changes during assisted breathing and reducing patient–ventilator asynchrony, decreasing oxygen consumption of respiratory muscles, and reducing pulmonary and systemic inflammation.

Extra corporeal membrane oxygenation (ECMO) and extracorporeal CO_2 removal (ECCOR)
Veno-venous ECMO may be needed to manage severe hypoxaemia and hypercarbia in refractory ARDS. Evidence from the CESAR trial[25] does establish ECMO as a valid support option but further evidence is required to determine benefit. It does help to prevent VALI by adhering to lung protective ventilation principles in severe ARDS with oxygenation and ventilation taken care of by ECMO. Advances in the technology have led to a widespread adoption but the invasiveness and significant risks including haemorrhagic and thromboembolic complications are still to be overcome.

ECCOR is a method which targets CO_2 clearance only. This allows relatively low extracorporeal blood flow (about 0.5 to 1 l/min as compared to 3-5 l/min in ECMO) and is therefore believed to be less invasive. By achieving CO_2 removal independent of ventilation, it may allow the safe application of low tidal volume and thereby avoid VALI. Two large randomised control trials are currently investigating this modality (REST (ClinicalTrials.gov: NCT02654327) and SUPERNOVA (ClinicalTrials.gov: NCT02282657)).

Inhaled pulmonary vasodilators
When the lung experiences regional differences in ventilation, the hypoxic pulmonary vasoconstriction reflex attempts to improve the subsequent ventilation/perfusion (V/Q) mismatch by reducing perfusion to regions of low oxygen tension. However, in severe inflammatory states such as ARDS and otherwise, inflammatory cytokines, and bacterial endotoxins, for example, which act as vasodilators, may overwhelm such reflex leading to increase perfusion to undesirable low oxygen tension regions.

The rationale of using pulmonary vasodilators is to essentially out compete the inflammatory vasodilators and thus improve V/Q mismatch and hypoxemia. Inhaled vasodilators will preferentially reach the well-ventilated regions and therefore only exert its vasodilating effects to those areas, decreasing shunting and improving V/Q mismatch. Two inhaled vasodilators are commonly used: nitric oxide (NO), via cyclic GMP and its positive actions on myocin light chain phophatase, and inhaled epoprostenol (prostacyclin), via the increase of cyclic AMP and its inhibition of myocin light chain kinase, ultimately leading to smooth muscle relaxation. It is expensive, requires specialised equipment for delivery, and it may carry a risk of pulmonary haemorrhage, nitrogen dioxide toxicity and methaemoglobinaemia.

Oxygenation does seem to improve against placebo[26]. However, a Cochrane analysis including 14 RCTs with a total of 1303 adult and paediatric participants showed that while there was improvement in oxygenation in the first 24 hours, there was no statistically significant effect on overall mortality (40.2 per cent versus 38.6 per cent)[27].

LUNG PROTECTIVE STRATEGIES IN DIFFERENT SETTINGS

ARDS
The landmark ARDSNET trial[12] published in 2000 was the first multicentre RCT comparing traditional, with low volume ventilation, strategies. Previously, traditional ventilation strategies targeted a tidal volume between 10-15 ml predicted body weight (PBW) with aims to reach normocarbia and subsequent correction of acidemia as quickly as possible, often at the expense of VALI. It concluded that lower tidal volumes significantly improved both primary and secondary end points. A serials of follow-up trials, in particular the assessment of low tidal volume and elevated end-expiratory volume to obviate lung injury (ALVEOLI)[18], LOVS[28] and EXPRESS[29] aimed to identify the effects of high and low PEEP settings. Separately, while all three trials showed no difference in primary end point of mortality, there were significant benefits of higher PEEP in the management of hypoxia, the use of rescue therapies, ventilator free days, ICU stays and multi-organ failure days. A meta-analysis of the 2299 patients in these three trials by Briel et al found that while there were statistically significant differences in mortality between high and low PEEP in patients with moderate to severe ARDS, it did not apply to mild ARDS[30]. The ARIES[31] trial further suggested that PEEP set just above the lower inflection point of the pressure volume curve conferred benefit.

There is good evidence for the following strategies:

- PEEP: 5-15 cmH_2O based on degree of severity.
  - No clear evidence of how to determine optimal PEEP.
- Tidal volume: Less than or equal to 6 ml/kg of predicted body weight.
- Plateau pressures: Aim for plateau pressures less than 30 cmH_2O.
- Driving pressure: A driving pressure of less than 14 cmH_2O is associated with reduced mortality.
- Paralysis: In severe ARDS for the initial 48 hours.
- Prone ventilation: Initiate early in severe ARDS for at least 16 hours a day if tolerated.

The following strategies have been suggested with less evidence:

- Though non-invasive ventilation (NIV) has been used in ARDS, there is no strong evidence for its benefit and is in fact associated with higher mortality.
- Volume and pressure controlled modes or APRV have been suggested with no clear superiority.
- Recruitment manoeuvres: Further evidence required on best technique and effect on outcome.
- Permissive hypercapnia: Except in case of TBI or raised ICPs due to any cause, hypercapnia is permissive if pH is greater than 7.20.
- FiO2: Titrate to SpO2 90-95 per cent.
- ECMO/ECCOR: If refractory to above mentioned ventilator strategies and adjuncts i.e. remains hypoxic with SpO_2 <90 per cent or hypercarbia with pH <7.15, there may be role for ECMO or ECCOR respectively. Patient may need to be retrieved to an ECMO centre for specialised care.

LPVS have also been assessed in a number of perioperative settings to evaluate changes in gas exchange and lung physiology (table 1). In addition some evidence supports its use based on clinical relevant endpoints:

Non-cardiac surgery

The successful adoption of lung protective ventilation strategy (LPVS) found from the ARDSNET trial[12] seems to be equally applicable for non-cardiac surgical patients. In 2013, Futier et al[32] demonstrated in a randomised trial involving 400 abdominal surgical patients that LPVS (VT=6-8 ml/kg; PEEP=6-8 cmH_2O) significantly reduced the likelihood of non-invasive ventilation or intubation for acute respiratory failure (5 per cent versus 17 per cent; p=0.001). Furthermore, secondary outcomes such as length of stay was also favourable compared to non-protective ventilation (V_T = 10-12 mL/ kg; PEEP = 0 cm H_2O). In another prospective randomised open-label trial, Severgnini et al[33] compared protective ventilation measures versus a standard ventilation strategy in 56 abdominal surgical patients, also finding improved respiratory function and a reduction of the modified Clinical Pulmonary Infection Score.

A Cochrane review in 2014 examining a total of 12 studies with a total of 1012 surgical patients showed mixed results using intraoperative LPVS. There were statistical improvements in post-operative pneumonia rates, need for postoperative ventilation (invasive and non-invasive), but no consistent difference in 30-day mortality, pneumothorax, hospital and ICU length of stay[34].

Cardiac surgery

The multitude of studies applying LPVS to cardiac surgery patients have shown either non-inferior or improved outcomes in terms biochemical inflammatory markers, lung mechanics, hospital and intensive care unit (ICU) length of stay (table 1). Authors have noted that any improvements in inflammatory markers due to LPVS may not be detected, resulting in difficulty in demonstrating statistical significance, due to the high background levels induced by the invasive nature of cardiac surgery and the use of cardiopulmonary bypass circuits. A single centre RCT study by Sundar et al[35] of 149 patients, showed that while the primary endpoint of time to extubation post-surgery were similar in both groups, LPVS had better secondary outcomes with a higher proportion of patients extubated at six hours and lower rates of reintubation.

Non-surgical/non-ARDS

LPVS also seem beneficial for out of hospital cardiac arrests (OOHCA) patients. In a cross sectional retrospective study, Sutherasan et al[36] found that higher plateau pressures and tidal volume with lower PEEP were associated with adverse outcomes. More recently, Beitler et al[37] showed that LPVS independently improved neurological outcomes, requiring less ICU and ventilator days for such patient population. A multicentre RCT[38] found that LPVS increased the number of eligible and actual donors whom were declared brain dead. Fuller et al[39] performed a systematic review in 2013 to evaluate the benefit of LPVS in non-ARDS patients, yielding one RCT and 12 observational studies. While the single RCT showed promise of benefit for LPVS, with decreased baseline lung injury scores and plasma IL-6 levels, no firm conclusions could be found due to the heterogeneity of the patient populations, and thus recommended a further large scale multicentre RCT specifically targeting the pre/non-ARDS patient population.

Table 1. Perioperative protective lung ventilation

(adopted from Coppola et al with modifications[40])

Type of surgery	Author	Year	Patient	V_T (ML/KG)		PEEP (CMH_2O)		Recruitment manoeuvres		Outcome	Benefit?
				Case	Control	Case	Control	Case	Control		
Abdominal	Wrigge[41]	2000	39	6/6	15	0/10	0	N	N	Inflammatory biomarkers	No
	Wrigge[42]	2004	30	6	12-15	10	0	N	N	Inflammatory biomarkers, PaO_2	No
	Determann[43]	2008	40	6	12	10	0	N	N	Inflammatory biomarkers	No
	Weingarten[44]	2010	40	6	10	12	0	Y	N	PaO_2, Respiratory mechanics, inflammatory biomarkers	Yes
	Treschan[45]	2012	101	6	12	5	5	N	N	Dynamic spirometry	No
	Severgnini[46]	2013	56	7	9	10	0	Y	N	CPIS, respiratory function	Yes

Type of surgery	Author	Year	Patient	V_T (ML/KG)		PEEP (CMH_2O)		Recruitment manoeuvres		Outcome	Benefit?
				Case	Control	Case	Control	Case	Control		
	Futier[47]	2013	400	6-8	10-12	6-8	0	Y	N	Respiratory complications, Hospital LOS	Yes
	PROVHILO[48]	–	900	<8	<8	12	≤2	Y	N	Respiratory complications	Yes
Thoracic	Wrigge[42]	2004	32	6	12-15	10	0	N	N	Inflammatory biomarkers	No
	Schilling[49]	2005	32	5	10	0	0	N	N	Inflammatory biomarkers	Yes
	Michelet[50]	2006	52	5	9	5	0	N	N	Inflammatory biomarkers, respiratory mechanics, LOMV	Yes
	Yang[51]	2011	100	6	10	5	0	N	N	PaO_2, Respiratory complications	Yes
Cardiac	Chaney[52]	2000	25	6	12	5	5	N	N	Respiratory mechanics	Yes
	Koner[53]	2004	44	6	10/10	5	0/5	N	N	Inflammatory biomarkers, LOS, respiratory mechanics	No
	Zupancich[54]	2005	40	8	10-12	10	2-3	N	N	Inflammatory biomarkers	Yes
	Reis[55]	2005	62	4-6	6-8	10	5	Y	N	Inflammatory biomarkers	Yes
	Wrigge[56]	2005	44	6	12	9	7	N	N	Inflammatory biomarkers	Yes
	Sundar[35]	2011	149	6	10	5	4.9	N	N	LOMV, reintubation	Yes

Studies are grouped according to specific surgical settings: abdominal, thoracic and cardiac surgery.

Case: lung-protective ventilation group; Control: conventional ventilation strategy group. Outcome results always refer to the case group. In the Thoracic surgery section, ventilatory parameters refer to one-lung ventilation. *PEEP levels set according to ARDSNET strategy. VT: tidal volume; PEEP: positive end-expiratory pressure; MV: mechanical ventilation; FRC: functional residual capacity; IL: interleukin; TNF: tumour necrosis factor; IFN: interferon; pts: patients; PaO_2: partial pressure of oxygen in arterial blood; LOS: length of stay.

CONCLUSION

Various lung protective strategies have been introduced into clinical practice over the past 20 years. Good evidence now exists for many of them, in particular for patients with the most severe form of lung injury (ARDS). There is mounting evidence suggesting that similar strategies are also beneficial in non-ARDS patients. At the same time the clinical recognition of ARDS is less than optimal and lung protective ventilation is not always adopted in routine clinical practice.

There is undoubtedly a delay in translating results and conclusions to clinical practice over the past two decades. While a retrospective multicentre cross sectional study with post cardiac arrest patients found a statistically significant decrease in V_T over time (2004: 9.0 ml/kg, 2010: 6.7 ml/kg PBW, p <0.001) suggesting relatively good penetration and translation[36], Needham et al[57] found only 41 per cent of the 6240 settings for 485 patients were adherent to LPVS. 2016 the European Society of Intensive Care Medicine (ESICM) endorsed LUNG-SAFE study[11] (involving 459 ICUs across 50 countries) concluded that “less than two-thirds of patients with ARDS

received a tidal volume of 8 mL/kg or less of predicted body weight. The adoption of prone ventilation (8 per cent) and neuromuscular blockade (22 per cent) was even poorer.

Various reasons have been proposed to explain the slow transition, including citing lack of evidence for some patient population, ventilator asynchrony, psychological barriers to use lower than usual settings, complexity of protocol, lack of ongoing active monitoring and adjustment as the patient's respiratory compliance improves, which is even evident at tertiary centres. Understanding and subsequent addressing of such barriers is important because it is estimate that for every 1 ml/kg increase above LPVS protocol recommendations there is up to 18 per cent increase in mortality[57].

Future research should increase the evidence of various measures of lung protection in ARDS and target the applicability of these measures in non-ARDS patients. In the meantime, clinical practice needs to adopt proven strategies more consistently to avoid harm.

REFERENCES

1. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013;369(22):2126-2136.
2. Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med. 2005;33(1):1-6.
3. Herbert HH, Webb DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis. 1974;110(5):556-565.
4. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis. 1988;137(5):159.
5. Fothergill J. Observations of a case published in the last volume of the medical essays of recovering a man dead in appearance, by distending the lungs with air. Philosoph Transact. 1744;43:275–281.
6. Keith A. Three Hunterian lectures on the mechanism underlying the various methods of artificial respiration practiced since the foundation of the Royal Humane Society in 1774. Lancet. 1909;173:745–749.
7. Ashbaugh DG, Bigelow D, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2:319–323.
8. Rubenfeld GD, Caldwell E, Granton J, Hudson LD, Matthay MA. Interobserver variability in applying a radiographic definition for ARDS. Chest. 1999;116(5):1347-1353.
9. Bernard GA, Brigham A, Carlet KL, Falke J, Hudson K, Lamy L, et al. Report of the American-European Consensus Conference on Acute Respiratory Distress Syndrome: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. J Crit Care. 1994;9(1):72-81.
10. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-2533.
11. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(8):788-800.
12. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301-1308.
13. Gattinoni L Presenti A, Torresin A, Baglioni S, Rivolta M, Rossi F, et al. Adult respiratory distress syndrome profiles by computed tomography. J Thorac Imaging 1986;1:25-30.
14. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747-755.
15. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med. 2008;359(20):2095-2104.
16. Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, et al. PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. Intensive Care Med. 2011;37(10):1595-1604.
17. Bouhemad B, Brisson H, Le-Guen M, Arbelot C, Lu Q, Rouby JJ. Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. Am J Respir Crit Care Med. 2011;183(3):341-347.
18. Brower RG1, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351(4):327-336.
19. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. New Engl J Med. 2013;368(23):2159-2168.
20. Pelosi P, Tubiolo D, Mascheroni D, Vicardi P, Crotti S, Valenza F, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. Am J Respir Crit Care Med. 1998;157(2):387-893.
21. Galiatsou E, Kostanti E, Svarna E, Kitsakos A, Koulouras V, Efremidis SC, et al. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. Am J Respir Crit Care Med. 2006 Jul 15;174(2):187-197.
22. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, et al. High-frequency oscillation for Acute Respiratory Distress Syndrome. N Engl J Med. 2013;368(9):806-813.
23. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al. High-frequency oscillation in early Acute Respiratory Distress Syndrome. N Engl J Med. 2013;368(9):795-805.
24. Papazian L, Forel J-M, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early Acute Respiratory Distress Syndrome. N Engl J Med. 2010;363(12):1107-1116.
25. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 374(9698):1351-1363.

26. Sawheny E, Ellis AL, Kinasewitz GT. Iloprost improves gas exchange in patients with pulmonary hypertension and ARDS. Chest. 2013;144(1):55-62.
27. Afshari A, Brok J, Moller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. Cochrane Database Syst Rev. 2010;07(7):CD002787.
28. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299(6):637-645.
29. Mercat A, Richard JM, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299(6):646-655.
30. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010;303(9):865-873.
31. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. Crit Care Med. 2006;34(5):1311-1318.
32. Futier E, Constantin J-M, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013;369(5):428-437.
33. Severgnini P, Selmo G, Lanza C, Chiesa A, Frigerio A, Bacuzzi A, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 2013;118(6):1307-1321.
34. Guay J, Ochroch EA. Intraoperative use of low volume ventilation to decrease postoperative mortality, mechanical ventilation, lengths of stay and lung injury in patients without acute lung injury. Cochrane Database Syst Rev. 2015 Dec 07(12):CD011151.
35. Sundar S, Novack V, Jervis K, Bender SP, Lerner A, Panzica P, et al. Influence of low tidal volume ventilation on time to extubation in cardiac surgical patients. Anesthesiology. 2011;114(5):1102-1110.
36. Sutherasan Y, Peñuelas O, Muriel A, Vargas M, Frutos-Vivar F, Brunetti I, et al. Management and outcome of mechanically ventilated patients after cardiac arrest. Crit Care. 2015;19(1):215.
37. Beitler JR, Ghafouri TB, Jinadasa SP, Mueller A, Hsu L, Anderson RJ, et al. Favorable neurocognitive outcome with low tidal volume ventilation after cardiac arrest. Am J Respir Crit Care Med. 2017;195(9):1198-1206.
38. Mascia L, Pasero D, Slutsky AS, Arguis MJ, Berardino M, Grasso S, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. JAMA. 2010;304(23):2620-2627.
39. Fuller BM, Mohr NM, Drewry AM, Carpenter CR. Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute respiratory distress syndrome: a systematic review. Crit Care. 2013;17(1):R11.
40. Coppola S, Froio S, Chiumello D. Protective lung ventilation during general anesthesia: is there any evidence? Crit Care. 2014;18(2):210.
41. Wrigge H, Zinserling J, Stüber F, von Spiegel T, Hering R, Wetegrove S, et al. Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. Anesthesiology. 2000;93(6):1413-7.
42. Wrigge H, Uhlig U, Zinserling Jr, Behrends-Callsen E, Ottersbach G, Fischer M, et al. The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery. Anesth Analg. 2004;98(3):775-781.
43. Determann RM, Wolthuis EK, Choi G, Bresser P, Bernard A, Lutter R, et al. Lung epithelial injury markers are not influenced by use of lower tidal volumes during elective surgery in patients without preexisting lung injury. Am J Physiol Lung Cell Mol Physiol. 2008;294(2):L344-L350.
44. Weingarten TN, Whalen FX, Warner DO, Gajic O, Schears GJ, Snyder MR, et al. Comparison of two ventilatory strategies in elderly patients undergoing major abdominal surgery. Br J Anaesth. 2010;104:16-20.
45. Treschan TA, Kaisers W, Schaefer MS, Bastin B, Schmalz U, Wania V, et al. Ventilation with low tidal volumes during upper abdominal surgery does not improve postoperative lung function. Br J Anaesth. 2012;109(2):263-271.
46. Severgnini P, Selmo G, Lanza C, Chiesa A, Friegerio A, Bacuzzi A, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 2013;118(6):1307-1321.
47. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. New Engl J Med. 2013;369(5):428-437.
48. Hemmes SN, Severgnini P, Jaber S, Canet J, Wrigge H, Hiesmayr M, et al. Rationale and study design of PROVHILO - a worldwide multicenter randomized controlled trial on protective ventilation during general anesthesia for open abdominal surgery. Trials. 2011;12:111.
49. Schilling T, Kozian A, Huth C, Buhling F, Kretzschmar M, Welte T, et al. The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. Anesth Analg. 2005 Oct;101(4):957-965.
50. Michelet P, D'Journo XB, Roch A, Doddoli C, Marin V, Papazian L, et al. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. Anesthesiology. 2006;105(5):911-919.
51. Yang M, Ahn HJ, Kim K, Kim JA, Yi CA, Kim MG, et al. Does a protective ventilation strategy reduce the risk of pulmonary complications after lung cancer surgery?: a randomized controlled trial. Chest. 2011;139(3):530-537.

52. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Protective ventilation attenuates postoperative pulmonary dysfunction in patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2000;14(5):514-518.
53. Koner O, Celebi S, Balci H, Cetin G, Karaoglu K, Cakar N. Effects of protective and conventional mechanical ventilation on pulmonary function and systemic cytokine release after cardiopulmonary bypass. Intensive Care Medicine. 2004;30(4):620-626.
54. Zupancich E, Paparella D, Turani F, Munch C, Rossi A, Massaccesi S, et al. Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: a randomized clinical trial. J Thorac Cardiovasc Surg. 2005;130(2):378-383.
55. Reis MD, Gommers D, Struijs A, Dekker R, Mekel J, Feelders R, et al. Ventilation according to the open lung concept attenuates pulmonary inflammatory response in cardiac surgery. Eur J Cardiothorac Surg. 2005;28(6):889-895.
56. Wrigge H, Uhlig U, Baumgarten G, Menzenbach J, Zinserling J, Ernst M, et al. Mechanical ventilation strategies and inflammatory responses to cardiac surgery: a prospective randomized clinical trial. Intensive Care Medicine. 2005;31(10):1379-1387.
57. Needham DM, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Sevransky JE, Dennison Himmelfarb CR, et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. BMJ. 2012;344:e2124.

Transnasal Humidified Rapid Insufflation Ventilatory Exchange (THRIVE) technique in paediatric anaesthesia practice

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INTRODUCTION

The insufflation of heated and humidified high fresh gas flows via nasal cannulae, exceeding the inspiratory demand of a patient during spontaneous breathing or used during the apnoeic phase for intubation, has emerged as a novel addition to anaesthetic practice, particularly for patients with physiologically or anatomically challenging airways[1, 2]. There is increasing evidence for its therapeutic use in acute respiratory failure, as an aid to preoxygenation, in the management of the difficult airway and during bronchoscopy[3]. This review explores the proposed mechanisms of action of nasal high flow (NHF) and transnasal humidified rapid insufflation (THRIVE) in the paediatric population, potential clinical applications, and outlines recommendations made on applied flow rates and use with total intravenous anaesthesia (TIVA).

CURRENT USE OF NASAL HIGH FLOW IN PAEDIATRICS

High flow nasal oxygen been used in both adult and neonatal intensive care units for many years[4]. The same technology has recently been adapted for use in clinical anaesthesia during apnoeic oxygenation (THRIVE) and in spontaneously breathing patients (NHF)[1, 5, 6]. This concept of heated, humidified high flow oxygen therapy was first introduced in paediatric intensive care as a method of relieving sleep related pharyngeal obstruction by the compression of air delivered via a nasopharyngeal tube[7]. It then became an alternative to continuous positive airway pressure (CPAP) to support babies with respiratory distress syndrome or apnoea of prematurity and is now commonly used as a form of non-invasive respiratory support for infants, children and adults with acute hypoxic respiratory failure[7-9].

NHF oxygen therapy is an innovative modality that has several advantages compared to other standard oxygen therapies. Observational studies in emergency departments and intensive care units have shown that infants with bronchiolitis respond to NHF therapy by reducing their heart and respiratory rates within the first few hours of treatment[10, 11]. Improvement in these vital signs discriminates reliably between responders and non-responders to NHF therapy and subsequently reduces the need for intubation[11, 12]. NHF therapy can be used very early in the disease process and is well tolerated by children thereby avoiding the need for sedation. NHF can also be safely used in non-critical care settings such as the general wards and lower acuity areas of the emergency department. The risk of decompensation requires very close monitoring in a setting that is equipped for rapid implementation of invasive ventilatory support. Discharge from the paediatric intensive care unit and transfer to a paediatric ward can be considered only once the continued improvement of these children is well under way. The ward admitting the child will nevertheless need to provide close surveillance and be equipped with a system for early detection of respiratory failure or signs of decompensation[9].

The available high-flow nasal cannula sets are open systems with leaks at the mouth and nose and can be used with nasal prongs of varying sizes. It is recommended for safety to use prongs which are no greater than half the diameter of the nares as the degree of leak at the nares prong interface is important. The NHF system allows a flow rate range of 1-70 L/min, with relative humidity of 100 per cent at a recommended delivery temperature of 37°C.

PHYSIOLOGICAL EFFECTS OF NHF

Several mechanisms have been proposed to explain the physiological effects of NHF in children. These include flow dependent flushing of the oropharyngeal dead space facilitating carbon dioxide clearance and alveolar ventilation. High flow rates also create a positive distending pressure on the small airways and lungs of 4-6 cmH_2O improving pulmonary conductance, compliance and decrease in the work of breathing by overcoming the resistance of the nasopharynx[13]. Humidification of the inspired gases also contributes to the reduction in the work of breathing, and provides greater comfort, allowing tolerance of higher flow rates and less nasal mucosal desiccation. Therefore, NHF may play an important supportive role during anaesthesia of the spontaneously breathing infant or child to improve oxygenation and carbon dioxide clearance, particularly during anaesthesia for upper airway surgery or during the apnoeic phase of airway instrumentation to improve FRC and enable improved intubating conditions. The flow rates delivered in paediatric practice are matched to expected peak inspiratory flows and are weight-related. This allows delivery of a known fraction of oxygen in inspired gas.

USE IN ANAESTHESIA

The objective of airway management in anaesthesia is to ensure safe and effective strategies to maintain alveolar ventilation and prevent hypoxia. Even so, hypoxia remains the leading cause of anaesthesia-related morbidity and mortality[14]. Pre-oxygenation has been used since 1955 as a mechanism for maximising oxygen reserves and prolonging the safe apnoeic time during induction of anaesthesia. This facilitates safe airway management in emergency and difficult intubations[15]. The displacement of nitrogen by oxygen into the functional residual capacity of the lungs, achieved by breathing 100 per cent oxygen via a close-fitting facemask for three to four minutes, increases the oxygen reserves available. Once these reserves are exhausted during the process of intubation in the setting of apnoea, patients can desaturate quickly because the oxygen supply is interrupted. Apnoeic oxygenation can prolong this supply by providing an ongoing oxygen source during intubation attempts. Provided that a patent airway exists between the lungs and the exterior, a negative pressure gradient is generated by the difference between the rate of oxygen absorption and carbon dioxide replacement allowing aventilatory mass flow which drives oxygen into the lungs. Also there is a concentration gradient generated between the oxygen concentration in the alveoli and that of the upper airway which enables diffusion of oxygen into the alveoli[16]. For this purpose it is a common anaesthesia practice to use the upper airway as an oxygen reservoir, delivering constant oxygen flow via an oxygen catheter placed in the nasopharyngeal cavity[17], or via nasal cannulae delivering low-flow dry oxygen at a rate of 5-15L per minute[17]. Extrapolating from this, THRIVE was first introduced into adult anaesthetic practice in 2015 as a method of delivering humidified oxygen via nasal cannulae to prolong the apnoeic oxygenation time in those with known difficult airway anatomy or significant comorbidities, thus allowing unhurried intubation[1]. Its use in adults has subsequently been expanded to preoxygenation, respiratory support post-extubation, and spontaneously breathing adults with difficult airways using TIVA as STRIVE HI (SponTaneous Respiration using IntraVEnous anaesthesia and Hi-flow nasal Oxygen) [18].

In infants and children, the incidence of an expected or unexpected difficult airway during anaesthesia is relatively uncommon compared to adults[15]. However, the onset of desaturation in apnoeic infants and children is much faster than in adults and is known to be age-dependent[21]. Infants and children have a proportionally smaller functional residual capacity which is just slightly above the closing volume resulting in atelectasis at normal tidal breathing[21]. They have a greater metabolic demand, utilising more O_2 per kg and generating a higher carbon dioxide output[21] and have a greater tendency to collapse their airways[22, 23]. Infants rely on a high respiratory rate with short expiratory times and laryngeal adduction in expiration to increase airway resistance [functional positive end-expiratory pressure (PEEP)] to maintain and dynamically increase their FRC[24-26]. These mechanisms are attenuated under general anaesthesia. Therefore, the time frame to establish a safe airway in infants and children is much shorter than in adults and these differences become more pronounced during emergency intubations and intubations for emergency surgery.

THRIVE IN INFANTS AND CHILDREN

In a recent randomised controlled trial of anaesthetised children it was shown that after pre-oxygenation, the use of THRIVE applied during the apnoeic phase of the intubation could prolong the safe apnoea time without desaturation up to twice the expected time for age without any complications[27]. The expected apnoea time in pre-oxygenated children is known to be age-dependent[28]. The studied children were medically well, appropriately fasted, ASA 1-3, with normal airways, hearts and lungs, presenting for elective surgery or medical imaging. This study also demonstrated that the rate of rise of carbon dioxide during the apnoeic period was not reduced to the same extent by THRIVE as was observed in adult studies. The use of THRIVE for difficult airways in the elective setting of paediatric anaesthesia needs further clinical evaluation and may not have such a big impact on practice as has been shown in adults, since the incidence of difficult mask ventilation and intubation is much lower[15]. However, we speculate that this technique may have a greater impact in the paediatric emergency intubation setting.

There are several reviews of the effect of apnoeic oxygenation during high-risk elective and also emergency intubation in the adult population but currently we have no evidence of its efficacy in children[17,29]. An Australian prospective study of emergency intubations in children at a tertiary paediatric hospital emergency department found that only 78 per cent of intubations were successful at first attempt and of these 14 per cent had a significant desaturation event with oxygen saturation falling below 90 per cent[30]. An increasing number of intubation attempts resulted in a greater incidence of desaturation and further adverse events[31]. A multi-centre, randomised controlled trial (Kids THRIVE) is currently underway in several Australian and New Zealand emergency departments and paediatric intensive care units, to investigate the role of THRIVE in emergency intubation. The aim of this study is to establish if the use of THRIVE during the apnoeic phase of intubation will reduce the incidence of hypoxia and other adverse events and increase the rate of successful first attempts.

USE OF NHF IN CHILDREN WITH ABNORMAL AIRWAYS

Oxygenation techniques during anaesthesia for children with abnormal airways, not necessarily requiring intubation, have traditionally included oxygen delivery via a nasopharyngeal airway or nasal cannulae delivering low-flow dry oxygen at a rate of 5-15L per minute, utilising the side-port of a rigid bronchoscope, or less commonly via jet ventilation[32]. Suspension laryngoscopy, rigid bronchoscopy, and flexible bronchoscopy are the commonly performed diagnostic and therapeutic procedures which require paediatric patients to maintain spontaneous breathing and patency of their own airways to allow investigation and management of complex congenital and acquired airway anomalies[5, 33]. Optimal surgical conditions generally preclude placement of an endotracheal tube in order to provide an unobstructed view of the larynx and trachea[34]. To allow dynamic airway assessment, the anaesthetic must achieve the delicate balance between adequate depth of anaesthesia to tolerate a highly stimulating procedure and maintenance of spontaneous ventilation, which requires a high degree of communication and cooperation between surgeon and anaesthetist.

Several different anaesthetic techniques can be employed for tubeless anaesthesia in children and may involve total inhalational anaesthesia or TIVA, augmented by airway topicalisation with local anaesthetic. Inadequate depth of anaesthesia may result in laryngospasm, bronchospasm, or barotrauma, requiring muscle relaxation and possibly intubation[35]. Excessive depth of anaesthesia can lead to hypoventilation or apnoea resulting in hypoxemia, necessitating rescue intubation or bag-mask ventilation and the consequent interruption of the procedure, prolonging surgical time.

NHF has been shown to be another minimally invasive oxygenation technique which obviates the need for nasal instrumentation, with a concomitant epistaxis risk, and equipment in the pharynx, a considerable advantage in these types of procedures. A recent case series in our institution demonstrated that the use of NHF in this setting allowed prolongation of oxygenation in the context of hypoventilation, and brief periods of apnoea without desaturation[5]. A greater depth of anaesthesia can then be achieved when necessary for the most stimulating procedures such as tracheal ballooning.

The children included in this study were considered to have high-risk airway abnormalities and for the purposes of classification in the study were grouped as microlaryngoscopy ± procedure, flexible bronchoscopy, expected difficult airway and, lastly, associated comorbidities relating to apnoea risk. Most surgical cases had presentations with stridor or increased work of breathing due to laryngomalacia, subglottic stenosis or compression of their upper airway. The children requiring flexible bronchoscopy included those with chronic lung pathology and inhaled foreign bodies. Of the children with expected difficult airways, both had congenital temporomandibular joint disease with little or no mouth opening and required intubation for their booked procedures. NHF facilitated optimal oxygenation conditions for intubation of both of these children, one with a videolaryngoscope and the other via a nasal fibreoptic technique.

Unexpected difficult airways in normal children are rare but in children with congenital disorders, an anticipated airway difficulty can be more predictable[15]. Assessing the site of the anatomical airway abnormality can predict what the difficulty will be. A child with a hypoplastic mandible may have an associated difficult intubation, whereas a child with a mid-face hypoplasia may be difficult to bag-mask ventilate. Macroglossia can cause both difficult intubation and difficult bag-mask ventilation. Airway pre-assessment in children is difficult. The Mallampati score is not practical in small children and doesn't accurately predict the view at laryngoscopy. Furthermore, standard thyromental and mandibular lengths do not exist for the paediatric population.

It is not uncommon for children with abnormal airways to be supported with NHF in neonatal or paediatric intensive care perioperatively. With the availability of portable high-flow devices we have successfully maintained this form of respiratory support during transfer to and from the operating suite. Care should be taken to note the FiO_2 as the addition of a blender allows delivery of oxygen between 21 and 100 per cent. Currently our paediatric high flow device for anaesthesia does not include a blender and thus our experience of use of NHF in paediatric anaesthesia practice has been limited to using 100 per cent oxygen. However, with scope for a blender, there may be improved safety if undertaking cases involving airway laser. A recent audit of airway procedures by our department (unpublished data) suggests that up to one third of children experience a hypoxic event during the course of their anaesthetic. An improved oxygenation technique is therefore of vital interest. The use of NHF in the post anaesthetic setting for those children at risk of hypoventilation and hypoxia is another potential application of its use in paediatric anaesthesia practice but we have no experience with this yet.

ANAESTHESIA TECHNIQUE AT LADY CILENTO CHILDREN'S HOSPTAL USING NHF

In our experience at the Lady Cilento Children's Hospital, the majority of patients are induced with sevoflurane in oxygen and nitrous oxide or with propofol (2 mg/kg to maintain spontaneous respiration) with a circle or t-piece circuit and then transitioned to TIVA over several minutes. Propofol is commenced at 200 mcg/kg/min (range 200-400 mcg/kg/min, 12-24 mg/kg/h or 1.2-2.4 ml/kg/h) most commonly in conjunction with alfentanil (0.3-0.8 mcg/kg/min) or remifentanil (0.05-0.2 mcg/kg/min). Once adequate depth of anaesthesia is achieved the epiglottis, larynx and upper trachea are topicalised via direct laryngoscopy with 2 per cent lignocaine to a maximum of 4 mg/kg. Atropine or glycopyrrolate may be given as an antisialagogue. Age-appropriate nasal high flow cannulae are then applied and humidified oxygen is delivered at weight related flows (table 1) with an Optiflow device (Fisher & Paykel Healthcare, Auckland, New Zealand). Once NHF is commenced the volatile anaesthetic can no longer be used as it is rapidly dispelled by the high flow of oxygen. Jaw thrust is maintained to ensure airway patency until the surgeon inserts their laryngoscope or bronchoscope. Close communication between the anaesthetist and surgeon is important prior to and during the case. In the event of a significant desaturation, rescue oxygenation can be achieved via either bag-mask ventilation with cessation of NHF or in cases of open airway surgery by direct placement of an endotracheal tube by the surgeon until oxygen saturations are optimised.

Table 1. Nasal high flow rates applied during anaesthesia

WEIGHT	NHF
0-12 kg	2 L/Kg/Min
13-15 kg	30 L/Min
15-30 kg	35 L/Min
30-50 kg	40 L/Min
>50 kg	50 L/Min

LIMITATIONS

To be effective, nasal high flow oxygen requires a patent airway but is still effective through a single nare when the other is used as a conduit for a fibre-optic bronchoscope. Nasal congestion may limit its efficacy and excessive suctioning by the surgeon may impair oxygen insufflation. Another limitation of the use of NHF in tubeless airway surgery is that it may mask apnoeic periods, since oxygen saturations are maintained for longer which may lead to higher arterial CO_2 levels than those seen with traditional oxygenation techniques[5]. In or experience to date with NHF in tubeless airway surgery, the average case duration has been less than an hour. It is difficult to accurately measure end-tidal carbon dioxide during these cases although NHF is associated with some carbon dioxide clearance. The rate of rise in children, of 2.4 mmHg per minute, appears to be higher than that seen in adults although the clinical sequelae of this in our patient population are unknown[1, 27]. In an adult study acute post-operative hypercapnia below 100 mmHg after bronchoscopy was not associated with any adverse effects and did not delay recovery[36]. In the occurrence of significant desaturation requiring alveolar recruitment, the CPAP effect of NHF will not deliver sufficient positive pressure, therefore bag-mask ventilation will be required to recruit regions of atelectasis and hence restore oxygen haemoglobin saturation. Use of NHF in the operating theatre for brief periods appears safe to date, however morbidities such as pneumothoraces and epistaxis have been observed with prolonged use in the paediatric intensive care setting, although the incidence is low[37].

Introducing new devices into the operating room environment always requires training of staff and the learning curve can be protracted when the equipment is only used occasionally, as is the case with NHF. This is even more challenging when the equipment is new not only to the department but to the specialty area as a whole. Usage guidelines, especially weight-related flow rates, attached to the device can be invaluable when the experience levels within the department can be highly variable on any particular day. The education of our departmental staff, including anaesthesia assistants, facilitated the introduction of NHF into our operating theatre environment.

CONCLUSION

The introduction of this NHF technique into paediatric anaesthesia practice has provided an alternative method of enabling safe management of children with abnormal airways for dynamic assessment and surgery without intubation, jet ventilation or nasopharyngeal instrumentation. The advantages include avoidance of epistaxis risk associated with nasopharyngeal instrumentation, improved surgical access to suspension laryngoscopy without bulky anaesthesia airway equipment, and prolonged oxygenation during potential periods of hypoventilation or apnoea. Its portability allows continuation of respiratory support during transfer to and from the theatre environment which may avoid the need for intubation. The extension of these advantages into its use for paediatric emergency intubations outside the operating room is currently under investigation and may reduce the adverse events associated with this high-risk procedure which is often undertaken by medical officers with limited experience in airway management.

REFERENCES

1. Patel A, Nouraei SA. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. Anaesthesia. 2015;70(3):323-329.
2. Mosier JM, Joshi R, Hypes C, Pacheco G, Valenzuela T, Sakles JC. The physiologically difficult airway. West J Emerg Med. 2015;16(7):1109-1117.
3. Ashraf-Kashani N, Kumar R. High-flow nasal oxygen therapy. BJA Educ. 2017;17(2):57-62.
4. Corley A, Rickard CM, Aitken LM, Johnston A, Barnett A, Fraser JF, et al. High-flow nasal cannulae for respiratory support in adult intensive care patients. Cochrane Database Syst Rev. 2017;5:CD010172.
5. Humphreys S, Rosen D, Housden T, Taylor J, Schibler A. Nasal high-flow oxygen delivery in children with abnormal airways. Paediatr Anaesth. 2017;27(6):616-620.
6. Booth AWG, Vidhani K. Spontaneous respiration using intravenous anaesthesia (STRIVE) facilitates fibreoptic intubation through supraglottic airway device. Acta Anaesthesiol Scand. 2017;61(6):696-697.
7. Klein M, Reynolds LG. Relief of sleep-related oropharyngeal airway obstruction by continuous insufflation of the pharynx. Lancet. 1986;1(8487):935-939.
8. Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, et al. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2013;369(15):1425-1433.
9. Milesi C, Boubal M, Jacquot A, Baleine J, Durand S, Odena MP, et al. High-flow nasal cannula: recommendations for daily practice in pediatrics. Ann Intensive Care. 2014;4:29.
10. Mayfield S, Jauncey-Cooke J, Hough JL, Schibler A, Gibbons K, Bogossian F. High-flow nasal cannula therapy for respiratory support in children. Cochrane Database Syst Rev. 2014;3:CD009850.
11. Schibler A, Pham TM, Dunster KR, Foster K, Barlow A, Gibbons K, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med. 2011;37(5):847-852.
12. Pham TMT, O'Malley L, Mayfield S, Martin S, Schibler A. The effect of high flow nasal cannula therapy on the work of breathing in infants with bronchiolitis. Pediatr Pulmonol. 2015;50(7):713-720.
13. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. Respir Med. 2009;103(10):1400-1405.
14. Ward DS, Karan SB, Pandit JJ. Hypoxia: developments in basic science, physiology and clinical studies. Anaesthesia. 2011;66(Suppl 2):19-26.
15. Frei FJ, Ummenhofer W. Difficult intubation in paediatrics. Paediatr Anaesth. 1996;6(4):251-263.
16. Bartlett RG, Jr., Brubach HF, Specht H. Demonstration of aventilatory mass flow during ventilation and apnea in man. J Appl Physiol. 1959;14(1):97-101.
17. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. Ann Emerg Med. 2012;59(3):165-175, e161.
18. Booth AWG, Vidhani K, Lee PK, Thomsett CM. Spontaneous respiration using intravenous anaesthesia and hi-flow nasal oxygen (STRIVE HI) maintains oxygenation and airway patency during management of the obstructed airway: an observational study. Br J Anaesth. 2017;118(3):444-451.
19. Erb T, Marsch SC, Hampl KF, Frei FJ. Teaching the use of fiberoptic intubation for children older than two years of age. Anesth Analg. 1997;85(5):1037-1041.
20. Schibler A, Hall GL, Businger F, Reinmann B, Wildhaber JH, Cernelc M, et al. Measurement of lung volume and ventilation distribution with an ultrasonic flow meter in healthy infants. Eur Respir J. 2002;20(4):912-918.
21. King W, Petrillo T, Pettignano R. Enteral nutrition and cardiovascular medications in the pediatric intensive care unit. JPEN J Parenter Enteral Nutr. 2004;28(5):334-338.
22. Schibler A, Yuill M, Parsley C, Pham T, Gilshenan K, Dakin C. Regional ventilation distribution in non-sedated spontaneously breathing newborns and adults is not different. Pediatr Pulmonol. 2009;44(9):851-858.
23. Schibler A HR. Positive end-expiratory pressure and ventilation inhomogeneity in mechanically ventilated children. Ped Crit Care Med. 2002;3:124-128.
24. von Ungern-Sternberg BS, Frei FJ, Hammer J, Schibler A, Doerig R, Erb TO. Impact of depth of propofol anaesthesia on functional residual capacity and ventilation distribution in healthy preschool children. Br J Anaesth. 2007;98(4):503-508.
25. von Ungern-Sternberg BS, Hammer J, Schibler A, Frei FJ, Erb TO. Decrease of functional residual capacity and ventilation homogeneity after neuromuscular blockade in anesthetized young infants and preschool children. Anesthesiology. 2006;105(4):670-675.

26. von Ungern-Sternberg BS, Regli A, Schibler A, Hammer J, Frei FJ, Erb TO. The impact of positive end-expiratory pressure on functional residual capacity and ventilation homogeneity impairment in anesthetized children exposed to high levels of inspired oxygen. Anesth Analg. 2007;104(6):1364-1368.
27. Humphreys S, Lee-Archer P, Reyne G, Long D, Williams T, Schibler A. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in children: a randomized controlled trial. Br J Anaesth. 2017;118(2):232-238.
28. Patel R, Lenczyk M, Hannallah RS, McGill WA. Age and the onset of desaturation in apnoeic children. Can J Anaesth. 1994;41(9):771-774.
29. White LD, Melhuish TM, White LK, Wallace LA. Apnoeic oxygenation during intubation: a systematic review and meta-analysis. Anaesth Intensive Care. 2017;45(1):21-27.
30. Long E, Sabato S, Babl FE. Endotracheal intubation in the pediatric emergency department. Paediatr Anaesth. 2014;24(12):1204-1211.
31. Lee JH, Turner DA, Kamat P, Nett S, Shults J, Nadkarni VM, et al. The number of tracheal intubation attempts matters! A prospective multi-institutional pediatric observational study. BMC Pediatr. 2016;16:58.
32. Benjamin B. Anesthesia for laryngoscopy. Ann Otol Rhinol Laryngol. 1984;93(4):338-342.
33. Oshan V, Walker RWM. Anaesthesia for complex airway surgery in children. CEACCP. 2013;13(2):47-51.
34. Mausser G, Friedrich G, Schwarz G. Airway management and anesthesia in neonates, infants and children during endolaryngotracheal surgery. Pediatr Anesth. 2007;17(10):942-947.
35. Thaung MK, Balakrishnan A. A modified technique of tubeless anaesthesia for microlaryngoscopy and bronchoscopy in young children with stridor. Pediatr Anesth. 1998;8(3):201-204.
36. Cheng Q, Zhang J, Wang H, Zhang R, Yue Y, Li L. Effect of acute hypercapnia on outcomes and predictive risk factors for complications among patients receiving bronchoscopic interventions under general anesthesia. PloS One. 2015;10(7):e0130771.
37. Baudin F, Gagnon S, Crulli B, Proulx F, Jouvet P, Emeriaud G. Modalities and complications associated with the use of high-flow nasal cannula: experience in a pediatric ICU. Respir Care. 2016;61(10):1305-1310.

Circulation

Heart failure with preserved ejection fraction: Diastole is important too!

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INTRODUCTION

Heart failure is a clinical syndrome. Diagnosis depends on the presence of clinical symptoms and signs including breathlessness, exercise intolerance, and ankle swelling. Heart failure is a result of failure of cardiac function, which is the end result of many disease processes. While the most common cause of heart failure is impaired left ventricular systolic function, 40-50 per cent of patients with heart failure have a normal or only mildly reduced left ventricular ejection fraction (LVEF)[1]. In these instances, heart failure with preserved ejection fraction (HFpEF) describes the syndrome of heart failure in the presence of a normal or low-normal LVEF where cardiac dysfunction is due to a cause other than left ventricular systolic failure[2-4].

Previously known as “diastolic heart failure”, recent changes in nomenclature have extended the diagnosis of HFpEF to include all causes of heart failure in patients with normal systolic function[5]. Diastolic dysfunction refers to an abnormal mechanical property of the myocardium whereas HFpEF refers a clinical syndrome[6]. Non-myocardial causes of HFpEF include valvular heart disease (11-22 per cent), pericardial disease, right heart failure, pulmonary vein stenosis and congenital heart disease[5]. After excluding non-myocardial causes of HFpEF, echocardiographic evidence of diastolic dysfunction is present in around 70 per cent of patients[1]. This review focuses primarily on this group of patients.

EPIDEMIOLOGY

HFpEF is prevalent in the elderly and the obese and is more common in women than men. Patients with diastolic dysfunction often have systemic hypertension (70-88 per cent), diabetes mellitus (17-46 per cent), atrial fibrillation (30-37 per cent), coronary artery disease (37-42 per cent) and/or pulmonary hypertension (83 per cent)[7]. These diseases are very common in the patient population seen in the perioperative period and may herald underlying diastolic dysfunction.

Despite having normal systolic function, patients with HFpEF have higher mortality rates than the general population. Annual mortality ranges from 10 per cent to 30 per cent with at least 60 per cent of deaths due to a cardiovascular cause[1]. Diastolic dysfunction is associated with an 8 to 10 fold increase in mortality[8]. Other mortality predictors in this group include age, diabetes mellitus, and severity of ischaemic heart disease[8,9].

HFpEF can pose a significant challenge for the anaesthetist in the perioperative period. Diastolic dysfunction is associated with higher rates of postoperative cardiovascular complications, increased length of stay and significantly higher rates of postoperative pulmonary oedema and myocardial infarction[10,11]. Despite this, diastolic impairment is often overlooked in preoperative evaluation and there is limited data on the risk stratification of patients with HFpEF.

Intraoperatively, patients with diastolic dysfunction often do not respond to the usual treatments for heart failure caused by systolic impairment. Additionally, there is no single treatment strategy that has been found to convincingly reduce mortality or morbidity in this patient group. However, by understanding the pathophysiology, diagnosis and current management strategies as well as effect of anaesthesia and surgery on the physiology of this patient group, anaesthetists can act to mitigate the risk of perioperative complications[12].

DIAGNOSTIC CRITERIA AND DEFINITIONS OF HFpEF

Many of the difficulties in diagnosing and managing this group of patients stem from the lack of consensus in the definition and diagnostic criteria for HFpEF. Currently, there are two diagnostic criteria in use for HFpEF. The American Heart Association (AHA) and American College of Cardiology (ACC) criterion relies on a definition of exclusion. That is, it relies on the presence of heart failure with echocardiographic evidence of not having a reduced ejection fraction[2]. As such, patients with all myocardial and non-myocardial causes of HFpEF will be included using this criterion. Patients with an ejection fraction of 40-50 per cent are considered to be in the intermediate range.

Conversely, the European Society of Cardiology (ESC) criterion requires the inclusion of evidence of both normal left ventricular size and function and objective evidence of diastolic impairment[3] (see table 1). The most recent European guidelines also include an intermediate group of heart failure with mid-range ejection fraction (HFmrEF)[3]. Only patients with diastolic dysfunction will be diagnosed with HFpEF.

Table 1. Differences between current ACC/AHA and ESC criteria for the diagnosis of HFpEF

	ACC/AHA (2013)	ESC (2016)
Symptoms +/- signs	Present	Present
Left ventricular ejection fraction	Not reduced	HFpEF: LVEF ≥ 50% HFmrEF: LVEF 40-49%
Natriuretic peptide levels	n/a	Elevated
Evidence of diastolic impairment	n/a	Present

Additionally, the European guidelines use natriuretic peptides as part of the diagnostic criteria and require evidence of an elevated B-type natriuretic peptide (BNP >35 pg/mL) or N-terminal pro-BNP (NT-proBNP >125 pg/mL). Natriuretic peptides have good negative predictive value but they also have somewhat less reliable positive predictive value. That is, they are useful for ruling out heart failure, but cannot be used to diagnose HFpEF on their own[3,13].

Importantly, older patients and those with hypertension often have evidence of diastolic impairment but do not have signs or symptoms of heart failure[14]. These patients do not have HFpEF as they are asymptomatic and do not have the clinical syndrome of heart failure.

While these newer criteria have assisted in the standardisation of the diagnosis of HFpEF, the differences between the two can lead to confusion and present a number of challenges.

Firstly, the differences between the two groups result in either including or excluding some patient groups. For example, by requiring only the evidence of a normal ejection fraction, the American criterion ensures that patients with underlying diastolic dysfunction, with a left ventricle that has been unloaded with diuretics or those whose diastolic dysfunction is only present during exercise, are correctly included[1,14]. These patients may be erroneously misdiagnosed as normal using the European guidelines, as they may not have diastolic impairment evident on echocardiography at rest.

Importantly, the European requirement of evidence of diastolic impairment ensures that patients who have symptoms similar to those of HFpEF but due to other causes are not inaccurately diagnosed. Common conditions such as interstitial lung disease, chronic obstructive pulmonary disease (COPD), obesity or haematological diseases are often confused with HFpEF and unnecessarily or inappropriately treated[3,14].

Another unintended consequence of changes in diagnostic criteria is the inclusion of patients with normal diastolic function in newer HFpEF trials. The heterogeneity of patients included in clinical trials in this area has been implicated in the large number of neutral trials in the management of HFpEF to date[5].

Additionally, before the publication of the current criteria, HFpEF has been inconsistently classified using ejection fractions of >40 per cent, >45 per cent, >50 per cent, and ≥55 per cent. This makes interpretation of older clinical trials for HFpEF difficult. As patients with mid-range or intermediate LVEFs have some degree of systolic dysfunction and their disease mechanisms are significantly different from those with normal systolic function, their inclusion in trials for HFpEF is problematic[2]. There also remains uncertainty in how to classify patients who present with a reduced LVEF, which then improves or even normalises with treatment[14].

Finally, while these diagnostic criteria provide a useful way of classifying patients, they are not useful in determining the underlying cause of the disease[14]. However, patients with normal systolic function who have symptoms of heart failure and evidence of diastolic dysfunction have undiagnosed or untreated HFpEF using either criteria. This makes them a higher preoperative risk, and they will need pre-optimisation prior to surgery. For this reason, anaesthetists should know how to manage diastolic dysfunction in the perioperative period.

PATHOPHYSIOLOGY OF DIASTOLIC DYSFUNCTION

In order to understand diastolic dysfunction and how anaesthesia and surgery affect it, it is important to first consider how normal diastole and ventricular filling occurs. Diastole is the time between closure of the aortic valve and closure of the mitral valve. It is the time during which the ventricle fills and is as important in cardiac output as systolic contraction. There are four phases of diastole:

Phase 1: Isovolumetric relaxation
When the heart contracts in systole, elastic recoil energy is stored in the myocytes. At the beginning of diastole, this stored energy is released when calcium is sequestered back into the sarcoplasmic reticulum and this results in ventricular relaxation. Sequestering of calcium requires adenosine triphosphate (ATP) so is energy dependent. This phase of diastole is effectively "set up" by the preceding systolic contraction. Isovolumetric relaxation occurs over a very short time period and is the time after aortic valve closure but before any filling occurs[15]. It can be delayed by conditions such as myocardial ischaemia, which impairs active relaxation, and is shortened

by raised LA pressure which causes the mitral valve to open too early[16].

Phase 2: Early-rapid filling
When the pressure in the ventricle drops below the pressure in the atrium, the mitral valve opens and the relaxing ventricle sucks in blood during the rapid passive filling phase. The negative pressure gradient between the two chambers drives filling[17]. Importantly, in the early filling phase ventricular volume increases without an increase in intraventricular pressure. Filling in this phase is determined by the rate of ventricular relaxation and recoil and the pressure in the left atrium. Early filling accounts for up to 80 per cent of ventricular filling[16].

Phase 3: Diastasis
In mid-diastole, the pressure equalises between the atrium and ventricle and flow into the ventricle slows. Filling in diastasis is predominantly determined by compliance, which can be affected by myocardial stiffness, ventricular mass and the pericardium that can constrain ventricular filling[16].

Phase 4: Late-rapid filling
Finally, atrial contraction occurs. This increases the atrial pressure and creates a positive pressure gradient between the atrium and the ventricle. This action squeezes more blood into the ventricle[15]. The atrial contribution to filling is determined by the left atrial contractility (non-existent in atrial fibrillation) and the compliance of the left ventricle (LV)[18]. During this phase, ventricular pressure rises, particularly if the ventricle is stiff and non-compliant or is restrained by conditions such as pericardial constriction or compression[18].

Diastolic impairment occurs when filling of the ventricle is impaired and the ventricle is unable to fill completely with normal pressures. This is because the ventricle either does not relax properly (impaired relaxation) in the early stages of diastole or is stiff (non-compliant) in the later phases. To maintain a normal cardiac output, a ventricle that does not relax properly requires an increase in filling from atrial contraction to compensate for less filling in the early phases. As diastolic dysfunction worsens and the ventricle becomes poorly compliant, a higher atrial pressure is required to maintain the pressure gradient over the higher ventricular pressure. This increase in left atrial pressure is responsible for the pulmonary congestion that causes symptoms of breathlessness and results in heart failure[12].

In some patients, diastolic impairment only becomes apparent during exercise. While at rest, ventricular filling occurs at normal pressures. However, during exercise the increase in filling required to provide a higher stroke volume and cardiac output cannot occur without an increase in pressure. These patients present a dilemma for the anaesthetist in the preadmission clinic as they will give a clear history of exercise intolerance but may have normal pulmonary function tests. Additionally, their systolic and diastolic function will appear normal on investigations carried out at rest. In these situations, screening for elevated natriuretic peptides can aid in diagnosis.

As mentioned, the two most commonly described mechanisms for diastolic dysfunction are impaired relaxation and reduced compliance. Ventricular compliance is inversely proportional to ventricular stiffness and both these terms are often used to describe the structural changes that affect ventricular filling. Other important factors in diastolic filling are ventricular-arterial coupling and preload.

Ventricular relaxation
Ventricular relaxation requires dissociation and removal of calcium from tropomyosin C and is an active process requiring energy from ATP. This process naturally declines with age. Importantly though, pathological conditions that impair this ATP-dependent process, such as myocardial ischaemia, will cause impaired relaxation. Impaired relaxation results in a longer isovolumetric relaxation time, a smaller negative gradient between the atrium and ventricle, and is present in nearly all patients with HFpEF[14,17].

Patients with diabetes mellitus, hypertension, obesity and coronary artery disease are at increased risk of HFpEF[19]. This is because all these states produce a systemic inflammatory state that has recently been implicated in the pathogenesis of diastolic impairment. An important modulator of ventricular relaxation is nitric oxide (NO) produced by the endothelium. Systemic inflammatory states result in coronary microvascular endothelial inflammation and a reduction in nitric oxide (NO)[20]. Strategies targeting this proinflammatory state may result in new therapies for HFpEF[14].

Compliance
The reduction in NO production has also been implicated in increased myocardial stiffness. The sarcomeric protein titin is responsible for both early ventricular recoil and in particular late ventricular distension. Two isoforms of titin have been identified: hypophosphorylated, stiff (N2B); and hyperphosphorylated, compliant (N2BA). An insufficiency of NO increases the hypophosphorylation of titin (N2B) and causes subendothelial migration of leukocytes that stimulate myofibroblast formation and collagen deposition, which increases myocardial stiffness[21,22]. Studies have demonstrated increased amounts of the stiff isoform N2B in patients with HFpEF[21].

Left ventricular hypertrophy (LVH) further heightens ventricular stiffness. LVH is commonly seen in systemic hypertension, aortic stenosis, obesity, increased age, and diabetes and is more common in women than men. Additionally, increased ventricular stiffness can be caused by myocardial fibrosis or other infiltrative disorders (e.g. amyloidosis)[12]. The presence of any of these medical conditions should alert the anaesthetist to the potential

presence of HFpEF.

Finally, as previously mentioned, pericardial constraint from pericarditis, pericardial effusions or mass effect will also result in reduced ventricular compliance and reduced filling.

Ventricular-arterial coupling
Arterial stiffness is also an important factor in diastolic impairment. Reduced endothelial NO results in impaired flow-mediated vasodilation and decreased arterial compliance. Normally, ventricular-arterial coupling ensures that the cardiovascular system works with maximal efficiency so that an increase in stroke volume is matched with increased vascular compliance, with little change in blood pressure. In patients with HFpEF, an increase in arterial stiffness means small changes in blood volume cause significantly larger changes in LV end-diastolic pressure both at rest and during exercise[7,15]. Consequently, left atrial pressure must also rise to promote forward flow.

Preload
Left ventricular preload is another factor that must be considered in diastolic impairment. As the intravascular volume increases, an increase in preload to the left heart will in turn result in an increase in left atrial pressure[15]. Normally, this is well tolerated. However, patients who have evidence of a baseline raised left atrial pressure are less tolerant of additional fluid boluses as these may trigger pulmonary oedema. Preoperatively, it is important to distinguish those with HFpEF who will respond well to fluid and those who will not. Grading the severity of their diastolic dysfunction can help with this.

GRADING DIASTOLIC DYSFUNCTION SEVERITY

Diagnosis of diastolic impairment requires evidence of increased left ventricular filling pressure measured either directly with a cardiac catheter study or by echocardiography. Invasive haemodynamic parameters consistent with diastolic impairment include a raised mean capillary wedge pressure (>15 mmHg) or an elevated left ventricular diastolic pressure (>16 mmHg)[3].

Echocardiography has an advantage of being non-invasive and readily available in the perioperative period. Furthermore, it can also provide information on systolic function, right ventricular function and valve pathology. Additionally, stress echocardiography can be performed using either exercise or pharmacological stressors (e.g. dobutamine) that could reveal exercise-induced diastolic impairment.

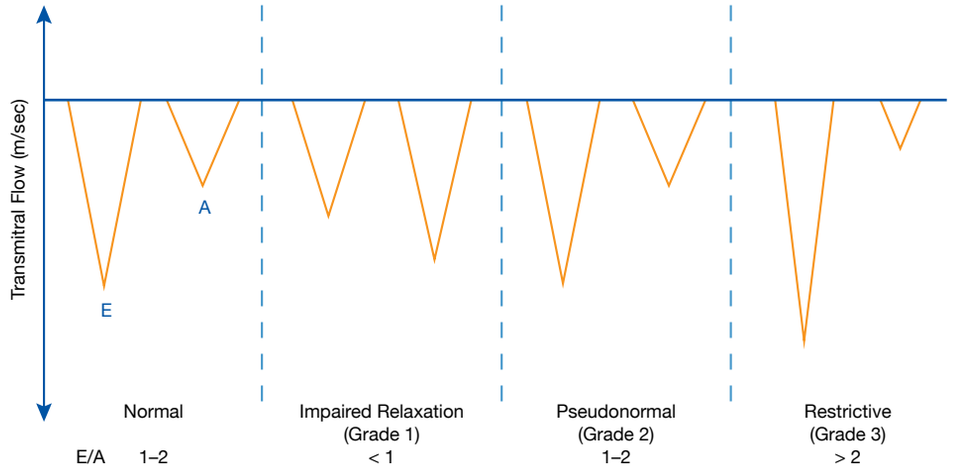
Unfortunately diastolic function is often not documented on routine echocardiography reports as it can be both difficult to assess in some patients and under-appreciated in its perioperative significance[18]. Additionally, while anaesthetists commonly look at left ventricular systolic function and valvular information on echocardiography reports, diastolic function parameters are often overlooked or poorly understood even when reported.

When reviewing echocardiography reports, diastolic function is often reported as either normal or abnormal. However, within the abnormal group, three grades of severity are recognised which have different perioperative requirements. For this reason, a basic understanding of the echocardiographic parameters used in grading diastolic impairment is required.

Recent published guidelines include an excellent discussion on the use of various echocardiographic parameters for diagnosing and grading diastolic dysfunction[23]. However, for those who have limited echocardiographic knowledge, a more simplified diagnostic approach is beneficial. A useful way to both diagnose and understand the underlying physiological state focuses on parameters that measure the blood flow across the mitral valve and the movement of the mitral annulus in diastole.

Transmitral blood flow velocity
One of the most helpful parameters is the ratio of peak blood flow velocity across the mitral valve in the early filling phase and the atrial contraction phase. Pulse wave Doppler measured at the tips of the mitral valve leaflets gives a characteristic transmitral waveform that correlates with the phases of diastole described above (figure 1). The E wave corresponds to early diastolic filling and the A wave to filling from atrial contraction. The E/A ratio can then be used to interpret diastolic filling.

Figure 1. Transmitral Doppler flow waveforms seen using transoesophageal echocardiography with increasing severity of diastolic dysfunction



Normal filling
Normally, the majority of blood flow occurs during the early filling phase, so the peak velocity of early filling (E) will be greater than in atrial filling (A) with a ratio of 1-2.

Grade 1: Abnormal relaxation
In grade 1 diastolic dysfunction, early left ventricular filling is reduced due to impaired ventricular relaxation and a reduction in the suction effect. As early filling is reduced, the E wave will have a lower velocity and there is a greater reliance on the "atrial kick" to maintain ventricular preload and cardiac output. Transmitral flow on echocardiography will demonstrate this as a reduced E/A ratio with higher peak atrial filling velocity than early filling velocity (ratio <1). As the filling pressures are normal, this group of patients often respond well to fluid boluses[16].

Importantly, this abnormal relaxation is actually a normal process of ageing and grade 1 diastolic impairment is common in those over 60 years.

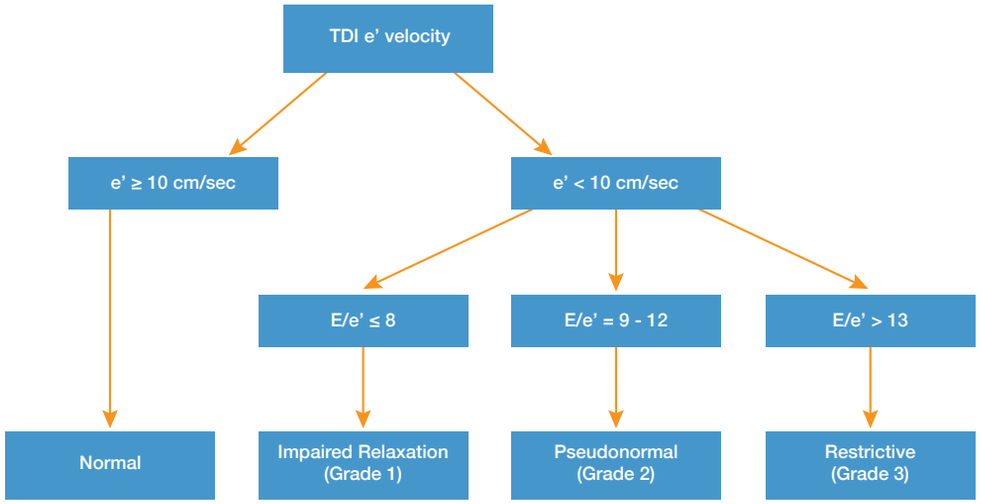
Grade 2: Pseudonormal
In grade 2 diastolic impairment, the left ventricular pressure rises early in filling due to poor relaxation, which leads to blood backing up into the left atrium and a rise in left atrial pressure. It is this elevation in left atrial pressure that helps maintain the pressure gradient and drives passive filling. This stage is termed "pseudonormal" as the transmitral flow profile appears normal (ratio 1-2). It is important to remember that this apparently normal filling profile is at the expense of an overall elevation in left atrial pressure and this group of patients is at risk of pulmonary congestion[18].

Grade 3: Restrictive
Restrictive diastolic function is the most severe grade of impairment. This group of patients has very stiff, non-compliant ventricles and an elevated left atrial pressure is required to assist in early filling. The elevated left atrial pressure results in very fast blood flow and rapid equalisation of LA and LV pressures so the E wave velocity is increased. Also, there is reduced filling from the atrial contraction as the left ventricular pressure is high and the A wave velocity is slower. The E/A ratio is therefore increased (E/A >2)[18]. These patients often respond poorly to fluid due to their high filling pressures.

Mitral annular velocity
While it is easy to determine impaired relaxation (E/A <1) and restrictive (E/A >2) patterns using transmitral Doppler waveforms, it is impossible to distinguish between normal and psuedonormal (E/A 1-2) patterns on transmitral Doppler alone. Advances in measuring low velocity but high amplitude signals have allowed measurement of tissue movement with tissue Doppler. Diastolic impairment is associated with a slowing of ventricular relaxation and therefore a slower mitral annulus movement in early diastole (e'). Normally, the velocity of the annulus adjacent to the septal wall is >7 cm/sec and adjacent to the lateral wall is >10 cm/sec. Patients with diastolic impairment will have reduced e' values and ratio of E/e' is a good marker of LV end-diastolic pressure.

A useful algorithm developed by Swaminathan et al uses the tissue Doppler measurements of the mitral valve annulus and mitral blood flow velocity in early diastole and provides a simple method for diagnosing and grading diastolic dysfunction (figure 2)[16,18,24]. Additionally, this algorithm has the advantage that E/e' ratio is not dependent on the patient being in sinus rhythm, so is very useful in patients with atrial fibrillation where there is no atrial contraction and no A wave.

Figure 2. Simplified algorithm from Swaminathan et al for grading diastolic dysfunction



TDI = Tissue Doppler Imaging; e' = mitral annulus lateral wall early diastolic tissue velocity; E = transmitral early filling wave

Finally, other echocardiographic features are useful in assessing both the presence and cause of diastolic function. A dilated left atrium in the absence of any chronic atrial arrhythmia or mitral valve pathology may indicate diastolic impairment[6]. In this situation, a dilated left atrium (>34 ml/m^2) reflects a high left atrial pressure[23]. The presence of left ventricular hypertrophy should increase suspicions of diastolic impairment as it is a common cause of reduced ventricular relaxation[23]. Finally, a hyperechoic thickened pericardium (pericarditis) or a pericardial effusion suggests there could be poor ventricular compliance, which can cause diastolic impairment.

MANAGEMENT OF HFPEF IN THE PERIOPERATIVE PERIOD

Preoperative optimisation

Patients who present in clinical heart failure should be optimised before elective surgery. Diuretics are useful for reducing pulmonary congestion and improving symptoms. However, there is limited evidence that they provide any mortality benefit. Spironolactone alone has been shown to reduce hospital admissions[14]. Patients in rapid atrial fibrillation should be rate controlled as tachycardia reduces diastolic filling time.

Unlike in heart failure with systolic dysfunction, very few large multi-centre trials have shown a significant benefit from long-term treatment modalities in patients with HFpEF. As previously discussed, patients included in trials in HFpEF are significantly heterogeneous. Differences in diagnostic inclusion and exclusion criteria and in the diverse mechanisms of underlying disease have meant that conducting trials in patients with HFpEF is difficult.

Angiotensin receptor blockers (candesartan) have been shown to produce a small reduction in hospitalisation but have no effect on mortality[14,22]. Other large trials have investigated the benefits of beta-blockers and found inconsistent results for mortality and symptom control. Other potential treatment options that have been investigated are ACEIs, nitrates, calcium channel blockers and sildenafil. These have also shown conflicting results. Therefore most treatment strategies are targeted at symptom control and management of underlying disease[22].

Hypertension is likely the most important risk factor to control in HFpEF[14]. While they have not been shown to be of significant benefit in HFpEF, ACEIs, beta-blockers and angiotensin receptor blockers are all recommended for the management of hypertension.

Myocardial ischaemia impairs the energy-consuming relaxation process of the left ventricle and will worsen diastolic function as well as causing potentially catastrophic harm to systolic function due to myocyte damage.

Active prevention and management of ischemic heart disease with optimisation of medication or revascularisation should be undertaken before elective surgery.

Obesity and diabetes mellitus and their sequelae can be difficult to optimise in the often limited lead-time to surgery. However, the perioperative period can provide an opportunity to implement long-term management strategies through referral to other specialties, with potential long-term benefits for heart function.

Intraoperative management

Despite attempts to determine the best anaesthetic for patients with diastolic dysfunction, no study has shown convincing differences between volatile, intravenous or regional anaesthesia techniques[25].

Management of preload is probably the most important task for the anesthetist caring for a patient with HFpEF. Patients with normal or grade 1 diastolic dysfunction will respond well to fluid challenges as they have normal left atrial pressure. Those with grade 2 or 3 have elevated left atrial pressure and are at risk of pulmonary congestion if too much fluid is administered. The presence of a elevated left atrial filling pressure is also associated with longer ICU and hospital stays and higher mortality[12]. Patients with grade 3 (restrictive) diastolic dyfunction may benefit from preload reduction with diuretics or head up positioning[6].

Diastolic function is not static during the intraoperative period. Positions such as Trendelenberg or lithotomy will increase cardiac preload and can increase the grade of diastolic function and trigger pulmonary oedema. Venodilation associated with anaesthesia may result in an improvement in LVEDP and filling by "off-loading" the left ventricle[16]. A patient who was previously fluid intolerant may now respond well to a fluid challenge. Blood loss may have either a beneficial effect on diastolic function by reducing preload in an overloaded left atrium, or a harmful effect by further reducing filling if a high left atrial pressure is required to overcome a stiff ventricle.

It is therefore important to know the current status of diastolic function in the patient. Monitoring of patients with HFpEF should therefore include methods that allow early detection of changes in heart rate, rhythm, preload and ischaemia. Invasive haemodynamic monitoring with an arterial line and/or central venous catheter may be indicated in some circumstances[12]. Intraoperative echocardiography can also be a useful tool in the diagnosis of diastolic function, particularly in the presence of haemodynamic instability.

Prevention of sympathetic stimulation from surgery is important because tachycardia reduces diastolic filling time. Preemptive administration of anxiolytics and multimodal analgesia is important. Judicious use of short-acting beta-blockers can help control tachycardia. Atrial fibrillation also reduces left ventricular filling due to loss of the atrial kick; efforts should be made to maintain sinus rhythm. New onset AF should be aggressively managed[25].

Intraoperative blood pressure should be kept within 10-20 per cent of baseline. The diastolic blood pressure is particularly important and should be kept above the pulse pressure. A high pulse pressure increases left ventricular wall stress and impairs early filling[12]. A good rule is the "Rule of 70s"; age >70, diastolic BP >70, HR = 70, pulse pressure <70[12].

Postoperative care

Postoperative care should be tailored to the individual patient. Patients with mild or well-controlled heart failure having minor surgery usually do well. However, those with evidence of severe diastolic dysfunction or those having major surgery may need closer monitoring in a high dependency ward. Initially, these patients may appear stable and well in the postoperative recovery room; however, rapid atrial fibrillation, acute onset pulmonary oedema and myocardial ischemia are more common in this patient group. Both sympathetic stimulation due to inadequately managed pain and iatrogenic fluid overload have been implicated. Good ongoing postoperative care is essential[11,12].

CONCLUSION

The presence of normal systolic function is insufficient to exclude the diagnosis of heart failure. Diastolic function and ventricular filling are as important as systolic contraction for an adequate cardiac output. HFpEF, while common, is not benign.

Changes in diagnostic criteria to date have only served to confuse the diagnosis and have limited the ability to conduct clinical trials in this area. Nevertheless, patients who have evidence of diastolic dysfunction, particularly at rest, are at significantly higher perioperative risk than the general population.

Perioperative care in this group needs to be tailored individually to each patient's current haemodynamic state, as treatment is not a "one size fits all" approach. By understanding the physiology of diastole and the mechanisms whereby ventricular filling is impaired, anaesthetists can mitigate the risk of heart failure and cardiovascular complications in this group.

REFERENCES

1. Ferrari R, Böhm M, Cleland J, Paulus W, Pieske B, Rapezzi C, et al. Heart failure with preserved ejection praction: uncertainties and dilemmas. Eur J Heart Fail. 2015;17(7):665–671.
2. Yancy C, Jessup M, Bozkurt B, Drazner M, Fonarow G, Geraci S, et al. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128:e240–e327.
3. Ponikowski P, Voors A, Anker S, Bueno H, Cleland J, Coats A, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(27):2129–2200.
4. Nicoara A, Jones-Haywood M. Diastolic heart failure: diagnosis and therapy. Curr Opin Anaesthesiol. 2016;29(1):61–67.
5. Gaasch W. Deliberations on diastolic heart failure. Am J Cardiol. 2017;119(1):138–144.
6. Nicoara A, Whitener G, Swaminathan M. Perioperative diastolic dysfunction: a comprehensive approach to assessment by transoesophageal echocardiography. Sem Cardiothorac Vasc Anesth. 2014;18(2):218–236.
7. Garg N, Senthilkumar A, Nusair M, Goyal N, Garg R, Alpert M. Heart failure with a normal left ventricular ejection fraction: epidemiology, pathophysiology, diagnosis and management. Am J Med Sci. 2013;346(2):129–136.
8. Redfield M, Jacobsohn E, Burnett J, Mahoney D, Bailey K, Rodeghiero R. Burden of systolic and diastolic ventricular dysfunction in the community. JAMA. 2003;289(2):194–202.
9. Al-Khatib S, Shaw L, O-Connor C, Kong M, Calif R. Incidence and predictors of sudden cardiac death in patients with diastolic heart failure. J Cardiovasc Electrophysiol. 2007;18(12):1231–1235.
10. Fleisher L, Fleischmann K, Auerbach A, Barnason S, Beckman J, Bozkurt B, et al. ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing non-cardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practical guidelines. Circulation. 2014;130(24):e278–e333.
11. Fayad A, Ansari M, Yang H, Ruddy T, Wells G. Perioperative diastolic dysfunction in patients undergoing noncardiac surgery is an independent risk factor for cardiovascular events. Anesthesiology. 2016;125(1):72–91.
12. Ryu T, Song S. Perioperative management of left ventricular diastolic dysfunction and heart failure: an anesthesiologist's perspective. Korean J Anesthesiol. 2017;70(1):3–12.
13. Gaggin H, Januzzi J. Biomarkers and diagnostics in heart failure. Biochim Biophys Acta. 2013;1832(12):2442–2450.
14. Abbate A, Arena R, Abouzaki N, Van Tassell B, Canada J, Shah K, et al. Heart failure with preserved ejection fraction: refocusing on diastole. Int J Cardiol. 2015;179:430–440.
15. Kovács S. Diastolic function in heart failure. Clin Med Insights Cardiol. 2015;9(Suppl 1):49–54.
16. Doughty R, Sidebotham D, Hussey M. Left ventricular diastolic dysfunction. In: Sidebotham D, Merry A, Leggett M, Edwards M, editors. Practical perioperative transoesophageal echocardiography, 2nd ed. London: United Kingdom: Elsevier Health Sciences, 2011. pp. 125–134.
17. Kapila R, Mahajan R. Diastolic dysfunction. CEACCP. 2009;9(1):29–33.
18. Matyal R, Skubas N, Sherman S, Mahmood F. Perioperative assessment of diastolic dysfunction. Anesth Analg. 2011;113(3):449–472.
19. Chatterjee K, Massie B. Systolic and diastolic heart failure: differences and similarities. J Cardiac Fail. 2007;13(7):569–576.
20. Paulus W, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263–271.
21. van Heerebeek L, Paulus W. Understanding heart failure with preserved ejection fraction: where are we today?. Neth Heart J. 2016;24(4):227–236.
22. Kanwar M, Walter C, Clark M, Patarroyo-Aponte M. Targeting heart failure with preserved ejection fraction: current status and future prospects. Vasc Health Risk Manag. 2016;12:129–141.
23. Nagueh S, Smiseth O, Appleton C, Byrd B, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiogrpahy and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277–314.
24. Swaminathan M, Nicoaroa A, Phillips-Bute B, Aeschlimann N, Milano C, Mackensen G, et al. Utility of a simple algorithm to grade diastolic dysfunction and predict outcome after coronary artery bypass graft surgery. Ann Thorac Surg. 2011;91(6):1844–1850.
25. Pirracchio R, Cholley B, De Hert S, Solal AC, Mebazza A. Diastolic heart failure in anaesthesia and critical care. Br J Anaesth. 2007;98(6):707–721.

Extra corporeal membrane oxygenation: Anaesthetic perspectives

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INTRODUCTION

Use of extracorporeal membrane oxygenation (ECMO) has dramatically increased in recent years[1]. The potential for anaesthetists to be exposed to ECMO is increasing. Opportunities include in an ICU or retrieval position, at a cardiac arrest proceeding to ECMO-Cardiopulmonary resuscitation (E-CPR) or in the operating theatre. An understanding of the technology, physiology and clinical management of ECMO is therefore increasingly important.

This article will describe the scientific principles behind ECMO and the relevant clinical considerations.

HISTORY

ECMO was adapted from cardiopulmonary bypass technology. It was initially used predominantly in neonates, for respiratory and subsequently for cardiovascular support[2,3]. In the 1970s interest developed in ECMO for adult acute respiratory distress syndrome (ARDS) and early single centre case series showed promise[4]. However the first major randomised control trial (RCT) for respiratory failure in the 1990s failed to show a survival benefit[5]. Interest waned, until the H1N1 epidemic of the early 2000s. Patients with otherwise desperate respiratory failure were treated with ECMO with apparently positive outcomes. The CESAR trial confirmed a survival benefit and led to the recommendation that patients with potentially reversible respiratory failure be transferred to an ECMO capable centre[6]. Simultaneously ECMO has been increasingly used as a bridge to recovery or transplant in respiratory and cardiovascular disease.

CONFIGURATION TYPES

An ECMO circuit consists of one or more large cannulae draining blood from a patient, a pump, a membrane oxygenator and another cannula returning the blood. The system often includes a heater[7]. The configuration of the ECMO cannulae depends on the type of support needed. The most commonly used configurations are veno-venous (VV) ECMO for respiratory support and veno-arterial (VA) ECMO for cardiovascular support – including of the arrested patient for E-CPR[8].

Less common configurations include hybrid modes, for example veno-arterial-venous (VAV) or veno-veno-arterial (VVA) ECMO, used when moving from primary cardiovascular or respiratory support to supporting both circulation and ventilation. Veno-Pulmonary artery (V-PA) ECMO supports the right ventricle after insertion of a left ventricular assist device (LVAD)[8]. These are beyond the scope of this article and will not be discussed further.

Whichever configuration, ECMO may further be described as central or peripheral. In central ECMO the cannulae are surgically grafted directly on to the central vessels in the operating theatre, often at cessation of cardio-pulmonary bypass[9]. In peripheral ECMO, cannulae are inserted via peripheral vessels usually under ultrasound guidance. They are then positioned appropriately using a combination of x-ray and echocardiographic techniques, including transoesophageal echocardiography (TOE)[8].

VA ECMO

In veno-arterial ECMO, venous blood is accessed from a large central vein. After oxygenation it is returned to an artery, usually the aorta. In this way, returning oxygenated blood flow to the arterial tree provides support to the failing circulation. This mode will also provide oxygenation support if needed[10].

In central VA ECMO, the access cannula is sited in the right atrium. The return cannula is sewn onto the proximal aorta. Both are tunnelled out through the chest wall. After cannula positioning the sternum is closed[8]. The requirement for sternotomy is clearly a disadvantage in many situations. However in the post cardiotomy patient this mode provides full cardiovascular and respiratory support. It also avoids some potential complications of peripheral VA ECMO[10].

In peripheral VA ECMO, the most common configuration is femoral-femoral, with the access cannula exiting a femoral vein and the return cannula entering a femoral artery (figure 1a). Ideally these are in opposite legs to reduce risk to a limb. The access cannula can also be inserted into the internal jugular vein. Echocardiography and x-rays are used to position the cannula tips: the access cannula in the right atrium, the return cannula directed to the lower aorta. The cannulae used in the most unstable patients (under CPR) are smaller than in more elective cannulations, to facilitate ease and speed of insertion[8].

The limb with the peripheral arterial return cannula will require a back-flow cannula to perfuse the leg distally. This anterograde cannula is much smaller than the arterial return cannula[8].

VV ECMO

In veno-venous ECMO, blood is again accessed from a large central vein – ideally the vena cava – in the same way as VA ECMO (figure 1b). Blood is returned to the venous circulation, ideally to the right atrium close to the tricuspid valve. VV ECMO cannulation is almost always peripheral with no requirement for sternotomy and used for respiratory support[10].

Various configurations of the venous cannulae are possible. Femoro-femoral and femoro-jugular configurations use a single access cannula with the tip in the IVC and a return cannula. In femoro-femoral VV ECMO the return tip is in the right atrium. In femoro-jugular VV ECMO the (jugular) return tip is positioned in the lower SVC, aiming flow across the tricuspid valve[8]. Combined catheters that have access ports designed to extract flow from both cava and direct return flow at the tricuspid valve also exist[8].High-flow VV ECMO, used when flow rates are not sufficient with one of the above configurations, uses both a jugular (SVC) and femoral (IVC) access cannula and a femoral return cannula.

Figure 1a. Peripheral veno-arterial ECMO configuration demonstrating retrograde flow up the descending aorta

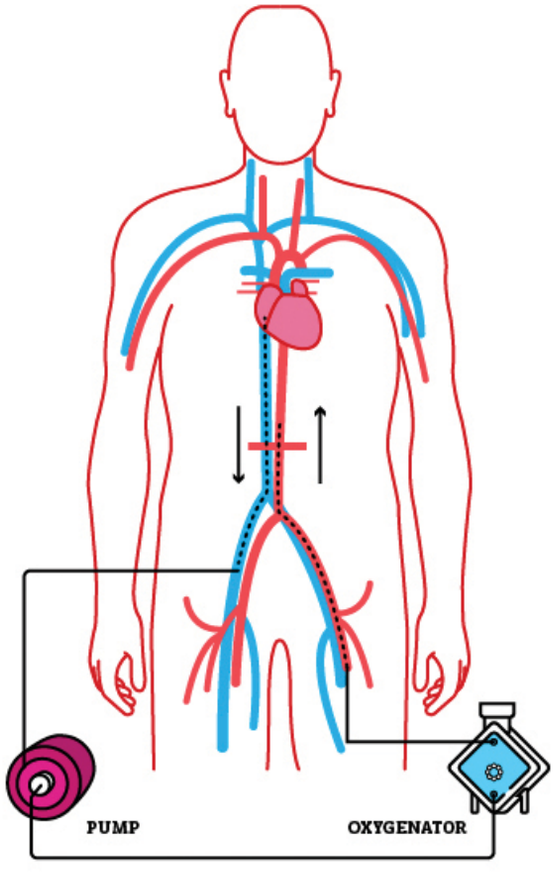
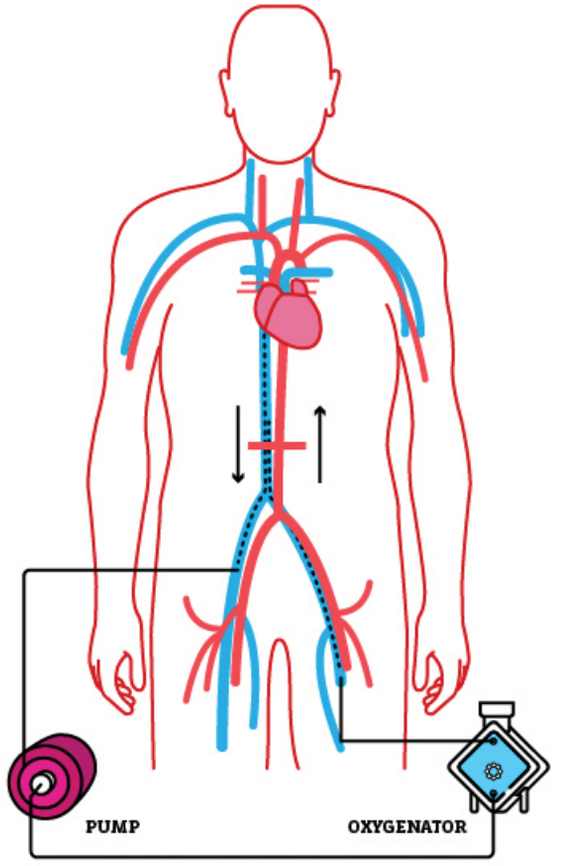


Figure 1b. Veno-venous ECMO configuration



$ECCO_2R$

Extra-corporeal carbon dioxide removal ($ECCO_2R$) can be considered a specialised form of VV ECMO. When oxygenation is adequate but hypercapnia uncontrolled the high solubility of carbon dioxide allows $ECCO_2R$ at much lower blood flows (<1 L/min) than VV ECMO. Therefore much smaller calibre cannulae such as a dual lumen dialysis catheter will suffice. Very limited oxygenation will be possible[11].

PHYSIOLOGY

Like the native cardiorespiratory system, the physiology of ECMO can be considered in terms of gas exchange and blood flow components.

Gas exchange

Instead of the alveoli, gas exchange occurs at the extracorporeal membrane oxygenator. These consist of a high surface area blood path and fresh gas flow path, separated by the membrane itself. The arrangement of the membrane provides the large surface area, usually by organisation into hollow fibre tubes. Commonly the lumens of these tubes are for gas flow and blood runs between the fibres. Various other configurations exist[11].

Diffusive flux of respiratory gases occurs down the partial pressure gradient at the membrane. Continual delivery of fresh gas (oxygen, without carbon dioxide) maintains these gradients. As in vivo, flux is dependent on Fick's Law of Diffusion:

$$\text{Flux} = -D.A\ \frac{\Delta C}{\Delta l}$$

Flux of solute across the membrane is thus proportional to the diffusivity coefficient (D), the area of the membrane (A) and the concentration gradient across the membrane (ΔC) and inversely proportional to membrane thickness (Δl)[11]. By combining the above with Henry's Law describing the amount of gas dissolved in a liquid (kO_2 = Henry's Law constant), membrane flux of oxygen (J) can be described by:

$$J = -kO_2.A \frac{P_{O2(Gas)} - P_{O2(Plasma)}}{\Delta l}$$

There will be an optimal duration of blood exposure to the membrane to allow maximum oxygenation without reaching equilibrium. Oxygenator design considers balancing blood flow rate with membrane length and resistance to flow to optimise oxygen flux[11].

Unlike pulmonary gas exchange, the membrane oxygenator is susceptible to build up of protein and clotting factors, resulting in film formation. Membrane thickness is therefore not uniform and available membrane area decreases over time[11].

The oxygen in a patient's blood is predominantly carried by haemoglobin, not dissolved in solution. Because haemoglobin is a saturable oxygen carrier, oxygen delivery is flow limited regardless of oxygen tension achieved at the oxygenator. In VV-ECMO, oxygen delivery relies on achieving circuit flow rates of an adequate proportion of the cardiac output[11].

Maximal saturation of Hb for example at 10 g/dL^{-1} allows a maximum oxygen carriage of ~13 mL/dL^{-1}. Assuming a venous saturation of 70 per cent (oxygen content ~9.3ml/dL^{-1}) only 37 mL of oxygen can be added per litre to typical mixed venous blood. With average oxygen consumption of 300 mL/min^{-1} ECMO flow and cardiac output would need to exceed 7 L/min^{-1}. Dropping native cardiac output (in VV ECMO) results in a fall in mixed venous saturation and allows more oxygen uptake[11].

As in vivo, the low [CO_2] at the oxygenator promotes oxygen uptake via the Haldane effect[11].

In contrast to oxygen, the high solubility and more linear dissociation curve of carbon dioxide means CO_2 can be easily cleared by exposure to the fresh gas flow. In fact in VV ECMO hypocapnia is often encountered requiring adjustment of the fresh gas flow rate. This allows clearance of physiological levels of CO_2 with much lower blood flow rates (~500 mL/min^{-1} versus 5 L/min^{-1}) for example with $ECCO_2R$[11].

Haemodynamics and flow

Flow in the ECMO circuit is driven via a pump, most commonly these are velocity pumps such as centrifugal constrained vortex pumps. A rotor generates a centrifugal force rotating the blood path and generating negative pressure at the central pump inlet and positive pressure towards the peripherally located outlet[11].

Flow of an ideal fluid in a solid conduit will occur from high pressure to low pressure and will be opposed by resistance, described by:

$$Q = \frac{P_{Inlet} - P_{Outlet}}{R}$$

The ECMO circuit can reasonably be considered a solid conduit. However blood is not a uniform fluid as cells are suspended in solution and plasma proteins may interact with the conduit walls. Blood is significantly more viscous than water and viscosity increases with haematocrit and lower blood velocities (due to intracellular adhesive forces). This will manifest as an increased resistance to flow[11].

Flow rates are displayed by the ECMO console. Flow requirements will vary between patients according to clinical picture. The minimum flow rate possible to support oxygenation or the circulation is selected to reduce complications such as vascular access insufficiency and haemolysis. 3-6L per minute is typical in adults[11].

CLINICAL APPLICATIONS

Indications

While the potential benefits are significant, ECMO remains an expensive, time consuming and potentially risky medical intervention. It is therefore vital that careful consideration is given to ensure its delivery to the right patient under the right circumstances. In order to initiate ECMO there must be a reasonable expectation of recovery/reversibility of the underlying condition and withholding ECMO must be deemed higher risk than initiating it[12].

Table 1. Indications for VV ECMO

RESPIRATORY FAILURE WITH PREDICTED MORTALITY >50 PER CENT DUE TO:
• Primary ARDS: infection, aspiration, trauma.
• Secondary ARDS: burns, distant infection.
• Primary graft failure post-transplant.
• Pulmonary vasculitis.
• Pulmonary haemorrhage.

The Extracorporeal Life Support Organisation (ELSO) recommend considering VV ECMO in hypoxic respiratory failure from any cause where mortality is deemed ≥50 per cent (table 1). Parameters to assess risk of mortality include PaO_2/FiO_2 ratios (<150 on FiO_2 0.9 suggests a 50 per cent mortality and <100 on FiO_2 0.9 suggests 80 per cent mortality) and the Murray Score (PaO_2/FiO2 on FiO_2 1.0, number of CXR quadrants infiltrated, PEEP and compliance)[13].

Conditions in which ECMO may be beneficial include primary and secondary acute respiratory distress syndrome (ARDS), pulmonary vasculitis, direct injury to the lung by trauma, and primary graft failure after lung transplantation[8].

ELSO recommend considering VA ECMO in cardiogenic shock persisting despite optimised resuscitation including fluid, vasopressors and inotropes or after cardiac arrest due to an easily reversible cause in which immediate good CPR has occurred (table 2). Causes include acute myocardial infarction, myocarditis, peripartum cardiomyopathy and post cardiotomy shock[14,15].

Table 2. Indications for VA ECMO

Refractory cardiogenic shock due to:

- Acute coronary syndrome.
- Acute fulminant myocarditis.
- Acute cardiomyopathy for example peri-partum.
- Pulmonary embolism.
- Toxidromes.
- Primary graft failure.
- Failure to wean from cardiopulmonary bypass.

Cardiac arrest with immediate CPR (from a reversible cause).

Various forms of decompensated chronic cardiac failure may be considered for ECMO if no contra-indications exist and recovery is expected. Less commonly, ECMO is considered for patients with non-recoverable cardiac disease as a bridge to VAD or transplant[14]. In practice this sometimes results in ECMO as a "bridge to decision" allowing time to consider potential destinations for critically unstable patients.

Contraindications

The boundaries of ECMO contraindications are being continually pushed and each patient is considered on their own merits. However some "absolute" contra-indications are still widely agreed upon (table 3). These include advanced age (variable but often >75), severe additional chronic organ failure (emphysema, cirrhosis, renal failure) and non-recoverable comorbidities such as severe brain injury or terminal malignancy[8].

ECMO is contraindicated if prolonged CPR has been on-going without adequate perfusion[15]. In addition, if a heart is deemed unrecoverable and the patient is not a candidate for a VAD or transplant, VA ECMO is inappropriate as a "bridge to nowhere"[14].

Table 3. Contraindications ECMO

- Advanced age (>75).
- Severe chronic organ failure (cirrhosis, renal failure, emphysema).
- Severe brain injury.
- Advanced malignancy.
- Non-recoverable pathology (and not a transplant candidate).

There are a number of "relative" contraindications in which ECMO is less likely to produce a good outcome. These depend on ECMO mode. VV ECMO is associated with poorer outcomes in patients who have been mechanically ventilated with high settings (FiO_2, PPlat) for more than seven days and in those showing signs of multi-organ failure including severe myocardial depression, failure of the microcirculation, high lactate and high vasopressor requirements[8].

Certain respiratory conditions respond less favourably including interstitial lung disease, cryptogenic organising pneumonia and cystic fibrosis (except as a bridge to transplant)[8].

VA ECMO is associated with poor outcomes in severe unrepaired valvular disease and in cardiogenic shock associated with multiple severe organ failure. Signs include renal failure (anuria >4h), hepatic failure (high transaminases and INR), microcirculatory failure and high lactate. VA ECMO cannot be successfully initiated in aortic dissection[8].

Initiation

Central ECMO is performed by cardiothoracic surgeons in the operating theatre. Peripheral ultrasound guided cannulation can involve emergency medicine physicians, intensivists and anaesthetists in the emergency department or intensive care.

The time critical nature of ECMO requires a rapid response from the ECMO team in order to enable assessment for eligibility (as described above) and prompt initiation, particularly in the arrested patient. Well-drilled teams with standardised equipment and bed space set-ups will be able to deliver the timeliest ECMO interventions[16].

Maintenance

Patients on ECMO will be cared for on the intensive care unit. In addition to the standard care for any critically ill patient and treatment of underlying pathology, ECMO patients will require specific management on pump. The response to ECMO emergencies is described in complications.

Each institution will need clearly defined protocols to guide supportive care on ECMO. Additional parameters requiring careful monitoring include cannula position, distal limb perfusion, plasma free haemoglobin, CO_2 and therefore fresh gas flow sweep rate, oxygenator pressure gradient and presence of clots anywhere in the circuit. Pressure area care is important and safe with peripheral ECMO as long as a dedicated person holds the cannulae throughout. Rolling is not advised with central ECMO[8].

Weaning

Assessing patient suitability for weaning from ECMO depends on the type of support. Weaning VV ECMO will be attempted when signs of lung recovery are present. These may include improved compliance (improving tidal volumes/reducing PPlat) and resolving pulmonary infiltrates[13].

To wean off VV support, the fresh gas flow rate is incrementally reduced until patients have tolerated several hours of no fresh gas flow. Ventilation will need to be increased to maintain oxygenation and CO_2 clearance. Generally while fresh gas flow is delivered it is at an FiO2 of 1.0. Circuit blood flow usually remains unchanged. No change in blood flow means there is no increased risk of haemostasis or need for additional anticoagulation[8].

In VA ECMO, formal echocardiographic weaning studies are required to assess the heart's ability to perfuse the systemic circulation at incrementally decreasing amounts of ECMO blood flow. This reducing blood flow will require additional anticoagulation. Various protocols are available to guide VA ECMO weaning echocardiographic studies[8].

Decannulation

Central ECMO will require a return to theatre to complete treatment, either for decannulation or for transition to VAD or transplant. Peripheral VV ECMO may be possible to decannulate outside of theatre (on the ICU) with pressure applied to the cannula sites after removal. Many centres will decannulate in theatre with vascular surgery available to repair vessels. This is necessary for removal of arterial cannulae[8].

Transport

Transport of the patient on ECMO is increasing and provides an additional set of challenges to those involved in transporting any critically ill patient. A patient unstable enough to require ECMO is likely to be extremely dangerous to move prior to its commencement. As such there may be a need for teams to travel to referring

hospitals without in house ECMO capabilities, cannulate on site and transport the patient back to the ECMO centre on pump[6].

Some non-ECMO centres are able to commence ECMO in extremis, for example in the context of E-CPR. Outcomes will be improved for these patients if, once stable, they are transported to an ECMO centre[6].

Logistical obstacles can be significant when travelling with a patient on ECMO. Standard size road and air vehicles may not be large enough to accommodate patient, equipment and staff. Adequate oxygen and power supplies are vital. Experienced ECMO staff with the knowledge and equipment to respond to ECMO emergencies must accompany patients. While complications are not uncommon, with high volume and experienced teams intra-hospital transportation is safe, with mortality at 0.5 per cent[17].

COMPLICATIONS

Complications on ECMO unfortunately remain common, although with increasing experience their management is becoming better understood. Complications are patient or circuit related (mechanical).

Patient complications

The most devastating patient related complication is massive intracranial haemorrhage, related to the need for systemic anticoagulation (table 4). It is therefore important to avoid hypertension. Patients are also at risk of other haemorrhagic complications, including bleeding around the cannulae (which can be extensive), bleeding at other surgical sites (intrathoracic, abdominal, retroperitoneal), gastrointestinal haemorrhage and pulmonary haemorrhage[10]. Overall bleeding and coagulopathy are the most common complications on ECMO, reported at 5-79 per cent. Careful monitoring of haematological parameters including maintenance of platelet count >100,000 cells/μL can reduce bleeding risk[18].

Table 4. Patient complications on ECMO

- Bleeding and coagulopathy.
- Thrombosis.
- Neurological catastrophe.
- Infection.
- Differential hypoxia (VA ECMO).

Conversely, patients on ECMO are also at risk of thrombotic complications, illustrating the delicate balance of anticoagulating this population. As well as thrombus in the ECMO circuit, patients on VA ECMO with poor or non-existent native cardiac pulsatility are at risk of forming intracardiac thrombus. This can then result in arterial embolisation and downstream ischaemia, including ischaemic stroke. Limb ischaemia as a result of the direct mechanical effects of the large cannulae is also seen[9].

Between the bleeding and thrombotic risks, the potential for neurological complications, sometimes disastrous, is high on ECMO[10].

After bleeding and thrombosis, infection is the most common patient-related complication seen on ECMO, reported in as many as 45 per cent. Many ECMO patients will have an initial underlying infective process. Critical illness and multi-organ failure increase the risk from infection[19].

Risk of iatrogenic infection is also high; these most critically ill patients require a variety of invasive indwelling equipment including the large ECMO cannulae themselves. Changing invasive lines is difficult and risky on ECMO and lines often therefore remain in for longer than standard[19].

Infection can be difficult to identify on ECMO. Heat loss via the circuit may mask a fever. Native ability to mount a standard immune response may be impaired by altered inflammatory responses due to blood exposure to the ECMO circuit. Strict aseptic techniques and vigilance in monitoring for infection, including surveillance blood cultures, is wise. No role has been established for prophylactic antibiotics[7].

These patients are critically ill and at risk of cardiac arrest. Management of cardiac arrest depends on the form of ECMO. On VA ECMO the aetiology of loss of cardiac contractility may include ventricular dysrhythmia, ventricular standstill or asystole. Cardiac compressions will not be required. However ECMO support should be optimised, the cause should be sought (with echo and attention to electrolytes) and dysrhythmias should be treated. Ventricular standstill or asystole should be treated with adrenaline as in standard advanced cardiac life support (ACLS) care[8].

On VV ECMO there is no cardiac support and so cardiac arrest will require immediate ACLS management including chest compressions as in any other patient. Again specific management of arrhythmias and identifying and managing reversible causes as in any ACLS algorithm resuscitation (electrolyte abnormality, pneumothorax)

is required. Access insufficiency is common under arrest on VV ECMO and may necessitate a reduction in pump speeds[8].

A complication specific to VA ECMO is differential hypoxia or harlequin man syndrome. This is often seen following the return of some native cardiac function when pulmonary gas exchange remains poor. The oxygenated blood from the ECMO circuit, being directed into the distal aorta, will preferentially perfuse the lower body. Blood coming from the left ventricle, which has been oxygenated via the lungs, will provide the majority of blood to the coronary and cerebral circulations. If pulmonary gas exchange is poor, these vital circulations may be inadequately oxygenated[10].

Monitoring saturations in the right arm enables surrogate monitoring of coronary and cerebral oxygenation, as the brachiocephalic trunk supplying the right arm and carotid originates immediately after the coronary arteries[11].

Mechanical (circuit) complications

Problems are possible at any point in the ECMO equipment and may be rapidly disastrous if the patient is fully dependent on ECMO support. A prompt response to any circuit complication is essential. Meticulous attention to cannula position both at insertion and throughout the ECMO run can reduce the risk of many mechanical complications (table 5)[7].

Table 5. Mechanical complications on ECMO

- Access insufficiency.
- Recirculation.
- Vascular injury.
- Circuit breach: air embolism, blood loss.
- Decannulation.
- Thrombus formation: consumptive coagulopathy, oxygenator failure.
- Pump failure.

One of the most commonly seen mechanical complications is some degree of access insufficiency. This represents inadequate venous flow as compared to the negative pressure exerted on the access cannula by the pump. The resulting suction of the venous walls into the access ports will result in their occlusion. Depending on severity, the access line may be seen to shake or “chatter”. Blood flow may fall and not respond to increasing pump speeds. When significant, this can result in a loss of adequate support[7].

A prompt response to access insufficiency including establishing the cause is necessary. Dropping the pump speed will reduce the negative pressure and may improve the situation, but this must be balanced carefully with the need to maintain adequate ECMO support. A cautious bolus of fluid is likely to improve flow; however this is not possible as a repeated strategy as massive volume overload can ensue[8].

Identification and correction of the underlying cause is ideal. The most common cause is hypovolaemia and access insufficiency should prompt a careful search for bleeding. Bedside echocardiography can help identify pneumothorax and cardiac tamponade. Change in patient status such as waking, moving or coughing should be identified and managed. Intra-abdominal hypertension may be a more subtle cause of access insufficiency[8].

If no patient causes are identified, careful assessment of ECMO settings and cannulae position is required. Excessive revolutions per minute will respond to lowering flow rate, as long as adequate support is maintained. Suboptimal cannula position (i.e. too distal in the IVC) will require repositioning. If reversible causes have been ruled out, insertion of a second access cannula (i.e. conversion to high flow ECMO) may be required[8].

Another potential cannula position related complication seen in VV ECMO is recirculation. If the tips of the two cannulae are not sufficiently distant from each other, blood may flow preferentially from one cannula to the other, with little oxygenated blood reaching the systemic circulation. Oxygenation will be inadequate and little colour difference will be seen between the cannulae. Ensuring cavo-atrial direction of flow and a distance of at least 10-15cm between cannulae tips should minimise the risk of significant recirculation[7].

Arterial cannulae are also vulnerable to malpositioning. Too low in the descending aorta and coronary and cerebral blood flow may be inadequate. Too high and the increased afterload may worsen left ventricular failure. If the cannula migrates through the aortic valve then valvular insufficiency and ventricular rupture are possible[7].

Any breach in the ECMO circuit can have immediate and catastrophic consequences. Alcohol containing solutions must not come into contact with the circuit due to the risk of brittleness and cracking. A breach after the pump head will result in immediate forceful ejection of blood. A breach before the pump head will cause massive entrainment of air, which will de-prime the pump and result in a loss of ECMO support. Any breach

which cannot be immediately controlled will likely require clamping of the circuit, cessation of the pump and an emergent circuit change whilst life support measures are in progress[8].

Similarly, accidental decannulation while dependent on ECMO support will require life support measures, clamping of the circuit and management of bleeding or assessment for air embolism depending on whether pre- or post-pump. Advancement may be possible of a partially removed cannula, otherwise emergent recannulation may be required. Meticulous attention to securing of cannulae and avoiding any tension on the lines is essential to reduce the risk of decannulation[8].

Air embolism can occur in the absence of an overt circuit breach or decannulation, for example during cannulation of a central vessel while on ECMO support (commonly at conversion to high-flow). The circuit must be clamped and the pump turned off. The patient should be placed head down while life support measures are in progress. Either a circuit change will be required or the existing circuit may be “de-aired” and reprimed with the patient’s blood[8].

As described earlier, the ECMO circuit is prone to formation of thrombus and some burden of clot within the circuit is not uncommon. Small clots may be well tolerated without incident and are often seen in the membrane oxygenator and other regions of turbulent flow such as at connection points. Careful surveillance of circuit clots is essential however as large clots can have significant sequalae[7].

Thrombus may travel into the patient’s circulation. A large burden of clot can cause coagulation system activation and platelet consumption. Monitoring of platelets, D-dimer and fibrinogen may illustrate the need for an elective circuit change. More dramatically, a large clot can lead to oxygenator failure, requiring a circuit change. Signs of oxygenator failure include an increased pressure gradient across the membrane, platelet consumption and haemolysis. Rarely this is acute and requires an urgent circuit change[7]. An important consideration is if a patient anticoagulated with heparin develops HITTS while still ECMO dependent; many of the non-heparin anticoagulants require factor Xa monitoring however this measurement is inaccurate in the presence of haemolysis.

Pump failure represents failure of the pump (itself or the console) to drive forward flow of blood. In a fully dependent circulation the absence of valves in the ECMO circuit will allow retrograde flow. If some degree of native cardiac contractility exists then varying degrees of hypotension +/- hypoxia will ensue. Causes of pump failure include power failure and pump head disengagement. Interim support is provided via the emergency drive unit (“hand crank”) while the cause is determined or the patient is transferred to a new console[8].

ANAESTHESIA ON ECMO

Why do ECMO patients go to the operating theatre?

Cardiac anaesthetists may be used to transitioning patients to ECMO when they cannot be weaned from CPB. In addition, theatre may be the location of ECMO cannulation either centrally or peripherally – whether percutaneously or via cut down. Central ECMO and peripheral VA ECMO will require decannulation in theatre[8].

Patients on ECMO may require surgery for procedures unrelated to the cannulae, often due to complications associated with ECMO. Common surgical problems seen on ECMO which may require operative intervention include neurosurgical catastrophe, limb ischaemia and GI bleeding or ischaemia[7].

Appreciating that in VA ECMO the circulation may be pulseless, the cardiac output fixed and the MAP controlled by vasopressors is important.

ECMO pharmacology

Generally patients on ECMO in the ICU may be deeply sedated to preserve cannula position by preventing movement and minimise discomfort. However there is an increasing trend to lighten sedation to reduce the complications associated with deep sedation and even allow more active physiotherapy and mobilisation[12,20]. As such, patients visiting theatre for surgery may well require additional anaesthesia. It is also not uncommon for large increases in doses of sedative and analgesic drugs to be required at the commencement of extracorporeal life support[21].

ECMO can alter drug pharmacokinetics and pharmacodynamics, although precise data on this remains scarce and predominantly exists in the neonatal population. This places patients at increased risk of both inefficacy and toxicity. The ECMO circuit increases effective volume of distribution and can sequester drugs, altering pharmacokinetics. Highly lipophilic or protein bound drugs are particularly vulnerable to sequestration, especially at the oxygenator due to its large surface area. In particular, propofol demonstrates very high levels of circuit binding, limiting efficacy[21].

Other commonly given drugs such as inotropes, vasopressors and antibiotics may also be subject to altered dose requirements on ECMO[21]. In addition, the anaesthetist must be aware of the current anticoagulation status and thus bleeding risk of the patient on the table.

Ventilation strategies
A key aim of VV ECMO is to facilitate lung recovery. As such, ventilation settings are kept minimalistic or ultraprotective. Evidence is still sparse on the best protocol, but common features include low rate, low tidal volume (<4 mL.kg^{-1}), low FiO_2, low plateau pressure, long inspiratory time and PEEP 5-15 mmHg. Inadequate oxygen saturations are best addressed not by adjusting ventilation, but by assessing adequacy of extracorporeal support[12].

EVIDENCE

The evidence base for ECMO is growing but limited. Literature review reveals many papers, but the vast majority detail single centre experiences with significant heterogeneity between patient populations. A Cochrane review published in 2015 identified only four RCTs comparing ECMO to standard care in the last four decades. These only covered VV ECMO, not VA, and were too heterogeneous to allow data pooling for meta-analysis[22].

Information on ECMO outcomes is increasing with experience however. The ELSO registry collects outcome data on all ECMO runs submitted. In adult ECMO, survival to discharge rates as of January 2015 for VV support were 57 per cent and for VA support were 41 per cent. These vary according to indication[1].

Although the body of experience and knowledge regarding the use of ECMO continues to grow, it is difficult to imagine designing robust and ethical RCTs comparing ECMO to standard care in those patients in extremis with few remaining treatment options.

ETHICAL CONSIDERATIONS

The increasing use of ECMO presents ethical questions. Careful patient selection is vital. Who gets this extremely resource intensive intervention and who doesn't? Can the cost of a long ECMO run be justified at all in comparison to other investment elsewhere in the health system?

Informed consent is often impossible as qualifying patients are likely to be too sick to participate in discussion. The time critical nature of initiating emergent ECMO support can mean that discussion with families is at risk of being rushed and inadequate[23].

One of the most difficult ethical issues is when to cease ECMO support if it has either become clearly futile or no longer in the patient's best interests. A frank discussion with family prior to commencement about what goals of support and reasonable time frames may look like can reduce subsequent conflict. A recent ethics committee review concluded that ethical issues surrounding this technology in many ways echo the traditional ethical concerns around appropriate use of more familiar life sustaining treatments[23].

CONCLUSION

Increasing use of ECMO means anaesthetists are likely to see more of this life saving technology. While controversies and complications remain, this is an exciting time in ECMO provision and understanding this technology will be beneficial to all involved in care of the critically ill.

REFERENCES

1. Extracorporeal Life Support Organisation. Extracorporeal life support registry report [Internet]. Ann Arbor: Extracorporeal Life Support Organisation, 2017. From: https://www.elso.org/Registry/Statistics/InternationalSummary.aspx. Accessed 22 June 2017.
2. Rashkind WJ, Freeman A, Klein D, Toft RW. Evaluation of a disposable, plastic, low volume pumpless oxygenator as a lung substitute. J Pediatr. 1965;66(1):94–102.
3. Dorson W Jr, Baker E, Cohen ML, Meyer B, Molthan M, Trump D, et al. A perfusion system for infants. Trans Am Soc Artif Intern Organs. 1969;15(1):155–160.
4. Hill JD, O'Brien TG, Murray JJ, Dontigny L Bramson ML, Osborn MD, et al. Prolonged extracorporeal oxygenation for acute post traumatic respiratory failure (shock lung syndrome). Use of the Bramson membrane lung. N Engl J Med. 1972;286(12):629–634.
5. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF Jr, Weaker LK. Randomised clinical trial of pressure controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med. 1994;149(3):295–305.
6. Peck GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalany MM, et al. Efficacy and economic assessment of conventional ventilator support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351–1363.
7. Allen S, Holena D, McCunn M, Kohl B, Sarani B. A review of the fundamental principles and evidence base in the use of extracorporeal membrane oxygenation (ECMO) in critically ill adult patients. J Intensive Care Med. 2011;26(1):13–26.
8. Pellegrino V, Sheldrake J, Murphy D, Hockings L, Roberts L. Alfred Health extracorporeal membrane oxygenation (ECMO) guideline [Internet]. 2012. From: www.alfredicu.org.au/assets/Documents/ICU-Guidelines/ECMOGuideline.pdf. Accessed 22 June 2017.
9. Martinez G, Vuysteke A. Extracorporeal membrane oxygenation in adults. Contin Educ Anaesth Crit Care Pain. 2012;12(2)57-61.
10. Makdisi G, Wang I. Extracorporeal membrane oxygenation (ECMO) review of a lifesaving technology. J Thorac Dis. 2015;7(7):166-176.

11. Brain MJ, Butt WW, Maclaren G. Physiology of extracorporeal life support (ECLS). In: Extracorporeal Life Support for Adults. Schmidt GA, editor. New York: Springer, 2016. p. 1–60.
12. Extracorporeal Life Support Organisation. ELSO guidelines for cardiopulmonary life support [Internet]. Ann Arbor: Extracorporeal Life Support Organisation, 2013. From: https://www.eslo.org/Portals/0/IGD/Archive/FileManager1929122ae88cusershyerdocumentselsoguidelinesgeneralalleclsversion1.3.pdf. Accessed 22 June 2017.
13. Extracorporeal Life Support Organisation. ELSO adult respiratory failure supplement to the ELSO general guidelines [Internet]. Ann Arbor: Extracorporeal Life Support Organisation, 2013. From: https://www.eslo.org/Portals/0/IGD/Archive/FileManager989d4d4d14cusershyerdocumentselsoguidelinesforadultrespiratoryfailure1.3.pdf. Accessed 22 June 2017.
14. Extracorporeal Life Support Organisation. ELSO adult cardiac failure supplement to the ELSO general guidelines [Internet]. Ann Arbor: Extracorporeal Life Support Organisation, 2013. From: https://www.eslo.org/Portals/0/IGD/Archive/FileManager/e76ef78eabcusershyerdocumentselsoguidelinesforadultcardiacfailure1.3.pdf. Accessed 22 June 2017.
15. Extracorporeal Life Support Organisation. ELSO ECPR supplement to the general guidelines [Internet]. Ann Arbor: Extracorporeal Life Support Organisation, 2013. From: https://www.eslo.org/Portals/0/IGD/Archive/FileManager/67131867cusershyerdocumentselsoguidelinesforecprcases1.3.pdf. Accessed 22 June 2017.
16. Bernard S. Alfred Health extracorporeal membrane oxygenation during cardiopulmonary resuscitation (ECMO-CPR) guideline [Internet]. 2012. From: www.alfredicu.org.au/assets/Documents/ICU-Guidelines/ECMO/ECMOCPRGuideline 2012 draft6.pdf. Accessed 22 June 2017.
17. Broman LM, Holzgraefe B, Palmer K, Freckner B. The Stockholm experience: interhospital transports on extracorporeal membrane oxygenation. Crit Care. 2015;19:278–283.
18. Mehta H, Eisen HJ, Cleveland JC. Indications and complications for VA-ECMO for cardiac failure [Internet]. American College of Cardiology Expert Analysis, 2015. From: www.acc.org/latest-in-cardiology/articles/2015/07/14/09/27/indications-and-complications-for-va-ecmo-for-cardiac-failure. Accessed 22 June 2017.
19. Sun HY, Ko WJ, Tsai PR, Sun CC, Ghan YY, Lee CW, et al. Infections occurring during extracorporeal membrane oxygenation use in adult patients. J Thorac Cardiovasc Surg. 2010;140(5):1125–1132.
20. DeGrado JR, Hohlfelder B, Ritchie BM, Anger KE, Reardon DP, Weinhouse GL. Evaluation of sedatives, analgesics and neuromuscular blocking agents in adults receiving extracorporeal membrane oxygenation. J Crit Care. 2017;37:1–6.
21. Taylor MA, Maldonado Y. Anaesthetic management of patients on ECMO. In: Extracorporeal membrane oxygenation – advances in therapy [Internet]. Firstenberg MS, editor. Intech, 2016. From https://www.intechopen.com/books/extracorporeal-membrane-oxygenation-advances-in-therapy. Accessed 23 June 2017.
22. Tramm R, Ilic D, Davies AR, Pellegrino VA, Romero L, Hodgson C. Extracorporeal membrane oxygenation for critically ill adults. Cochrane Database Syst Rev. 2015;(1):CD010381.
23. Makdisi T, Makdisi G. Extracorporeal membrane oxygenation support: ethical dilemmas. Ann Transl Med. 2017;5(5):112–116.

With thanks to James Farndon at jfarndondesign for the figures.

Coagulation

Introducing viscoelastic haemostatic assay-guided blood product transfusion into your hospital

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INTRODUCTION

There are always challenges when new technology is introduced. In 2015, our hospital campus decided to integrate thromboelastometry into our practice by way of rotational thromboelastometry, ROTEM®. The term “viscoelastic haemostatic assays” (VHA) is used to describe the point-of-care coagulation testing used in patients with clinically significant bleeding to guide whether the patient requires tranexamic acid, cryoprecipitate, fresh frozen plasma (FFP) or platelets. There are two VHA-technologies in use: ROTEM® and thromboelastography, TEG®. There was no previous experience of VHA in any speciality across any of the four hospitals that are co-located on the campus (adult, children’s, women’s and private hospital). We were the first centre in Australia to purchase the new generation ROTEM® sigma machine. With this system, a whole-blood sample is added to a cartridge and a result is available in less than 10 minutes. This test can be performed with minimal training. This has been very useful on our campus and has added a new dimension to the analysis and management of the bleeding patient. This article will examine the science of VHA and how it was introduced on our campus.

PART ONE

WHAT ARE VISCOELASTIC HAEMOSTATIC ASSAYS?

VHA is not a new concept, it was developed during World War II and was described by Hartert in 1948[1] when he used the viscoelastic properties of blood to measure coagulation. The technology has been widely used in Europe for the last 20 years[2], initially for hepatic patients[3] and later in cardiac surgical patients and today to help manage general surgical, trauma and obstetric patients.

ROTEM® analyses whole blood and creates a graphical representation (the Temogram) of clot formation and clot lysis. It provides information more aligned with the cell-based model of coagulation.

- ROT – refers to the rotational aspect of the test (some technologies use laminated plates rather than rotational technology).
- TEM – refers to the Temogram that is produced, which is a graphical representation of the viscoelastic forces produced during clot formation and clot lysis.

In 2015, newly developed cartridge-based VHA[4] became available, including the TEG6® and ROTEM® sigma machines. This significant advance in VHA technology means that testing can now be easily performed by staff present at the point of patient care.

THE BENEFITS OF VISCOELASTIC HAEMOSTATIC ASSAYS

VHA have the potential to reduce the use of unnecessary blood products thereby saving resources, money and potentially improving patient outcomes. When using massive transfusion protocols (MTPs), most centres use ratio of 1:1:1 [FFP: platelets: red blood cells (RBC)]. Recent studies suggest higher ratios might be beneficial[5,6] as transfusion-related adverse events, such as transfusion-related acute lung injury, are more common with increasing volumes of blood product transfused[7,8]. Balancing optimal transfusion ratios with transfusion-related adverse events is an inherent challenge when using MTPs.

Traditionally MTPs have dictated the products that a patient may need, accompanied by traditional coagulation testing. In the critically bleeding patient there is still a place for a MTP initially, to allow red cells to be released, with VHA guiding the use of other products. VHA reveal underlying clotting abnormalities that can be corrected before results of traditional activated partial thromboplastin time (APTT), international normalised ratio (INR) or fibrinogen testing[9] can be made available. The results allow transfusion to be tailored to the individual clinical scenario.

THE SCIENCE OF VISCOELASTIC HAEMOSTATIC ASSAYS

The following information is sourced from the ROTEM® company, research conducted by the National Health Service in Scotland[10] and other supporting documents[11-15].

How do you perform a VHA test using the ROTEM®?

A sample of the patient's blood is added to a blue-top citrate-containing coagulation tube. The tube is inverted and placed within a cartridge that has five adjacent cuvettes/cups. Blood is channelled along the cartridge to fill the cuvettes, each of which assesses a different aspect of haemostasis, including a control. The cuvettes contain a reagent that activates clotting. Some also have an additive that inhibits one component of coagulation, thus isolating and assessing a separate component of haemostasis.

Each cuvette has a pin suspended by a torsion wire. During the test the pin oscillates within the cup. While the blood is liquid this rotational movement is unrestricted, but as the blood clots the rotation of the pin is increasingly restricted. This resistance to rotation is detected, measured and displayed as a Temogram. The Temogram displays amplitude versus time. The amplitude is a measure of clot strength – the bigger the amplitude, the stronger the clot.

How do you interpret a ROTEM®?

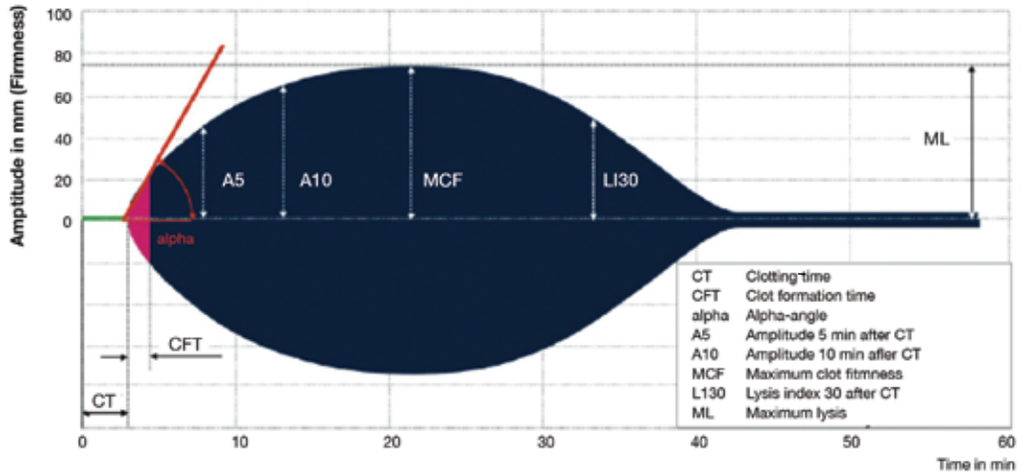
The ROTEM® sigma tests: Four tests are run simultaneously. Each one assesses a different aspect of coagulation. For cardiac surgery patients, a HEPTEM cartridge is used (which tests EXTEM, FIBTEM, INTEM, HEPTEM) while the APTEM cartridge is usually used in non-cardiac patients (tests EXTEM, FIBTEM, INTEM, APTEM), see table 1.

Table 1.

TEST	SIMILAR TRADITIONAL TEST	INFORMATION
EXTEM	PT	Assess EXTrinsic pathway
FIBTEM	Fibrinogen level	Assess FIBrinogen contribution
INTEM	aPTT	Assess INTrinsic pathway
HEPTEM	aPTT with heparin removed	Assess the effect of heparin SAME test as INTEM without the effect of heparin
APTEM	PT with tranexamic acid added	Rapid detection of lysis SAME test as EXTEM test with antifibrinolytic added

The TEMOGRAM[16]: Each of the ROTEM® tests produces a separate Temogram. The key parameters to note in a Temogram are shown in figure 1.

Figure 1. Temogram[15, 17]



CT[RR1]: Clotting Time – measured in seconds. Time from when the test commences to when the amplitude of the Temogram reaches 2mm. It indicates adequacy of clot initiation. Reasons the CT could be prolonged: low fibrinogen, clotting factor deficiencies, anti-coagulants
A5: Amplitude at 5 minutes – measured in mm. It is a measure of clot strength. The two main contributors to clot strength are fibrinogen and platelets. Thus, a low amplitude could be due to low fibrinogen, low platelets, both low fibrinogen and low platelets, and/or hyperfibrinolysis.
MCF: Maximum Clot Firmness – measured in mm. This is a measure of the maximum amplitude (maximum clot strength) achieved on the Temogram. This usually occurs after 30-40 mins. However, assessing the amplitude at 5 minutes (A5) provides sufficient information about clot strength on which clinical decisions can be based.
ML: Maximum Lysis – measured as a percentage (%). It assesses the percentage decrease in amplitude of the Temogram relative to the MCF over an hour. A decrease of greater than 5% indicates hyperfibrinolysis.

PART TWO

THE INTRODUCTION OF VISCOELASTIC HAEMOSTATIC ASSAYS INTO CARDIOTHORACIC THEATRES AND THE CARDIAC INTENSIVE CARE UNIT, INCLUDING THE DEVELOPMENT OF OUR LOCAL ALGORITHM

In early 2015 we trialled the TEG6® and ROTEM® technologies. We were guided by haematologists to purchase the ROTEM® system. The first two ROTEM® sigma machines were installed in the fourth quarter of 2015. The initial algorithm used was chosen by senior clinicians. This was the Scottish National Health Service (NHS) algorithm, developed by Professor Nimmo (Appendix 1[18]). No education was provided prior to the arrival of the machines as there was no on-campus expertise, nor any reason to expect that implementation would be problematic.

In the first quarter, we paradoxically experienced an increase in blood product transfusion rates as clinicians followed old and new guidelines for transfusion. In response to feedback, a simplified local algorithm (figure 2) was created with an accompanying traffic light label (figures 3 and 4) for communicating results. This made it easier for junior staff to make clinical decisions based on test results. The key data is transcribed from the ROTEM® screen onto the label and the JMO or nurse are then able to circle the range identified and communicate red zone results with appropriate urgency.

Figure 2. Cardiac and vascular ROTEM® transfusion algorithm

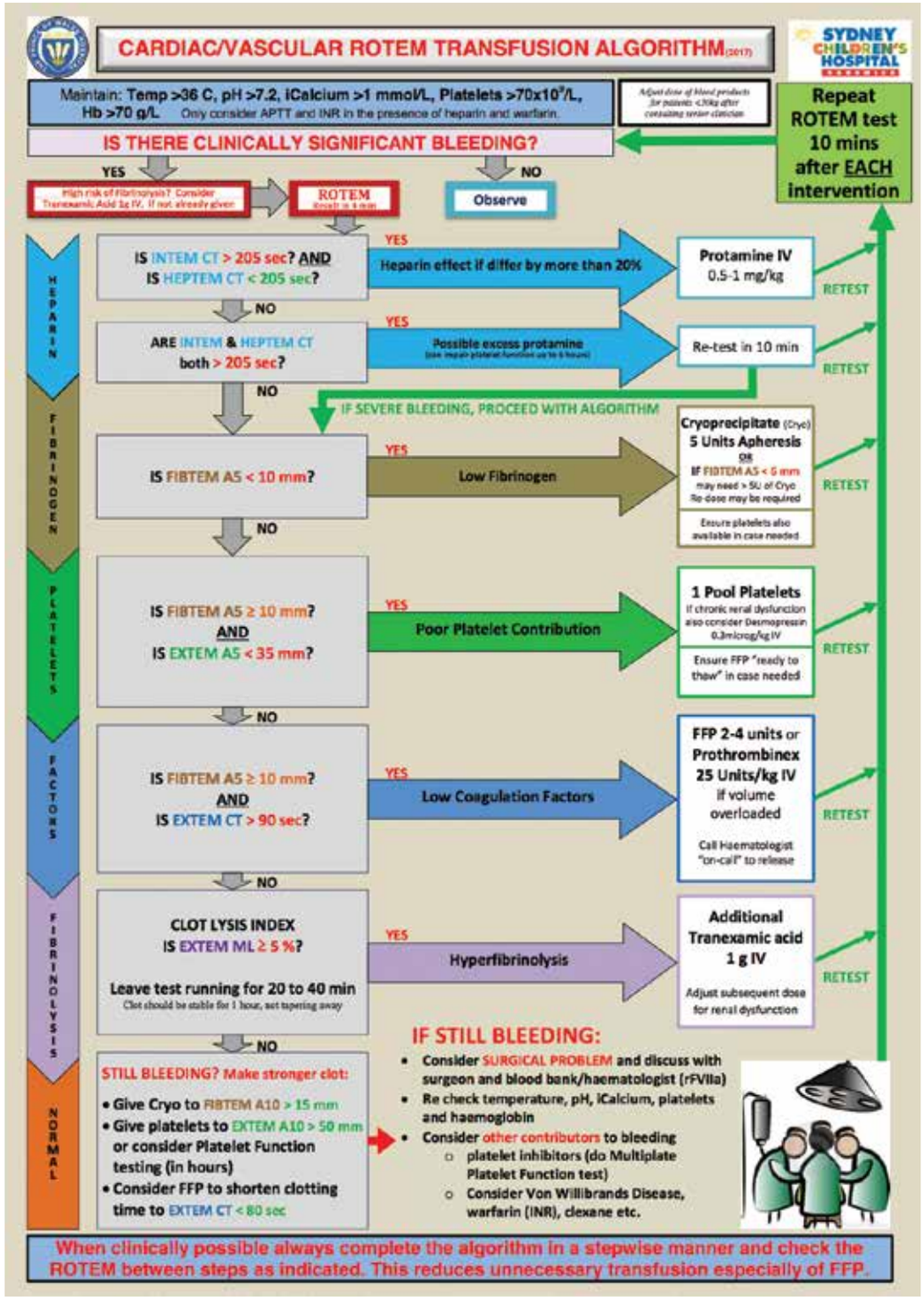


Figure 3. ROTEM® analysis and treatment plan label

Please stick this label in the patients progress notes

ROTEM ANALYSIS AND TREATMENT PLAN

**Nurse or JMO to circle algorithm used then insert results from ROTEM
Next circle range (action red range) and use algorithm to create a plan.**

Date: / / Time:

ALGORITHM USED (circle one):
CARDIAC/VASCULAR or GENERAL/OBSTETRIC

- For CARDIAC/VASCULAR start here and do all:

INTEM CT = ... Below 205 / 205 & Above
HEPTEM CT = ... Below 205 / 205 & Above

- For GENERAL/OBSTETRIC start here (this section only):

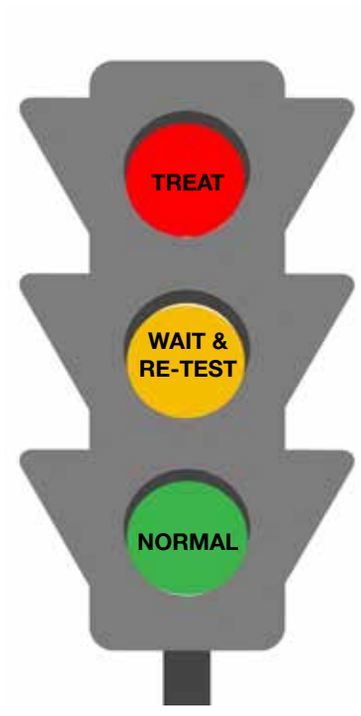
EXTEM A5 = ...Below 35 / 35-40 / Above 40
FIBTEM A5 = ...Below 10 / 10-15 / Above 15

EXTEM CT =.....Below 80 / 80-90 / Above 90
EXTEM ML =.....Below 5 / 5 & Above

Management Plan: .....

Please stick this label in the patients progress notes

Figure 4. Traffic light guide



As education continued and interpretation of algorithms was refined, there was a reduction in transfusion rates over the subsequent quarters throughout 2016. This reflected acceptance that there was scope for improvement as well as familiarity by staff with the indications, technology and interpretation of the cardiac transfusion algorithm.

Specific to the cardiac scenario is the option to check a ROTEM® during rewarming on cardiopulmonary bypass whereby normal clot strength, as measured at EXTEM and INTEM A5, is reassuring. The ROTEM® test should be performed at least ten minutes after the initial dose of protamine to look for effective reversal of heparin and guide product transfusion.

LOCAL DATA BEFORE AND AFTER THE IMPLEMENTATION OF ROTEM®

To assess if the implementation of ROTEM® had been successful, Ethics Committee approval was obtained and a local study was conducted. Data was collected on blood product use in all patients undergoing cardiac surgery from April 2015 to the end of December 2016. We examined the use of RBC, FFP, platelets and cryoprecipitate, and the incidence of reoperation for bleeding. Costs of blood product use were estimated. The implementation period from arrival of the ROTEM® machine during the fourth quarter of 2015, to the development and education around our local algorithm took nine months. We compared data for the two quarters prior to the arrival of the ROTEM® machine, to the two quarters after the nine-month implementation period.

We included a total of 435 patients; 204 in the pre-ROTEM® implementation group and 231 in the post-ROTEM® implementation group. After implementation of the algorithm, fewer patients required FFP (43/204 (21%) versus 26/231 (11.2%) Chi^2 = 7.8, P=0.005) (figure 5) and pooled platelets (61/204 (30%) versus 44/231 (19%) Chi^2 = 4.24, P=0.04) (figure 6). There was no statistically significant change in RBC transfusion (103/204 (50%) versus 95/231 (41%), P=0.05) (figure 7) or cryoprecipitate transfusion (12/240 (6%) versus 16/231 (7%), Chi^2 0.16, P=0.67) (figure 8) or the number of cases requiring surgical re-exploration for bleeding (6/204 (3%) versus 3/231 (1%), P=0.23) (figure 9). The calculated cost of blood products used went from a median of $803.88 to $401.94 per patient (P=0.12).

Figure 5. FFP transfusion rate – (43/204 (21%) versus 26/231 (11.2%) Chi^2 = 7.8, P=0.005)

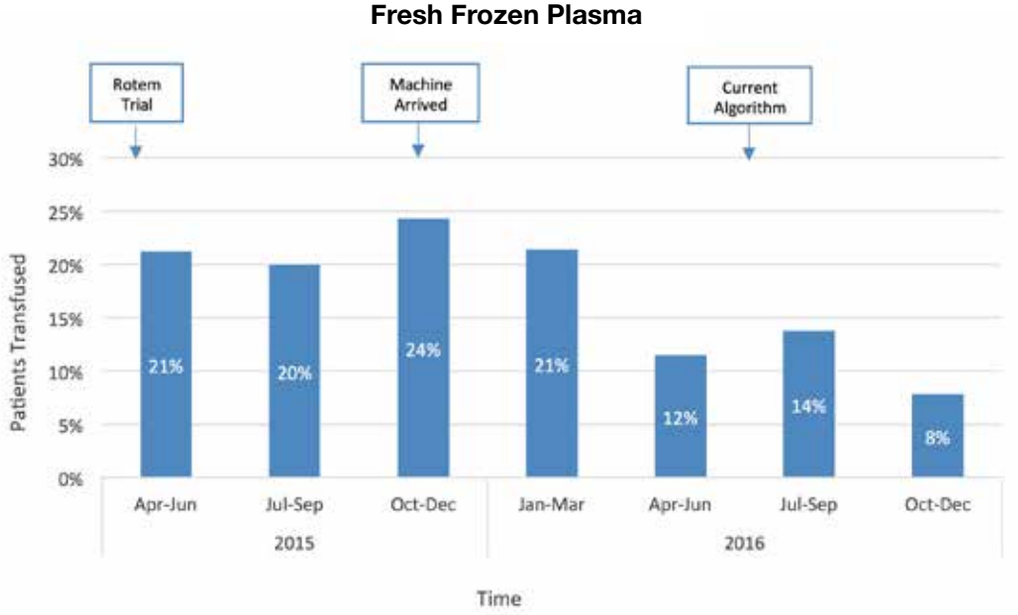


Figure 6. Pooled platelets transfusion rate – (61/204 (30%) versus 44/231 (19%), Chi^2 = 4.24, P=0.04)

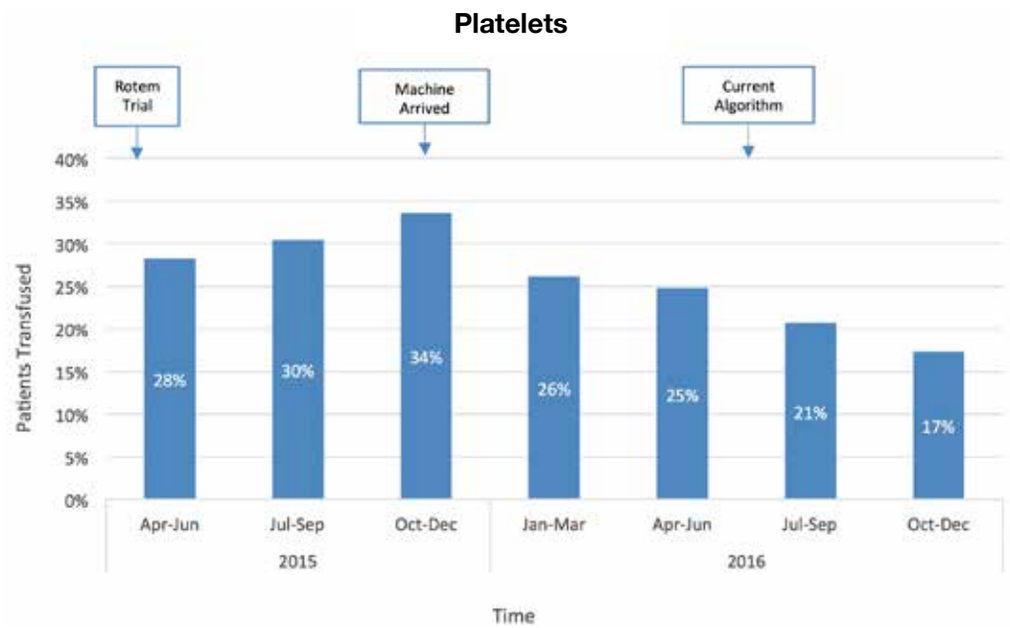


Figure 7. RBC transfusion rate – (103/204 (50%) versus 95/231 (41%), P=0.05)

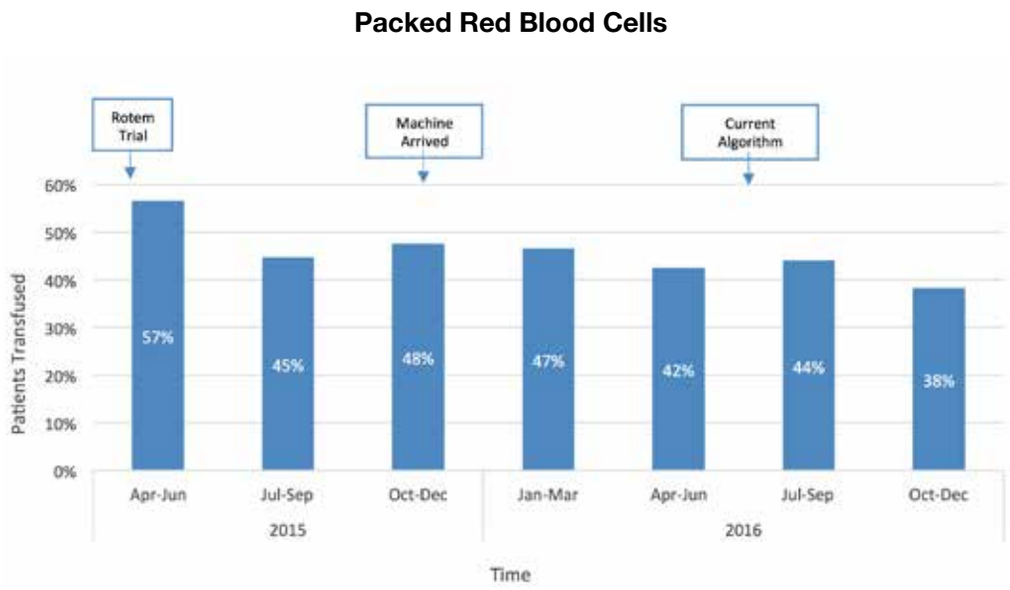


Figure 8. Cryoprecipitate transfusion rate – (12/240 (6%) versus 16/231 (7%), Chi² 0.16, P=0.67)

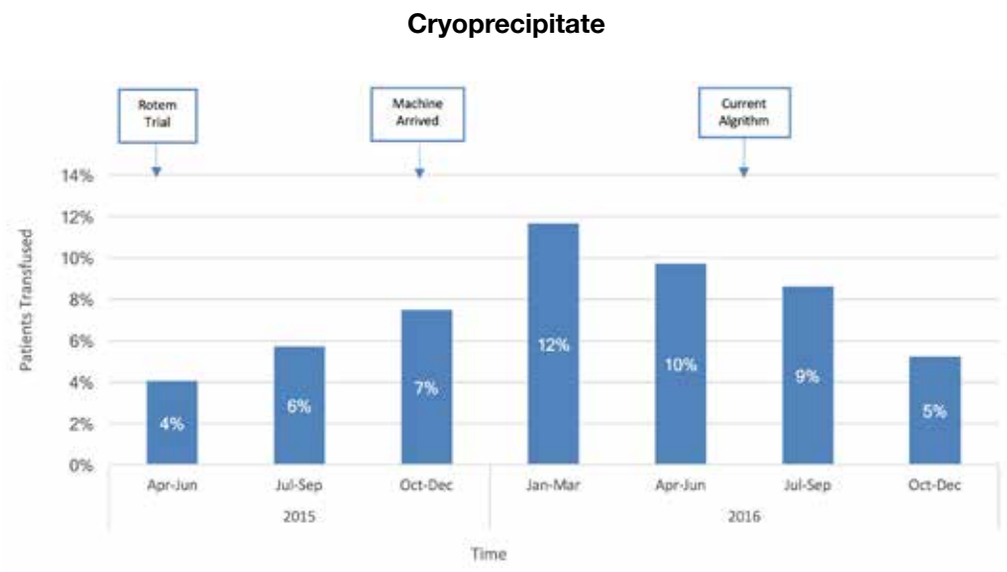
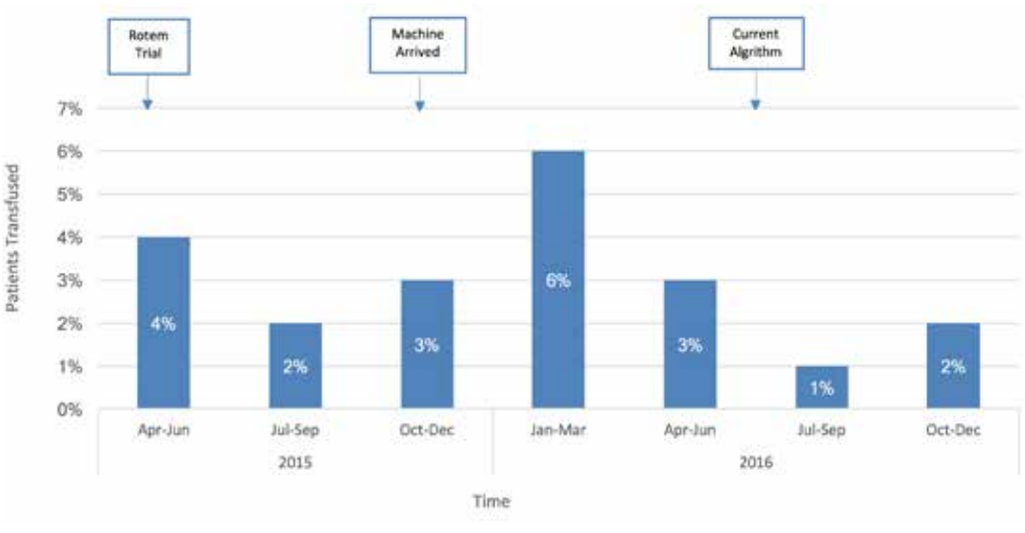


Figure 9. Reoperation for bleeding rate – (6/204 (3%) versus 3/231 (1%), P=0.23)



The introduction of a ROTEM®-guided algorithm for blood product transfusion resulted in a statistically significant reduction in patients receiving FFP and platelets. An increase in cryoprecipitate use was anticipated by the new algorithm but did not occur. There was no statistically significant change in the transfusion of RBCs. We found a non-statistically significant reduction both in the number of surgical cases re-explored for bleeding and the median cost of blood transfusion. Although neither reduction was statistically significant, our estimates of the magnitude of these reductions would be clinically significant if confirmed in a larger sample. We recommend further data be sought in this regard. These results support the use of the ROTEM®-guided blood transfusion algorithm in management of bleeding patients in cardiac surgery.

PART THREE

THE EVIDENCE FOR VHA IN NON-CARDIAC SURGICAL PATIENTS

Viscoelastic haemostatic assays in obstetrics

There is some evidence to support the use of VHA as an aid to guiding blood product administration in major obstetric haemorrhage. The obstetric patient is unique in her pro-coagulant state. Traditionally the management of major obstetric haemorrhage has been the formula-driven MTP – a recommendation based on evidence extrapolated from observational studies in the non-pregnant population (PROMMTT)[19] and the military setting[20,21]. This formulaic approach means that obstetric patients receive products from donors with comparatively reduced fibrinogen levels and other clotting factors.

A group at Liverpool Women's Hospital[22] in the United Kingdom have demonstrated the superiority of VHA-guided fibrinogen concentrate administration compared to use of a MTP in the treatment of major obstetric haemorrhage. The fibrinogen concentrate group received fewer RBCs, FFP, platelets and cryoprecipitate, as well as less transfusion-associated circulatory overload and a non-significant reduction in hysterectomy. They have since expanded on their findings with a four-year retrospective analysis of VHA-guided fibrinogen concentrate, with further convincing evidence of improved clinical outcomes, and reduced transfusion rates compared to patients who had received blood products directed by a MTP[23].

Viscoelastic haemostatic assays in trauma settings

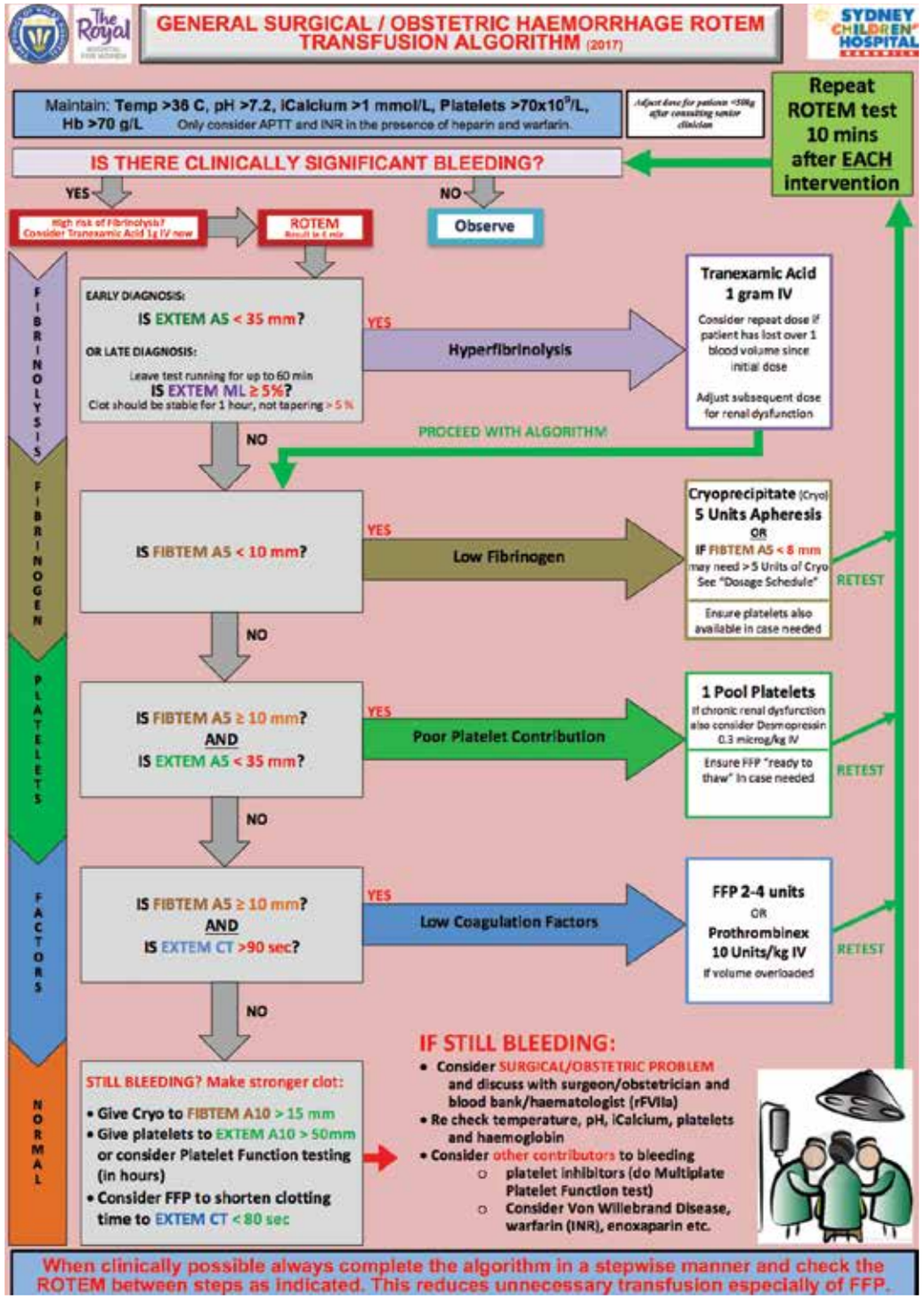
The trauma patient presents a unique situation where haemorrhage can be complicated by a multi-factorial trauma-induced coagulopathy (TIC)[16,20,24,25]. The best transfusion strategy to manage this is still not clear. Similar to the obstetric patient, MTPs are used, although debate surrounds the optimal ratio of blood products[5,6]. More recently, VHA-guided algorithms have been incorporated. These are used exclusively, or in combination with a MTP, whereby resuscitation begins with a MTP and then transitions to VHA-guided management once available.

VHA can quickly identify the specific coagulopathy, allowing a targeted transfusion approach, and avoiding transfusion where no coagulopathy exists. Many European trauma resuscitation protocols use factor concentrates in conjunction with a VHA-guided algorithm. This approach allows correction of coagulopathy, while potentially reducing transfusion-related adverse events and volume overload[26-28]. Gonzalez et al in 2016 found improved mortality with a VHA-guided versus standard blood test-guided MTP[29]. A systematic review in 2014 of observational studies showed VHA offer early diagnosis of TIC, and may predict transfusion and mortality in trauma[30]. European and American trauma transfusion guidelines recommend a VHA-guided transfusion protocol[31,32].

THE DEVELOPMENT OF AN ALGORITHM FOR GENERAL SURGICAL AND OBSTETRIC PATIENTS

With data supporting the ROTEM®-guided cardiac transfusion algorithm, the next focus was on developing a general surgical and obstetric algorithm ready for the arrival of machines in general areas. In early 2017 the cardiac, general and obstetric anaesthetists collaborated to develop this second algorithm with significant assistance from the intensivists and haematologists (figure 10). Two new ROTEM® sigma machines have been installed in the general theatres and obstetric theatres, networked to the intensive care unit and delivery suite respectively. Furthermore, the machines could eventually be networked to paediatric intensive care where there is evolving data for the use of ROTEM® in children as young as three months[33-35].

Figure 10. General surgical and obstetric haemorrhage ROTEM® transfusion algorithm



Our general and obstetric algorithm development centred around algorithms already in place at King Edward Memorial Hospital (Perth, Western Australia) and Gold Coast University Hospital (Queensland). Since development we have seen our algorithm implemented for use in other centres in the Sydney area, allowing clinicians working at multiple sites familiarity and simplicity of interpretation. It will also facilitate collaboration of research and refinements of the algorithm.

Step-by-step guide to the general and obstetric algorithm

1. PHYSIOLOGICAL TARGETS

Ensure that physiological targets are within standard limits.

2. PRIORITISE THE MANAGEMENT OF HYPERFIBRINOLYSIS

We chose to include a clause allowing tranexamic acid to be given early if there is a high likelihood of hyper fibrinolysis. It is futile to give fibrinogen if it is going to be rapidly consumed. The WOMAN trial[36] supports the use of early tranexamic acid in post-partum haemorrhage. Early low values of clot strength in the extrinsically activated assay (EXTEM A5 <35 mm) predicts fibrinolysis, thus assisting in its early detection and management[37].

3. GIVE FIBRINOGEN EARLY

Fibrinogen has a key role in coagulation, and is commonly the first to fall to critical levels in major haemorrhage[38]. Obstetric patients in the third trimester have a mean fibrinogen of 4-6 g/L, compared to the non-pregnant patient of 1.5-4 g/L[39]. A low fibrinogen is strongly predictive of significant postpartum bleeding[21,40,41]. If the amplitude of the fibrinogen Temogram is less than 10 mm at five minutes, this correlates to a fibrinogen level of <2 g/L[41]. We chose a FIBTEM A5 <10 mm as the trigger for fibrinogen administration. We administer cryoprecipitate because fibrinogen concentrate is not yet available to us. In Europe, fibrinogen concentrate as an alternative to cryoprecipitate is widely available for use in the setting of major haemorrhage.

For obstetric haemorrhage some centres[22] use a higher FIBTEM figure (A5 <12 mm) to trigger the transfusion of fibrinogen. We chose to use the same FIBTEM trigger (A5 <10 mm) for all patients (obstetric, general and cardiac) based on the premise that adult clotting will be sufficient at that level of fibrinogen (i.e. at 2 g/L). This also allowed us to use the same ROTEM® analysis/treatment plan labels for both the obstetric/general and cardiac transfusion algorithms.

We have developed a cryoprecipitate dosing schedule (see below) to achieve a FIBTEM greater than 10 mm. The lower the FIBTEM result, the more cryoprecipitate is required to bring it up to 10 mm. This will then be audited and reviewed regularly.

TABLE 2. CRYOPRECIPITATE DOSING SCHEDULE

GENERAL SURGICAL / OBSTETRIC HAEMORRHAGE ROTEM TRANSFUSION ALGORITHM (2017)

CRYOPRECIPITATE (Apheresis) DOSING SCHEDULE

If the Fibtem A5 is:	Dose of **Apheresis** Cryoprecipitate
>9 mm	NONE
8-9 mm	5 U per 70 kg
6-7.9 mm	8 U per 70 kg
4-5.9 mm	10 U per 70 kg
< 4 mm	12 U per 70 kg

IF FIBTEM A5 is less than 6 please ensure that platelets are readily available as they may be indicated on retesting after dose of fibrinogen.

4. ASSESS THE NEED FOR PLATELETS

Both platelets and fibrinogen contribute to clot strength in the extrinsically activated assay. If the fibrinogen level is adequate (FIBTEM A5 >10 mm) and the amplitude of the extrinsic pathway Temogram is less than 35 mm at five minutes, then an EXTEM A5 <35 mm demonstrates inadequate platelet contribution to clot strength. One pooled bag of platelets should be transfused. Ideally a corroborative platelet count should be measured. Platelets should be maintained at >50x10^9/L. To achieve this in patients who are actively bleeding, platelets should be infused when the platelet count falls below 70x10^9/L[42,43].

5. CLOTTING FACTORS – ASSESSED AND TREATED ONLY AFTER NORMALISING CLOT STRENGTH

Clotting factors should be the last to be assessed as they are in the greatest reserve. A low fibrinogen can prolong the clotting time in the extrinsic pathway Temogram, EXTEM CT, thus it is important to correct the fibrinogen (FIBTEM A5 >10 mm) before interpreting and acting on the EXTEM CT result. This is why the algorithm should be followed in a sequential manner. An EXTEM CT greater than 90 seconds in the setting of a FIBTEM A5 >10 mm would suggest deficient coagulation factors. In this case four units of FFP, or prothrombin complex concentrate (PCC) 10 units/kg is indicated. We chose a low dose of PCC due to the possible associated risk of a thrombotic/thromboembolic event. The PCC dose could always be repeated if the EXTEM CT remains prolonged.

6. MAKE A STRONGER CLOT

If bleeding continues despite all parameters being in the "orange zone", the algorithm recommends further administration of coagulation products. This creates the truly optimal clot and once this is achieved the surgeon or obstetrician needs to consider surgical or obstetric causes other than coagulopathy. The haematologists should also be involved in case of any underlying clotting deficiency or anticoagulant medications that need to be managed.

PART FOUR

THE JOURNEY TO SUCCESS: TIPS FOR INTRODUCING VISCOELASTIC HAEMOSTATIC ASSAYS INTO YOUR CENTRE

In early 2015 we trialled two cartridge-based VHA machines: the ROTEM® sigma and the TEG6®. During the trial phase, transfusion rates trended down, possibly as we reflected on our practice. We were guided by the haematologists to purchase the pin and cup technology of ROTEM® as opposed to resonance technology of TEG6® or the old pipetting machines[44] (such as the ROTEM® delta) because of the larger body of evidence at the time and the simplicity of use.

In December of 2015, two ROTEM® machines were installed, one in the cardiothoracic theatres and one in the adjoining cardiac intensive care unit. Following this, the ROTEM® company began running information sessions with the consultant anaesthetists and intensivists to familiarise them with the technology. The senior clinicians agreed, following a presentation by Professor Nimmo, to use the Scottish NHS-developed algorithm (Appendix 1[18])[1], for interpretation of the Temograms.

No reduction in transfusion rates occurred in the first quarter of the machine's use. In fact, there was a paradoxical increase, perhaps as we continued with the historical treatment of the bleeding patient, while also transfusing what the Temogram interpretation was guiding. Education sessions continued and targeted both senior and junior staff, including anaesthetists, intensivists, surgeons, perfusionists and nurses, which allowed staff to become more familiar with the technology. Mentors were identified in the departments, being those who had shown special interest in the project, allowing for education to continue in the absence of the equipment representatives.

Despite the education and the evidence published by national and international studies, it still took time for the clinical body to acknowledge that there was room for a reduction in the rates of transfusion. The main area in which we could have done better was in the education of medical staff. Because the technology was driven from cardiac theatres, the initial focus was in the intraoperative setting, with uptake by anaesthetists and perfusionists. We should have engaged the junior staff in the intensive care unit earlier – they are usually responsible for the decision to transfuse blood products. Some other centres have initiated VHA testing in the intensive care unit. The important learning point is early education of all relevant craft groups. Management of bleeding in the post cardiac surgical patient can be stressful, and some staff felt overwhelmed by the new concepts. It was understood that it would take time for staff to feel comfortable with this new technology.

The initial algorithm chosen by the senior staff had been successful in the Scottish centre which had used ROTEM® for 20 years. Their staff were familiar with ROTEM®-guided transfusion. In 2016, as our transfusion

data became available and showed an increase in transfusion, we decided to rethink our approach. We reflected on the cause of the initial worsening transfusion rates. The main problem appeared to be the algorithm that had been chosen. The NHS algorithm was multi-dimensional and required interpretation of multiple aspects of the Temogram to create a treatment plan. Senior consultants agreed it was appropriate for our clinical needs, but some staff struggled to follow it. Subsequently, a local second-generation algorithm was developed, which was a single dimensional model, similar to other Australian centres. The local algorithm required sequential interpretation whereby only one Temogram was examined at any given step, simplifying the process of interpretation. There was input from anaesthetists, perfusionists, intensivists and haematologists in development of this algorithm.

The new algorithm was paired with a label that translated the complicated results from the ROTEM® into a "traffic light" system allowing documentation of results and the accompanying treatment plan. The label visually represents the escalation ranges, whereby nursing staff complete the label and circle the escalation range. Results were assigned as green for accepted values, orange for "watch and re-test" values and red for values requiring action using the algorithm. The label was also an opportunity to document the process of using the ROTEM® in a systematic way that ensured appropriate goal-directed therapy and good clinical handover. On our campus, these labels have been placed in the patient's anaesthetic chart or progress notes. Ideally they would always be placed in the patient's progress notes.

The algorithm and accompanying label were developed locally between the anaesthetists and perfusionists in the context of cardiac surgery. The plan was to optimise the ROTEM® project in cardiac services before rolling out a separate algorithm for general and obstetric cases across the other hospital areas.

Simplifying the algorithm and adding the traffic light labels turned the project into a success. It became apparent that simply displaying the algorithm was not enough. Therefore, we not only redesigned the cardiac algorithm, and subsequently developed the general and obstetric algorithm, to be more user friendly, we also created a ROTEM® workstation (figure 11). The workstation was designed to include a collection of infographics that relate to the bleeding patient, as well as reminders of things that needed to be considered by clinicians operating the analyser. In consultation with the haematologists, additional information included the cryoprecipitate dosing guidelines, a quick reference guide for reversal of anticoagulants, and a series of cartoons that made the wall more engaging were introduced. Anecdotal evidence has demonstrated that more clinicians, both medical and nursing, are engaged with ROTEM® since the workstations were created.

Figure 11. ROTEM® workstation

Engaging the nurses was a key part of the success of the ROTEM® project. It was acknowledged early on that while the medical staff needed to engage with the interpretive side of the Temogram, it would mostly fall to nursing staff to physically run the tests and provide the results needed for interpretation. Subsequently, when education was rolled out to the junior medical staff, it was also offered to senior nurses so that an understanding of the technology and how results are interpreted transcended the specialties. This education was continued by senior nurse educators to junior nursing staff as the use of ROTEM® became more popular.

By teaching nursing staff to run the ROTEM® tests, medical staff are available for other duties, acknowledging that it is appropriate for a nurse to run the sample. This is particularly true in the case of cardiac surgical patients, where the times when the tests are run are usually times that require the senior medical officer's attention, such as bleeding after separation from cardiopulmonary bypass. As such, delegating nursing staff to run the tests facilitates the generation of results without compromising patient care. The machines have been networked to the monitors in the cardiac theatres to facilitate accurate communication of the graphs to clinicians. In much the same way as running an arterial blood gas, the creation of a label was a way for nurses to accurately communicate the results of the test. It has also allowed for some nurses to engage with the algorithms and therefore understand the reasons behind why products are transfused. This enables them to pre-empt the intervention and prepare equipment necessary for what the Temogram interpretation suggests, particularly where the results fall in the red zone and need urgent attention; for example, preparing platelet giving sets where it is recommended that platelets be transfused.

Our nursing staff in cardiothoracic theatres and the intensive care unit are responsible for the quality control of the ROTEM® sigma machine. Testing occurs weekly and is performed early in the day so that the machines are available and functioning correctly when needed to assess post-bypass and post-surgical patients. In our unit, anaesthetic nurses run quality control testing once per week on a Monday. This test takes about 10 minutes three out of four Mondays. On the fourth week, additional ROTROL testing is done to calibrate the machine by way of biological solutions[45]. The process takes half an hour, all of which is documented in a ROTEM® roster and log book. Quality control would need to be done more frequently if we were doing more tests – some large centres implement daily testing. Maintaining the machines has given nursing staff ownership over the equipment and helped remove some of the mystery that occurs with new technology.

KEY POINTS TO FACILITATE INTRODUCING VHA TESTING WERE:

- To effect change, the clinician must be convinced that there is scope for improvement, in this case that there was scope for improving the rates of transfusion.
- Early evidence-based education is important, before the technology arrives.
- An algorithm with sequential logic, using one aspect of the Temogram at a time makes it easier for clinicians without prior experience.
- Engaging the nursing staff is key.
- Encouraging use of the labels and "traffic light" escalation ranges enhances rapid communication of abnormalities and communication with the intensive care unit.

CONCLUSION

VHA testing is now cartridge-based and can be run at the bedside by any clinician with minimal training. In 2016 we implemented ROTEM® into cardiac surgery and significantly reduced our use of FFP and platelets. A second local algorithm is now being implemented for general surgical and obstetric patients. The development of a sequential algorithm, early education of all staff and pairing the algorithm with our traffic light label system have been instrumental in enabling success on our campus.

ACKNOWLEDGEMENTS

The entire ROTEM® project would not have been possible without the generous donation from the McPherson family. Their generosity in purchasing the initial ROTEM® technology for our campus has helped many children and adults and brought quality improvements which continue day by day.

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Dr James Winearls, Intensivist, Gold Coast Hospital, Queensland, Australia.

Dr Roger Browning, King Edward Memorial Hospital, Western Australia, Australia.

Soft copies of the algorithms are available.
Email bluebook@anzca.edu.au.

REFERENCES

1. Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. Am J Hematol. 2014;89(2):228–232.
2. Napolitano LM. Advances in trauma – 2016: goal zero preventable deaths after injury. Crit Care Clin. 2017;33(1):xi–xiii.
3. Thomas W, Wyatt M. Basic Surgical Principles. London: Elsevier Health Sciences, 2015.
4. Kaplan J, Augoustides J, Manecke G, Maus T, Reich D. Kaplan's Cardiac anesthesia. 7th ed. Philadelphia: Elsevier, 2017.
5. Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg. 2008;248(3):447–458.
6. Baraniuk S, Tilley BC, del Junco DJ, Fox EE, van Belle G, Wade CE, et al. Pragmatic randomized optimal platelet and plasma ratios (PROPPR) trial: design, rationale and implementation. Injury. 2014;45(9):1287–1295.
7. Clifford L, Jia Q, Subramanian A, Yadav H, Wilson GA, Murphy SP, et al. Characterizing the epidemiology of postoperative transfusion-related acute lung injury. Anesthesiology. 2015;122(1):12–20.
8. Clifford L, Jia Q, Yadav H, Subramanian A, Wilson GA, Murphy SP, et al. Characterizing the epidemiology of perioperative transfusion-associated circulatory overload. Anesthesiology. 2015;122(1):21–28.
9. Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, et al. Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med. 2011;39(12):2652–2658.
10. Craig J A-IR, Bhattacharya S, Downie S, Duffy S, Kohli H, et al. The clinical and cost effectiveness of thromboelastography/thromboelastometry: health technology assessment report. Edinburgh: NHS HTA Programme, 2008.
11. ROTEM®. Sigma, proven technology, haemostasis information, algorithms [Internet]. 2017. From: https://www.rotem.de/en/products/rotem-sigma/. Accessed 17 October 2017.
12. ROTEM®. Thromboelastometry, TEG®, haemostasis disorder [Internet]. 2017. From: https://www.rotem.de/en/methodology/thromboelastometry/. Accessed 17 October 2017.
13. ROTEM®. Interpretation, assessment, clot firmness, NCF [Internet]. 2017. From: https://www.rotem.de/en/methodology/interpretation/. Accessed 17 October 2017.
14. ROTEM®. Analysis, haemostasis information, measurement results [Internet]. 2017. From: https://www.rotem.de/en/methodology/analysis/. Accessed 17 October 2017.
15. Health Policy Advisory Committee on Technology. Rotational thromboelastometry (ROTEM) targeted therapy for coagulation management in patients with massive bleeding [Internet]. 2012. From: https://www.health.qld.gov.au/__data/assets/pdf_file/0023/427145/wp024.pdf. Accessed 17 October 2017.
16. Kauvar DS, Wade CE. The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. Crit Care. 2005;9(Suppl 5):S1–9.
17. Winearls J, Mitra B, Reade MC. Haemotherapy algorithm for the management of trauma-induced coagulopathy: an Australian perspective. Curr Opin Anaesthesiol. 2017;30(2):265–276.
18. Moores C, Nimmo A. Core topics in vascular anaesthesia. 1st ed. Cambridge: Cambridge University Press, 2012.
19. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127–136.
20. Reed MJ, Nimmo AF, McGee D, Manson L, Neffendorf AE, Moir L, et al. Rotational thrombolelastometry produces potentially clinical useful results within 10 min in bleeding emergency department patients: the DEUCE study. Eur J Emerg Med. 2013;20(3):160–166.
21. Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost. 2007;5(2):266–273.
22. Mallaiah S, Barclay P, Harrod I, Chevannes C, Bhalla A. Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage. Anaesthesia. 2015;70(2):166–175.
23. Smith RMS, Chevannes C, McNamara H. Lessons from four years' experience in the use of ROTEM-guided fibrinogen concentrate in major obsteric haemorrhage. Int J Obstet Anesth. 2017;31:S7.
24. Tien HC, Spencer F, Tremblay LN, Rizoli SB, Brenneman FD. Preventable deaths from hemorrhage at a level I Canadian trauma center. J Trauma. 2007; 62(1):142–146.
25. Cothren CC, Moore EE, Hedegaard HB, Meng K. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. World J Surg. 2007;31(7):1507–1511.
26. Schöchl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care. 2010;14(2):R55.
27. Innerhofer P, Westermann I, Tauber H, Breitkopf R, Fries D, Kastenberger T, et al. The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Injury. 2013;44(2):209–216.
28. Ponschab M, Voelckel W, Pavelka M, Schlimp CJ, Schochl H. Effect of coagulation factor concentrate administration on ROTEM® parameters in major trauma. Scand J Trauma Resusc Emerg Med. 2015;23:84.
29. Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A, et al. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. Ann Surg. 2016;263(6):1051–1059.

30. Da Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NK. Effect of thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. Crit Care. 2014;18(5):518.
31. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care. 2016;20:100.
32. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. Anesthesiology. 2015;122(2):241–275.
33. Kim J SY, Kil H, Park M, Lee J. Reference intervals of thromboelastometric evaluation of coagulation in pediatric patients with congenital heart disease: a retrospective investigation. Med Sci Monitor. 2016;22:3576–3587.
34. Oswald E, Stalzer B, Heitz E, Weiss M, Schmugge M, Strasak A, et al. Thromboelastometry (ROTEM) in children: age-related reference ranges and correlations with standard coagulation tests. Br J Anaesth. 2010;105(6):827–835.
35. Haas T, Goobie S, Spielmann N, Weiss M, Schmugge M. Improvements in patient blood management for pediatric craniosynostosis surgery using a ROTEM®-assisted strategy – feasibility and costs. Paediatr Anaesth. 2014;24(7):774–780.
36. WOMAN Trial Collaborators. Effect of early tranexamic acid adminstration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10084):2105–2116.
37. Dirkmann D, Gorlinger K, Peters J. Assessment of early thromboelastometric variables from extrinsically activated assays with and without aprotinin for rapid detection of fibrinolysis. Anesth Analg. 2014;119(3):533–542.
38. Carroll RC, Craft RM, Langdon RJ, Clanton CR, Snider CC, Wellons DD, et al. Early evaluation of acute traumatic coagulopathy by thrombelastography. Transl Res. 2009;154(1):34–39.
39. Szecsi PB, Jørgensen M, Klajnbard A, Andersen MR, Colov NP, Stender S. Haemostatic reference intervals in pregnancy. Thromb Haemost. 2010;103(4):718–27.
40. Cortet M, Deneux-Tharaux C, Dupont C, Colin C, Rudigoz RC, Bouvier-Colle MH, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. Br J Anaesth. 2012;108(6):984–989.
41. Collins PW, Lilley G, Bruynseels D, Laurent DB, Cannings-John R, Precious E, et al. Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. Blood. 2014;124(11):1727–1736.
42. Association of Anaesthetists of Great Britain and Ireland, Thomas D, Wee M, Clyburn P, Walker I, Brohi K, et al. Blood transfusion and the anaesthetist: management of massive haemorrhage. Anaesthesia. 2010;65(11):1153–1161.
43. Collis RE, Collins PW. Haemostatic management of obstetric haemorrhage. Anaesthesia. 2015;70(Suppl 1):78–86,e27–28.
44. Hildyard C, Curry N. Point-of-care testing: a standard of care?. Anaesthesia. 2015;70(10):1113–1118.
45. ROTEM®. Two levels of control ROTROL N and ROTROL P [Internet]. 2017. From: https://www.rotem.de/en/products/rotem-delta/controls/. Accessed 17 October 2017.

APPENDIX 1. SCOTTISH ALGORITHM BY PROFESSOR A NIMMO[18]

ROTEM®

Author: Alastair Nimmo Version 2.2 Modified

DIAGNOSIS

1. Clot firmness

-

CLOT FIRMNESS		A10 in EXTEM / INTEM / HEPTEM / APTEM		
		< 22 mm	22-38 mm	≥ 39 mm
A10 in FIBTEM	< 5 mm	Low fibrinogen Low platelets	Low fibrinogen (†platelets - see below)	Low fibrinogen
	5-7 mm	Low platelets Low fibrinogen	Low platelets Low fibrinogen	Clot firmness appears satisfactory. See Sections 2, 3 & blue box below. (If bleeding isn't controlled consider: -raising fibrinogen (FIBTEM A10≥10mm) -in patients on aspirin* or clopidogrel* giving platelets and/or desmopressin).
	≥ 8 mm	Low platelets	Low platelets	

†Typically fibrinogen < 1.5 g/l & platelets 50-100. Also consider giving platelets if ongoing bleeding

2. Clotting time

- in the presence of heparin run a HEPTEM test

Causes of a prolonged CT	
Fibtem A10 < 5 mm	= Low fibrinogen
CT prolonged in Intem but normal in Heptem	= Heparin effect
Fibtem A10 ≥ 5 mm and no heparin effect	= Low coagulation factors

When to treat CT		
CT in Intem / Heptem > 300	or	CT in Extem / Aptem > 100s
CT in Intem / Heptem 240 - 300 s	or	CT in Extem / Aptem 80 - 100s
CT in Intem / Heptem < 240 s	or	CT in Extem / Aptem <80 s

3. Hyperfibrinolysis

Lysis of clot within 20 mins	Fulminant lysis
Lysis of clot within 20 – 40 mins	Early lysis
Lysis of clot after more than 40 mins	Late lysis - ?treat

Repeat Rotem tests including Aptem after treatment (or if no treatment is given)

TREATMENT

Treat	Treat if bleeding / high risk of bleeding	See below*

Low fibrinogen – FFP or fibrinogen concentrate or cryoprecipitate
Low platelets – platelets
Low coagulation factors – FFP or PCC Heparin – protamine (if reversal appropriate)
Hyperfibrinolysis – tranexamic acid (1 g – 2 g bolus)

*** IMPORTANT**
Rotem® does not detect the effect of aspirin, clopidogrel or Reopro® on platelets
Rotem® is not a sensitive test for some anticoagulants e.g. warfarin, LMWH
Rotem® does not detect von Willebrand factor deficiency

Rotational thromboelastometry (ROTEM®) in obstetrics

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INTRODUCTION

Rotational thromboelastometry (ROTEM®) is a point-of-care diagnostic device that provides rapid and specific coagulation assessment. ROTEM® provides information regarding all coagulation steps and fibrinolysis in one test and results are made rapidly available on screen in real time. The use of ROTEM® is well established in hepatic and cardiac surgery, but not as yet in the obstetric setting[1, 2]. Small-scale studies have reported ROTEM® values in non-pregnant women, normal pregnancies, postpartum and in active labour, but not in obstetric patients with pre-eclampsia, pregnancy-induced thrombocytopaenia, hepatic disease, haematological disease or other pathologies[1, 3-7].

Haemostasis is a complex network of interactions between the vasculature, platelets, coagulation factors, coagulation inhibitors, fibrinolytic factors and natural anticoagulants, all of which contribute to maternal haemostatic alterations in the peripheral vasculature as well as the utero-placental vasculature[8]. There is an increase in hypercoagulability throughout the three trimesters of pregnancy[5] and there is good correlation between FIBTEM (a component of the ROTEM® test panel) results with fibrinogen levels[9-11]. Only case reports have described the successful use of ROTEM® to guide intraoperative haemostatic treatment for acute obstetric haemorrhage. Much of the data is extrapolated from other settings such as trauma or cardiac surgery and haemostatic derangements in these settings are likely to differ from those in post-partum haemorrhage (PPH)[12].

ROTEM® MECHANICS – HOW DOES IT WORK?

ROTEM® was initially developed in 1995 in Munich, Germany. A blood sample is placed into a cuvette and a cylindrical pin is immersed and rotated by a spring. As the blood clots, the rotation of the pin is restricted increasingly with increasing clot firmness. From this, a curve is computed along with numerical parameters such as clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF) and maximum lysis (ML). Various activators or inhibitors are added to the citrated blood sample in order to represent different processes of haemostasis and to provide continuous viscoelastic profiles of blood clot formation.

ROTEM® is a modification and improvement on thromboelastography (TEG®) which was initially described in 1948 by Hertert[13]. Both ROTEM® and TEG® provide a real-time dynamic assessment of viscoelastic clot strength in whole blood via a point of care device that can analyse both coagulation and fibrinolysis. In contrast to ROTEM®, the TEG® system comprises a cylindrical cup containing a whole blood sample which oscillates periodically, while a pin on a torsion wire is suspended in the blood sample, which renders it sensitive to vibration

and must be maintained level on a stable bench[13]. TEG® has been studied extensively in the obstetric population including normal healthy parturients and complicated pregnancies, but prior to this, TEG® was underused for nearly six decades due to technological limitations[14], poor awareness regarding technique and interpretation, lack of full standardisation, and the unavailability of large clinical studies[8].

Both viscoelastic tests utilise different nomenclature to describe the same parameters. CT in ROTEM® and reaction rate (R) for TEG® are defined as the time taken for the trace to reach an amplitude of 2 mm[13]. CFT for ROTEM® and kinetics time (K) are defined as the time required for clot amplitude to increase from 2 mm to 20 mm[13]. MCF for ROTEM® and maximum amplitude (MA) for TEG® are the peak amplitudes (strength) of the clot[13]. Lysis index at 30 minutes (LI30) in ROTEM® and LY30 in TEG® represents the percentage decrease in amplitude 30 minutes after MCF or MA is reached respectively. ROTEM® and TEG® provide essentially identical information on clot formation kinetics and strength, but due to differences in operating characteristics, results are not interchangeable. Different assays are used with each device, with differences between reagents and their concentrations for equivalent assays. Also, it has been shown that when the same reagents are used, clot amplitude results are not consistent across the two devices. Unlike TEG®, ROTEM® has the ability to differentiate between different causes of coagulopathy. ROTEM® provides the values for the clot amplitude at 5 (A5) and 10 (A10) minutes, which are not validated with TEG® technology. For TEG®, the clinician is required to wait for the MA value which may take more than 30 minutes to derive.

THE ROTEM® PANEL

The ROTEM® analysis covers the entire process of whole blood coagulation, from the formation of the first fibrin strands, to maximum firmness of the clot until fibrinolysis occurs[15]. The standard ROTEM® panel comprises the EXTEM, INTEM and FIBTEM. EXTEM assesses the extrinsic coagulation pathway and allows assessment of factors I, II, V, VII, X, platelets and fibrinolysis. Coagulation is activated by the addition of a small amount of thromboplastin (tissue factor) which leads to clot initiation within 70 seconds, allowing clot formation to be assessed within 10 minutes. INTEM assesses the intrinsic pathway and allows assessment of factors I, II, V, VIII, IX, X, XI, XII, platelets and fibrinolysis. Coagulation in INTEM is activated via the contact phase (as in the activated partial thromboplastin time (aPTT) and activated clotting time (ACT)). The INTEM test is sensitive for factor deficiencies of the intrinsic system and for the presence of heparin within the sample. The FIBTEM test measures the effect of fibrinogen by eliminating the contribution of platelets to clot strength, via the addition of cytochalasin D which blocks platelets to allow for assessment of fibrin formation and fibrin polymerisation. Additional ROTEM® assays include the APTEM and HEPTEM. APTEM allows for rapid detection of fibrinolysis within 10 to 20 minutes. HEPTEM utilises the addition of heparinase as the reagent which degrades heparin to detect heparin-related coagulation defects.

ECATEM and NATEM are additional tests that are not available as yet in Australia. ECATEM has been developed to analyse direct thrombin inhibitor effects[16]. The ECATEM assay uses the viper venom, ecarin, as an activator, which directly converts prothrombin to meizothrombin[16]. Meizothrombin is inhibited by hirudin, argatroban, bivalirudin, and dabigatran, but not by heparin, warfarin or direct factor Xa inhibitors (rivaroxaban, apixaban)[16]. The NATEM assay can be used to detect pathophysiological changes from trauma-induced coagulopathy (TIC) to disseminated intravascular coagulopathy (DIC), as it is activated by recalcification and is sensitive to any endogenous activator such as tissue factor expression on circulating monocytes in infection, sepsis, cirrhosis, and in patients treated with extracorporeal assist devices[16].

Currently, both the ROTEM® delta and the newer ROTEM® sigma cartridge modules are in use. Results are comparable and the same test reagents are used, except that the ROTEM® delta reagents are in liquid form, while the ROTEM® sigma reagents are freeze-dried accuspheres. All current ROTEM® algorithms have been validated for both ROTEM® delta and ROTEM® sigma instruments. ROSI-EVA, a multicentre trial, has been registered, which proposes to perform simultaneous ROTEM® sigma and delta tests in 240 patients, including both healthy volunteers and patients with expected coagulopathy.

WHAT IS THE UTILITY OF VISCOELASTIC TESTING?

ROTEM®-guided transfusion of blood products has shown consistently significant reduction in bleeding and transfusion requirements[17-19]. However, there is a lack of standardisation and data for the definition of normal values and controls in obstetrics, with existing variability of reagents.

ROTEM® measures the viscoelastic properties on multiple aspects of coagulation in a 3.5 mL sample of citrated whole blood. Critical blood loss is associated with significant patient morbidity and mortality. Coupled with standard algorithms for coagulation management, this technology has the potential to enable targeted treatment to reduce bleeding and blood product wastage in the perioperative setting.

Case reports have described the successful use of viscoelastic testing in the setting of an emergency Caesarean section. For example, ROTEM® was successfully used to guide transfusion in a patient with acute fatty liver of pregnancy (AFLP) where prothrombin complex concentrate and fibrinogen concentrate was administered[20] and the use of TEG® in Gray Platelet Syndrome showed a degree of platelet inhibition and an overall borderline hypercoagulable state[21]. Interestingly, ROTEM® demonstrated hypercoagulable changes during pregnancy in

women with factor XI deficiency, despite prolonged clot initiation[22]. These patients had increased clot consolidation and clot strength compared to non-parturient controls[22]. Meanwhile, TEG® revealed prolonged clot initiation in a parturient with haemophilia B, which was corrected with factor IX administration[23]. Additionally, TEG® was used in two parturients with lupus anticoagulant receiving heparin to assess the levels of circulating heparin prior to the insertion of an epidural catheter for labour analgesia[24]. Lupus anticoagulant is an immunoglobulin that interferes with in-vitro phospholipid dependent coagulant tests such that there is prolongation of aPTT, but these patients are usually prescribed heparin as they are at greater risk of arterial and venous thrombosis.

Amniotic fluid embolism (AFE) is a rare but catastrophic obstetric complication. The use of TEG® revealed a significantly decreased time to first clot formation (R time), increased platelet function and no evidence of fibrinolysis using in vitro blood samples with the addition of amniotic fluid[25]. Others have reported hyperfibrinolysis with TEG® and ROTEM®[10, 26]. Helviz et al reported on three case studies of suspected AFE with TEG® parameters indicating severe coagulopathy. In one patient, MA on TEG® was low, which reflected reduced clot strength while in two other patients, the initial TEG® did not show any coagulation activity which correlated with unrecordable levels for the standard coagulation profile[27].

COAGULATION AND NEURAXIAL ANAESTHESIA

Patients with coagulopathies are at increased risk of developing a spinal or epidural haematoma following neuraxial anaesthesia. Pregnancy also causes engorgement of the venous plexus within the epidural space and hence the risk of blood vessel injury is increased with the administration of a neuraxial block[28]. The use of ROTEM® to monitor coagulation in obstetric patients with severe factor XI deficiency has been described in women who were given recombinant factor VIIa to achieve haemostasis in order to allow for a neuraxial block to be performed[28]. It is considered that significant thrombocytopaenia is a contraindication to the placement of an epidural catheter due to the potential risk of an epidural haematoma which could lead to permanent neurological deficit. Attempts to illustrate the utility of TEG® during neuraxial blockade in the parturient with thrombocytopenia have been made by recruiting women with a platelet count of less than 100,000 mm^{-3} to analyse the incidence of neurologic complications related to regional anaesthesia[29]. This case series of 24 women suggested that neuraxial techniques can be performed in parturients with a platelet count greater than 56,000 mm^{-3} provided that their TEG® results were normal. However, this study was significantly underpowered and none of the patients experienced any neurologic complication[29] which is not unexpected, as the incidence of a spinal or epidural haematoma in the obstetric population is 0.2-3.7 in 100,000 compared to 1 in 150,000-200,000 in the general population[28].

The effect of differing anaesthetic techniques on coagulation has also been analysed using TEG® where general anaesthesia for Caesarean section was associated with accelerated coagulability when compared with spinal anaesthesia[30]. Local anaesthetics are widely used in obstetrics, in the form of neuraxial anaesthesia for labour pain, Caesarean sections or epidural blood patches to treat post-dural puncture headaches. TEG® has also been used to study the effects of local anaesthetics on coagulation in the parturient. Amide local anaesthetics such as bupivacaine, lignocaine and ropivacaine are more commonly used in this setting, and they are known to enhance fibrinolysis[31] and inhibit coagulation by stabilizing platelet membranes, inhibiting calcium and alpha-granule release, inhibiting activation-dependent change in the conformation of the GPIIb/IIIa complex, protein kinase C, platelet aggregation and clot stability[32]. The effects of bupivacaine on coagulation are reflected on TEG® as a dose-dependent decrease in MA, a measure of clot formation and strength[33]. Lignocaine has also been reported to significantly decrease blood coagulation and enhance fibrinolysis in blood samples from healthy volunteers[33, 34]. In contrast, one study used whole blood samples from healthy parturients and did not show any fibrinolytic changes or hypocoagulable changes from the use of amide local anaesthetics[35]. Furthermore, modest alterations in MA, coagulation time and alpha angle on TEG® have been seen with varying concentrations of ropivacaine in the systemic circulation secondary to epidural administration, but these changes were not clinically significant[31]. The only ester local anaesthetic studied with TEG® in healthy term parturients is 2-chloroprocaine which demonstrated significant fibrinolysis in addition to decreasing coagulation, which is in contrast with previous studies that analysed the effects of amide local anaesthetics[32].

POSTPARTUM HAEMORRHAGE

Postpartum haemorrhage (PPH) is still one of the leading causes of maternal morbidity and mortality worldwide[36,37]. In Africa and Asia, obstetric haemorrhage accounts for more than thirty percent of all maternal deaths[38]. By comparison, obstetric haemorrhage is responsible for lower rates of maternal death in the developed world: 3.4 per cent in the United Kingdom between 2006 and 2008 and 11.4 per cent in the United States between 2006 and 2010[38]. Overall, PPH remains responsible for over 10 per cent of maternal deaths in high-income countries[39] and 25 per cent of the estimated 358,000 maternal deaths globally each year[12]. A standardised multidisciplinary approach, described in locally validated protocols and based on international guidelines is imperative for the prevention of such deaths[39]. Despite the relatively low rates of death from PPH in well-resourced countries, concern has been raised regarding the rising incidence of PPH, driven by increasing incidence of uterine atony, increasing maternal age and doubling of the Caesarean section rate[40-42].

Primary PPH is blood loss from the genital tract that occurs within 24 hours of delivery and secondary PPH is

blood loss occurring over 24 hours postpartum up to six weeks post-delivery. Primary PPH is the most common form of major obstetric haemorrhage and is defined as greater than 500 mL for a vaginal delivery and greater than 1000 mL for a Caesarean section. Despite being able to identify risk factors for PPH in the antenatal and intrapartum period, the majority of women who ultimately develop PPH do not have any such factors and every pregnancy is at risk[12, 43]. The coagulopathy associated with massive PPH may be due to haemodilution, failure of liver synthetic function as occurs with acute liver failure of pregnancy, or disseminated intravascular coagulation (DIC)[43].

In non-pregnant women, uterine blood flow constitutes less than 1 per cent of their cardiac output, but towards the end of pregnancy, this increases to 15 per cent[12]. Given that placental blood flow at term can exceed 750 mL per minute, obstetric haemorrhage can potentially be rapid and catastrophic. Furthermore, the amount of bleeding is often systematically underestimated[39]. Early and aggressive fluid resuscitation with large-bore venous access should be implemented for rapid and massive transfusion[39]. The institution of massive transfusion protocols allows the treating clinician to obtain the necessary blood products quickly in order to enable rapid empirical treatment of major blood loss when necessary and can decrease the overall number of products transfused and improve overall patient outcomes[44]. This resuscitation process needs to be guided by laboratory results with a rapid turnaround time for optimal management.

During early PPH, it has been shown that hypofibrinogenaemia is an important predictor for the later development of severe PPH[38]. ROTEM® can be used to identify decreased fibrin clot quality during PPH, which correlates with low fibrinogen levels. Overall, the use of ROTEM® or TEG® can provide increased sensitivity in identifying deficits in the coagulation cascade in comparison to conventional coagulation tests[10]. Data from clinical trials to guide transfusion management in the setting of PPH are lacking, but there are likely to be similarities in severe PPH and major bleeding in other clinical situations[12]. However, pathophysiological processes that contribute to a massive PPH may necessitate different transfusion strategies such as the ratio of red blood cells to plasma components, in particular fibrinogen[12]. Both TEG® and ROTEM® are increasingly being incorporated into transfusion algorithms for high-risk populations such as trauma patients and patients undergoing cardiac surgery[13]. Some evidence suggests that these algorithms might reduce transfusions, but further studies are required to assess patient outcomes[13]. Transfusion algorithms need to be developed based on the expected normal ranges of ROTEM® parameters for the obstetric population rather than the general non-pregnant population and more specific transfusion targets need to be defined to optimise blood transfusion in this population.

A novel combined strategy of obstetric haemorrhage management during Caesarean section has also been studied, using intrauterine balloon tamponade, early surgical haemostasis and TEG®-guided transfusion[45]. This was only an open controlled trial which included 119 women who experienced a PPH, with 90 patients in the novel strategy group and only 29 patients in the conventional strategy group[45]. The novel strategy resulted in a significantly lower number of peripartum hysterectomies[45], but the aetiology of PPH can be classified as per the “four Ts” (tone, thrombin, trauma and tissue) and the management needs to be tailored to the aetiologies involved. In cases of uterine atony, uterotonics need to be administered as part of PPH management. For example, oxytocin is a naturally occurring polypeptide which acts on oxytocin-specific receptors in uterine myometrium promoting uterine smooth muscle contraction. TEG® analysis has demonstrated that exogenous oxytocin is associated with modest hypercoagulable effects in healthy term parturients[46, 47].

COAGULATION IN THE OBSTETRIC POPULATION

In pregnancy, there is a physiological shift towards hypercoagulation[48] despite compensatory mechanisms of haemodilution and an increase in tissue factor-pathway inhibitor (TFPI) activity. Hypercoagulability in pregnancy is due to a slowdown of blood flow, a reduction of protein S activity, and increase in prothrombin activity and a higher concentration of some plasma coagulation factors (fibrinogen, factors VII, VIII and von Willebrand factor)[48]. This state of hypercoagulability persists during the first three weeks postpartum[49].

Several studies have confirmed a hypercoagulable state, slightly shorter clotting time (CT), and significantly greater clot firmness in pregnancy[4, 6, 7, 50], but these studies did not have adequate sample sizes. One study showed an increase in hypercoagulability throughout the three trimesters of pregnancy[5]. Huissoud et al compared ROTEM® results in 20 non-pregnant women, 17 women in their first trimester, 9 in their second trimester and 58 in their third trimester of pregnancy[9]. Clotting time (CT) and clot lysis index (CLI(30)) were not significantly different during pregnancy whereas maximum clot firmness (MCF), early clot amplitude at five minutes (CA(5)) and 15 minutes (CA(15)) (INTEM, EXTEM, FIBTEM) increased significantly between the second and third trimesters[9]. TEG® parameters have demonstrated hypercoagulability as well as decreased fibrinolysis during pregnancy in 45 healthy pregnant women at various gestational weeks up to eight weeks postpartum with a faster initiation in haemostasis and a minor increase in clot strength[51]. TEG® parameters have also been shown to reflect accelerated clot initiation as well as decreased clot stability and fibrinolysis in women with massive obstetric haemorrhage exceeding a blood loss of 2000 mL[52]. Macafee et al confirmed this in 50 pre-operative pregnant women and also showed similar TEG® parameters before and immediately following LSCS and four

hours post-prophylactic enoxaparin[53].

All studies with ROTEM® have been performed in uncomplicated pregnancies, and have found significant changes towards a hypercoagulable state, especially in the third trimester[5, 54]. Miscarriage is associated with hypercoagulable changes in TEG®/ROTEM® compared to healthy non-pregnant and pregnant women[54]. Twenty-six case reports concerning women with specific coagulation disorders were identified and TEG/ROTEM® was used for guiding therapeutic decision making[54].

Armstrong et al analysed 54 pregnant women and 54 non-pregnant women. Parturients had significantly lower haemoglobin values and platelet counts[6]. Despite this, thromboelastometry exhibited significantly lower INTEM CT (7.3%), INTEM CFT (11.1%) and EXTEM CFT (18.0%) in the pregnant group[6]. MCF values were significantly higher (INTEM (10.9%), EXTEM (10.6%) and FIBTEM (47.1%)) in the pregnant group compared to the non-pregnant group[6]. Polak et al confirmed that it may not be suitable to use the same reference ranges for pregnant women as for the general population[48]. There were statistically significant differences between the healthy non-pregnant fertile group (n=43) and healthy third trimester group (n=60). Hill et al developed a transfusion algorithm based on TEG® parameters from 57 healthy, term parturients pre-Caesarean and again confirmed the presence of relative hypercoagulability in pregnancy and that the reference interval is assay-dependent[55].

FIBRINOGEN AND ROTEM® FIBTEM

Fibrinogen levels increase significantly from 28 weeks of gestation and are almost double the levels seen in non-pregnant women[56]. These levels remain elevated until 15 days postpartum[49]. Fibrinogen levels have been shown to correlate well with the volume of haemorrhage and is one of the most useful markers of developing haemostatic impairment[57]. Fibrinogen plays a crucial role in the course of PPH and can be used as an early predictor of the severity of PPH[44, 3]. There is good correlation of FIBTEM results with fibrinogen levels in pregnant women pre- and postpartum [9-11, 58] and FIBTEM values decline even more rapidly than fibrinogen levels[3], thus providing early guidance of necessary interventions. A fibrinogen level less than 2 g/L is associated with increased risk of severe PPH[4] (RR=12)[58]. Women presenting with lower fibrinogen levels at the time of diagnosis of PPH have poorer outcomes and might benefit from early fibrinogen replacement[44]. Huissoud et al studied 91 women in their third trimester, of who 37 experienced a PPH and concluded that ROTEM® might be helpful in guiding fibrinogen transfusion during PPH[9]. In the OBS2 trial, which was a multicentre, prospective, double-blinded, randomised control study, Weeks et al compared fibrinogen concentrate with placebo for the treatment of postpartum haemorrhage, with 28 patients in each arm[59]. This trial showed that infusion of fibrinogen concentrate when the FIBTEM A5 is <12 mm or fibrinogen <2 g/L may be beneficial and should be investigated further[59]. They also postulated that if FIBTEM A5 is greater than 12 mm, fibrinogen replacement is not needed[59].

INDICATIONS FOR ROTEM®

ROTEM® would be of greatest value when obstetric patients are bleeding or at major risk of bleeding but very few studies have been conducted in the obstetric population. Cortet et al performed a study in 2012 with the aim to determine whether the fibrinogen level at the time of diagnosis of PPH is associated with the severity of bleeding[58]. This was a secondary analysis of a population-based study in 106 French maternity units identifying cases of PPH prospectively. PPH was defined by a blood loss exceeding 500 mL during the 24 hours after delivery or a peripartum haemoglobin decrease of more than 20 g/L. This analysis included 738 women with PPH after vaginal delivery. Fibrinogen levels were compared in patients whose PPH worsened and became severe and those whose PPH remained non-severe. Severe PPH was defined as haemorrhage by occurrence of one of the following events: peripartum haemoglobin decrease ≥40 g/L transfusion of concentrated red cells, arterial embolisation or emergency surgery, admission to intensive care, or death. The mean fibrinogen concentration at diagnosis was 4.2 g/L among the patients without worsening and 3.4 g/L in the group whose PPH became severe. The fibrinogen level was associated with PPH severity independently of other factors. Further to this, Zhou et al examined non-pregnant patients with congenital (hypo)dysfibrinogenaemia to suggest that abnormal TEG® values in the non-pregnant state could be used to predict a higher risk of obstetric complications occurring during pregnancy[60].

Only case reports have described the successful use of ROTEM® to guide intraoperative haemostatic treatment for acute obstetric haemorrhage. Much of the data is extrapolated from other settings such as trauma or cardiac surgery and haemostatic derangements in these settings are likely to differ from those in PPH. Coagulopathy in placental abruption was described by McNamara et al involving four separate cases utilising ROTEM® to guide fibrinogen replacement therapy[61]. Prior to this, TEG® parameter changes have also been analysed in placental abruption, in a larger cohort of thirty patients to confirm a strong correlation between fibrinogen levels and TEG® parameters (MA and k time)[62].

Butwick et al recorded TEG® parameters in 52 patients pre- and post-elective LSCS and showed a weak association between clot strength and estimated blood loss in these patients[63]. It also showed a modest reduction in the degree of maternal hypercoagulability in the early postpartum period following the elective LSCS[63]. Saha et al analysed platelet count, coagulation profiles and ROTEM® in 46 women and demonstrated a persistent hypercoagulation three weeks postpartum with a low clotting time and clot formation time[49]. Maximum clot firmness, alpha angle and amplitude at 20 minutes were raised until day 19[49]. While, comparing vaginal delivery against Caesarean section there were no significant increases in thrombotic parameters in Caesarean section[49].

ROTEM® VERSUS STANDARD COAGULATION TESTS

Very few studies have compared ROTEM® to standard tests. Huissoud et al showed significant correlations between the results obtained with ROTEM® and those from standard coagulation tests[9]. Mallaiah et al conducted a prospective observational cohort study comparing cryoprecipitate (n=42) and fibrinogen concentrate (n=51) transfused with a ROTEM® algorithm[36]. Following the introduction of ROTEM® guided fibrinogen concentrate administration for PPH, less blood products were given and no circulatory overload was seen[36]. Fibrinogen concentrate was given to all patients with a FIBTEM A5 below 7 mm, which is indicative of a fibrinogen level of 1.5-2 g/L[36]. Secondary coagulopathy due to PPH or its treatment is often underestimated and subsequently remains untreated, potentially causing progression to even more severe PPH[3]. Conventional coagulation test results are usually not available for 45 to 60 minutes. ROTEM® provides the advantage of a point of care coagulation test with more rapid turnaround times and potentially greater utility in the setting of an obstetric haemorrhage. The use of ROTEM® in massive bleeding in non-obstetric patients is widely practiced and it has been proven to be cost-effective[3].

Pre-eclampsia is associated with complex coagulation abnormalities that include altered platelet function and consumption and activation of the fibrinolytic system[64]. In 1995, Wong et al demonstrated that TEG® was not an effective means of predicting abnormal coagulation, as diagnosed by routine coagulation tests in pre-eclamptic parturients, but this was based on normal TEG® values for non-pregnant patients[65]. This emphasises the importance of the need to establish normal reference values. Magnesium sulphate is used for the prevention of seizures in pre-eclamptic patients, which was known to have anticoagulant and antiplatelet effects, but Harnett and Kodali utilised TEG® to prove that there was no effect on overall coagulation[64]. Recently, Ahmad et al aimed to correlate TEG® variables with conventional coagulation profiles in patients with pre-eclampsia[66]. Mao et al and Sharma et al have shown that there were no significant differences among TEG® parameters between severe pre-eclamptic patients and normal healthy parturients[67, 68]. However, there were significant changes seen in severe pre-eclamptic patients with thrombocytopenia, including a smaller alpha angle (reduced rate of clot formation), shorter MA value (reduced clot strength) and lower coagulation index (CI), denoting a hypocoagulable state and consequently, a high risk of bleeding[67, 68].

One hundred pre-eclamptic patients undergoing a Caesarean section under neuraxial anaesthesia were recruited and 20 patients demonstrated hypocoagulation. Platelet count showed a strong positive correlation with MA which was also confirmed by Beilin et al[69] and it was concluded that TEG® could lead to improved decision-making regarding the safety of using regional anaesthesia. Meanwhile, Bulbul et al also assessed 49 patients with severe pre-eclampsia and 54 patients with inherited thrombophilia against 31 controls and demonstrated prolonged clot initiation patterns and shorter clot lysis times compared to controls, indicating a possible increment in clot turnover, which eventually results in increased depletion of coagulation substrates[70]. However, it is difficult to comment on the safety of neuraxial blockade in this setting. For TEG® to be proven as a predictive assessment for neuraxial safety, a more extensive randomised-controlled trial would need to be completed. Furthermore, more specific platelet function analysis via PFA-100, Multiplate® or the proposed new ROTEM® Platelet test would provide greater utility for this purpose.

NORMAL RANGES

Most reviews and experts suggest that each centre evaluates its own normal ranges for TEG® and ROTEM®. Furthermore, gender, age and oral contraception have been shown to have a significant influence on ROTEM® parameters[71]. Sucker et al analysed five different cohorts of healthy patients: males below and above 45 years of age, females below 45 years of age with or without oral contraception and females above 45 years of age without hormone replacement therapy[71]. Hypercoagulability was seen with increasing age, the female gender and with the use of oral contraception[71]. Shortened clotting times and clot formation times, broader clot amplitudes and wider alpha-angles were seen in higher age-groups, irrespective of gender[71]. This can be explained by an increase in coagulation factor activities (factor VIII and von Willebrand factor) with advancing age that are reflected by a decreased partial thromboplastin time and prothrombin time on the standard coagulation profile[71, 72]. Females also had a shorter clotting time and clot formation time, broader clot amplitudes and wider alpha-angles in comparison to males[71]. This greater prothrombotic haemostatic profile in women can be explained by effects of sex hormones and may be further enhanced by exogenous hormone administration which increases the activity of coagulation factor VII, X and fibrinogen, reduced levels of antithrombin and protein S and a lower activity of plasminogen activator inhibitor-1[71].

Although parameters can be variable among healthy people during the same day, from one week to another and between different machines, parameters that showed the greatest consistency were MCF, ML and LI30[73]. This was demonstrated by Nagler et al who studied 40 healthy volunteers, taking two samples from each individual: 20 patients at 8am and 4pm and 20 patients on day 1 and day 28[73]. However, the highlighted inconsistencies with ROTEM® results did not take into account, the differences of gender, age and BMI. Formal baseline parameters need to be established in normal pregnancy and the effect of complex pathologies on coagulation and changes in ROTEM® findings are yet to be investigated.

FUTURE DIRECTION

Newer tests based on the ROTEM® ECATEM are planned for release in late 2017 with capabilities to detect the presence and existing effect of direct oral anticoagulants. ROTEM® Platelet will be available in 2018 which will provide information on platelet function and in particular, platelet aggregation, in whole blood samples using impedance aggregometry.

There is increasing use of ROTEM® for point-of-care coagulation monitoring in patients with massive haemorrhage[12], but there still remains limited data on reference ranges in normal pregnancies and subsequently limited understanding of the effects of complicated pregnancies on ROTEM® interpretation. Additional research is required to further define the optimal role of viscoelastic testing in major obstetric haemorrhage[74].

ACKNOWLEDGEMENTS

The National Blood Authority, ASA PhD Support Grant, and the RBWH Foundation Scholarship.

REFERENCES

1. King K, Setty S, Thompson K, McGlennan A, Wright A. Rotational thromboelastometry (ROTEM) – the future of point of care testing in obstetrics? Arch Dis Child Fetal Neonatal. 2011;96:Fa120-Fa121.
2. Wegner J, Popovsky MA. Clinical utility of thromboelastography: one size does not fit all. Semin Thromb Hemost. 2010;36:699-706.
3. De Lange NM, Lance MD, De Groot R, Beckers EA, Henskens YM, Scheepers HC. Obstetric hemorrhage and coagulation: an update. Thromboelastography, thromboelastometry, and conventional coagulation tests in the diagnosis and prediction of postpartum hemorrhage. Obstet Gynecol Surv. 2012;67(7):426-435.
4. De Lange NM, van Rheenen-Flach LE, Lancé MD, Mooyman L, Woiski M, van Pampus EC, et al. Peri-partum reference ranges for ROTEM® thromboelastometry. Br J Anaesth. 2014;112(5):852-859.
5. van Rheenen-Flach LE, Zweegman S, Boersma F, Lenglet JE, Twisk JWR, Bolte AC. A prospective longitudinal study on rotation thromboelastometry in women with uncomplicated pregnancies and postpartum. Aust N Z J Obstet Gynaecol. 2013;53(1):32-36.
6. Armstrong S, Fernando R, Ashpole K, Simons R, Columb M. Assessment of coagulation in the obstetric population using ROTEM® thromboelastometry. Int J Obstet Anesth. 2011;20(4):293-298.
7. Huissoud C, Carrabin N, Benchaib M, Fontaine O, Levrat A, Massignon D, et al. Coagulation assessment by rotation thrombelastometry in normal pregnancy. Thromb Haemost. 2009;101(4):755-761.
8. Othman M, Falcon BJ, Kadir R. Global hemostasis in pregnancy: are we using thromboelastography to its full potential? Semin Thromb Hemost. 2010;36(7):738-746.
9. Huissoud C, Carrabin N, Audibert F, Levrat A, Massignon D, Berland M, et al. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. BJOG. 2009;116(8):1097-1102.
10. Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. Br J Anaesth. 2012;109(6):851-863.
11. Butwick AJ. Postpartum hemorrhage and low fibrinogen levels: the past, present and future. Int J Obstet Anesth. 2013;22:87-91.
12. Mclintock C, James AH. Obstetric hemorrhage. J Thromb Haemost. 2011;9:1441-1451.
13. Whiting D, Dinardo JA. TEG and ROTEM: technology and clinical applications. Am J Hematol. 2014;89(2):228-232.
14. Reikvam H, Steien E, Hauge B, Liseth K, Hagen KG, Storkson R, et al. Thrombelastography. Transfus Apher Sci. 2009;40(2):119-123.
15. Afshari A, Wikkelso A, Brok J, Moller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev. 2011;(3):CD007871.
16. Gonzalez E, Moore HB, Moore EE. Trauma induced coagulopathy. Switzerland: Springer, 2016; pp.270-272.
17. Theusinger OM, Madjdpour C, Spahn DR. Resuscitation and transfusion management in trauma patients: emerging concepts. Curr Opin Crit Care. 2012;18:661-670.
18. Keene DD, Nordmann GR, Woolley T. Rotational thromboelastometry-guided trauma resuscitation. Curr Opin Crit Care. 2013;19:605-612.
19. Lier H, Vorweg M, Hanke A, Görlinger K. Thromboelastometry guided therapy of severe bleeding. Essener Runde algorithm. Hamostaesologie. 2013;33(1):51-61.
20. Crochemore T, de Toledo Piza FM, Silva E, Correa TD. Thromboelastometry-guided hemostatic therapy: an efficacious approach to manage bleeding risk in acute fatty liver of pregnancy: a case report. J Med Case Rep. 2015;9:202.
21. Clements A, Jindal S, Morris C, Srivastava G, Ikomi A, Mulholland J. Expanding perfusion across disciplines: the use of thrombelastography technology to reduce risk in an obstetrics patient with Gray Platelet Syndrome--a case study. Perfusion. 2011;26(3):181-184.
22. Davies J, Harper A, Kadir RA. The role of rotational thromboelastometry in assessment of haemostasis during pregnancy in women with factor XI deficiency. Haemophilia. 2015:[Epub ahead of print].
23. Przkora R, Euliano TY, Roussos-Ross K, Zumberg M, Robicsek SA. Labor and delivery in a patient with hemophilia B. Int J Obstet Anesth. 2011;20(3):250-253.
24. Harnett M, Kodali BS. Thromboelastography assessment of coagulation status in parturients with lupus anticoagulant receiving heparin therapy. Int J Obstet Anesth. 2006;15(2):177-178.
25. Harnett MJ, Hepner DL, Datta S, Kodali BS. Effect of amniotic fluid on coagulation and platelet function in pregnancy: an evaluation using thromboelastography. Anaesthesia. 2005;60(11):1068-1072.

26. Annecke T, Geisenberger T, Kurzl R, Penning R, Heindl B. Algorithm-based coagulation management of catastrophic amniotic fluid embolism. Blood Coagul Fibrinolysis. 2010;21:95-100.
27. Helviz Y, Einav S, Hersch M, Shapiro H, Ioscovich A. Thromboelastography as a part of management of amniotic fluid embolism. Case Rep Perinat Med. 2014;3(2):97-101.
28. Setty S, Reddell A, England A, Gomez K, Kadir R. The role of recombinant factor VIIa for obstetric block in women with severe factor XI deficiency. Haemophilia. 2011;17(6):906-909.
29. Huang J, McKenna N, Babins N. Utility of thromboelastography during neuraxial blockade in the parturient with thrombocytopenia. AANA J. 2014;82(2):127-130.
30. Sharma SK, Philip J. The effect of anesthetic techniques on blood coagulability in parturients as measured by thromboelastography. Anesth Analg. 1997;85(1):82-86.
31. Porter JM, McGinley J, O'Hare B, Shorten GD. The effects of ropivacaine hydrochloride on coagulation and fibrinolysis. An assessment using thromboelastography. Anaesthesia. 1999;54(9):902-906.
32. Kodali BS, Sa Rego M, Kaynar AM, Urman RD. The effects of 2-chloroprocaine on coagulation and fibrinolysis in the parturient: an in vitro study. J Anesth. 2014;28(6):906-910.
33. Tobias MD, Henry C, Augostides YG. Lidocaine and bupivacaine exert differential effects on whole blood coagulation. J Clin Anesth. 1999;11:52-55.
34. Tobias MD, Pilla MA, Rogers C, Jobes DR. Lidocaine inhibits blood coagulation: implications for epidural blood patch. Anesth Analg. 1996;82:766-769.
35. Siau C, Ng HP, Tan GM, Ho BS, Pua HL. In vitro effects of local anaesthetics on the thromboelastographic profile of parturients. Br J Anaesth. 2005;94(1):117-120.
36. Mallaiah S, Barclay P, Harrod I, Chevannes C, Bhalla A. Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage. Anaesthesia. 2015;70(2):166-175.
37. Stocks G. Monitoring transfusion requirements in major obstetric hemorrhage: out with the old and in with the new? Obstet Anesth Digest 2012;32(4):207-208.
38. Butwick AJ, Goodnough LT. Transfusion and coagulation management in major obstetric hemorrhage. Curr Opin Anaesthesiol. 2015;28(3):275-284.
39. Le Gouez A, Mercier FJ. Major obstetric hemorrhage. Transfus Clin Biol. 2016; 23(4):229-232.
40. Mehrabadi A, Hutcheon JA, Lee L, Kramer MS, Liston RM, Joseph KS. Epidemiological investigation of a temporal increase in atonic postpartum haemorrhage: a population-based retrospective cohort study. Br J Obstet Gynaecol. 2013;120(7):853-862.
41. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. Anesth Analg. 2010;110(5):1368-1373.
42. Rossen J, Okland I, Nilsen OB, Eggebo TM. Is there an increase of postpartum hemorrhage, and is severe hemorrhage associated with more frequent use of obstetric interventions? Acta Obstet Gynecol Scand. 2010;89(10):1248-1255.
43. James AH, McLintock C, Lockhart E. Postpartum hemorrhage: when uterotonics and sutures fail. Am J Hematol. 2012;87(S1):S16-S22.
44. Onwuemene O, Green D, Keith L. Postpartum hemorrhage management in 2012: predicting the future. Int J Gynecol Obstet. 2012;119(1):3-5.
45. Barinov SV, Zhukovsky YG, Dolgikh VT, Medyannikova IV. Novel combined strategy of obstetric haemorrhage management during caesarean section using intrauterine balloon tamponade. J Matern Fetal Neonatal Med. 2017;30(1):29-33.
46. Butwick A, Harter S. An in vitro investigation of the coagulation effects of exogenous Oxytocin using thromboelastography in healthy parturients. Anesth Analg. 2011;113(2):323-326.
47. Golparvar M, Esterabi M, Talakoub R, Saryazdi H. Evaluation of in vivo effects of Oxytocin on coagulation of parturient during cesarean delivery by thromboelastography. J Res Pharm Pract. 2014;3(1):28-33.
48. Polak F, Kolnikova I, Lips M, Parizek A, Blaha J, Stritesky M. New recommendations for thromboelastography reference ranges for pregnant women. Thromb Res. 2011;128(4):e14-e17.
49. Saha P, Stott D, Atalla R. Haemostatic changes in the puerperium '6 weeks postpartum' (HIP Study) - implication for maternal thromboembolism. BJOG. 2009;116(12):1602-1612.
50. Oudghiri M, Keita H, Kouamou E, Boutonnet M, Orsini M, Desconclois C, et al. Reference values for rotation thromboelastometry (ROTWM®) parameters following non-haemorrhagic deliveries. Correlations with standard haemostasis parameters. Thromb Haemost. 2011;106(1):176-178.
51. Karlsson O, Sporrong T, Hillarp A, Jeppsson A, Hellgren M. Prospective longitudinal study of thromboelastography and standard hemostatic laboratory tests in healthy women during normal pregnancy. Anesth Analg. 2012;115(4):890-898.
52. Karlsson O, Jeppsson A, Hellgren M. Major obstetric haemorrhage: monitoring with thromboelastography, laboratory analyses or both? Int J Obstet Anesth. 2014;23(1):10-17.
53. Macafee B, Campbell JP, Ashpole K, Cox M, Matthey F, Acton L, et al. Reference ranges for thromboelastography (TEG®) and traditional coagulation tests in term parturients undergoing caesarean section under spinal anaesthesia*. Anaesthesia. 2012;67(7):741-747.
54. Bolte AC, Hermans FJ, Van Rheenen-Flach LE. [227-POS]: Thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) in pregnancy: a systematic review. Pregnancy Hypertens. 2015;5(1):114-115.
55. Hill JS, Devenie G, Powell M. Point-of-care testing of coagulation and fibrinolytic status during postpartum haemorrhage: developing a thrombelastography®-guided transfusion algorithm. Anaesth Intensive Care. 2012;40(6):1007.
56. Pérez-Calatayud ÁA, Briones-Garduño JC, Rojas-Arellano ML. Use of thromboelastography and thromboelastometry for the rational and opportune transfusion of hemoderivatives in obstetric hemorrhage. Ginecol Obstet Mex. 2015;83(9):569-577.

57. De Lloyd L, Bovington R, Kaye A, Collis RE, Rayment R, Sanders J, et al. Standard haemostatic tests following major obstetric haemorrhage. Int J Obstet Anesth. 2011;20(2):135-141.
58. Cortet M, Deneux-Tharaux C, Dupont C, Colin C, Rudigoz RC, Bouvier-Colle MH, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. Br J Anaesth. 2012:108(6):984-9.
59. Weeks A, Collis R, Mallaiah S, Elton C, Dick J, Aawar N, et al. Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: a multicentre, prospective, double-blind, randomised controlled study (OBS2). Poster presented at the RCOG World Congress, 20-22 June 2016; Birmingham, UK. From: http://www.epostersonline.com/rcog2016/node/8882. Accessed 28 August 2017.
60. Zhou J, Xin Y, Ding Q, Jiang L, Chen Y, Dai J, et al. Thromboelastography predicts risks of obstetric complication occurrence in (hypo)dysfibrinogenemia patients under non-pregnant state. Clin Exp Pharmacol Physiol. 2016;43(2):149-156.
61. McNamara H, Mallaiah S, Barclay P, Chevannes C, Bhalla A. Coagulopathy and placental abruption: changing management with ROTEM-guided fibrinogen concentrate therapy. Int J Obstet Anesth. 2015;24(2):174-179.
62. Moopanar D, Naidu S, Moodley J, Gouws E. Thromboelastography in abruptio placentae. J Obstet Gynaecol. 1997;17(3):229-233.
63. Butwick A, Ting V, Ralls LA, Harter S, Riley E. The association between thromboelastographic parameters and total estimated blood loss in patients undergoing elective cesarean delivery. Anesth Analg. 2011;112(5):1041-1047.
64. Harnett MJ, Datta S, Bhavani-Shankar K. The effect of magnesium on coagulation in parturients with preeclampsia. Anesth Analg. 2001;92(5):1257-1260.
65. Wong CA, Liu S, Glassenberg R. Comparison of thrombelastography with common coagulation tests in preeclamptic and healthy parturients. Reg Anesth. 1995;20(6):521-527.
66. Ahmad A, Kohli M, Malik A, Kohli M, Bogra J, Abbas H, et al. Role of thromboelastography versus coagulation screen as a safety predictor in pre-eclampsia/eclampsia patients undergoing lower-segment caesarean section in regional anaesthesia. J Obstet Gynecol India. 2016;66:340-346.
67. Mao YJ, Yang ZJ. Significance of thromboelastography in the monitoring of maternal coagulation disorders in preeclampsia. J Shanghai Jiaotong University Med Sci. 2013;33(12):1612-1615.
68. Sharma SK, Philip J, Whitten CW, Padakandla UB, Landers DF. Assessment of changes in coagulation in parturients with preeclampsia using thromboelastography. Anesthesiology. 1999;90(2):385-390.
69. Beilin Y, Arnold I, Hossain S. Evaluation of the platelet function analyzer (PFA-100) vs. the thromboelastogram (TEG) in the parturient. Int J Obstet Anesth. 2006;15(1):7-12.
70. Bulbul M, Atalay MA, Cetinkaya DB, Turker G, Esmer A. Detecting coagulability status by thromboelastography in women with a history of pre-eclampsia and inherited thrombophilia. Clin Exp Obstet Gynecol. 2015;42(4):462-468.
71. Sucker C, Tharra K, Litmathe J, Scharf RE, Zotz RB. Rotation thromboelastography (ROTEM) parameters are influenced by age, gender, and oral contraception. Perfusion. 2011;26(4):334-340.
72. Zotz RB, Gerhardt A, Scharf RE. New approach for evaluation of quantitative risk factors of venous thromboembolism using individualized reference values. J Thromb Haemost. 2005;3:316.
73. Nagler M, Cate H, Kathriner S, Casutt M, Bachmann LM, Wuillemin WA. Consistency of thromboelastometry analysis under scrutiny: results of a systematic evaluation within and between analysers. Thromb Haemost. 2014;111(6):1161-1166.
74. Gehrie EA, Baine I, Booth GS. Pathology consultation on viscoelastic studies of coagulopathic obstetrical patients. Am J Clin Pathol. 2016;146(2):149-155.

Fibrinogen concentrate for acquired hypofibrinogenaemia

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INTRODUCTION

Fibrinogen concentrate is a human fibrinogen extract licensed in Australasia for the treatment of congenital fibrinogen deficiency. Its use in acquired hypofibrinogenaemia is increasing as a result of a transition towards point-of-care testing and factor concentrates in the management of bleeding. This article outlines the importance of fibrinogen in coagulation and explores the use of fibrinogen concentrate as a primary haemostatic product during haemorrhage.

FIBRINOGEN

Fibrinogen (factor I) is a hepatically-synthesised platelet-bound glycoprotein with a central role in coagulation. In primary haemostasis, fibrinogen sustains platelet aggregation by binding to platelet surface membrane receptors (glycoprotein (GP) IIb/IIIa) and crosslinking adjacent platelets[1]. Additionally, soluble fibrinogen is cleaved to insoluble fibrin monomers by thrombin, trapping platelets and erythrocytes in a fibrin mesh and enhancing clot stability (secondary haemostasis). Fibrin polymers are cross-linked by thrombin-activated factor XIII, increasing the elasticity of the clot and its resistance to fibrinolysis[1-3].

FIBRINOGEN DURING TISSUE TRAUMA

Fibrinogen is present in human plasma at a concentration between 2.0-4 g/L, where it has a half-life of approximately three days[4]. Its concentration is increased both during pregnancy and the acute phase response. Fibrinogen is the first clotting factor to decrease to critically low levels (<1 g/L) during major haemorrhage, when rapid consumption outstrips hepatic synthesis[2,5,6]. Tissue trauma, hypoperfusion and hypothermia lead to acidosis, impaired thrombin function, accelerated fibrinogen consumption and contribute to coagulopathy and hyperfibrinolysis. In addition, volume resuscitation causes a dilutional coagulopathy[2], while the use of synthetic colloids (especially starches) impair the polymerisation of fibrin, resulting in reduced clot stability[6,7].

Fibrinolysis is regulated by the plasminogen activator system. In response to venous occlusion, and mediated by thrombin, tissue-derived plasminogen activators (tPA, uPA) are released from endothelial cells. tPA and uPA cleave circulating plasminogen to active plasmin, thereby dissolving thrombus by hydrolysis of the cross-linked fibrin molecules. Rapid release of tissue factor after severe trauma leads to uncontrolled tPA and activated protein C release and is responsible for the hyperfibrinolysis which underpins trauma induced coagulopathy[8].

Hypofibrinogenaemia is associated with haemorrhage in numerous perioperative settings, including trauma[9], cardiovascular surgery[10] and obstetrics[2,11], leading to increased transfusion requirements, morbidity (e.g. sepsis) and higher mortality[9].

MEASUREMENT OF FIBRINOGEN LEVELS AND FUNCTION

The Clauss method is the most common laboratory technique for estimating fibrinogen concentration. Plasma samples are diluted to remove the effects of inhibitory substances, and mixed with calcium, phospholipids and a high concentration of thrombin[12]. The latter ensures clotting times are independent of the thrombin concentration in the sample. Clotting time is measured optically and calibrated against a reference sample with a pre-determined fibrinogen concentration. This assay is time-consuming (30 to 40 minutes), and may overestimate fibrinogen concentration in the presence of fibrin degradation products and artificial colloids, such as hydroxyethyl starch (HES)[7,13,14].

Point-of-care haemostatic assays provide an alternative method of measurement, and can rapidly extrapolate fibrinogen concentration indirectly from the viscoelastic properties of whole blood[14]. ROTEM® (TEM international GmbH, Munich, Germany) and TEG® (Haemonetics Corp, Braintree, MA, US) display the coagulation process, from initiation and propagation of the clot through to maximum stability and eventual dissolution by fibrinolysis[15]. They are commonly used perioperatively to guide the diagnosis and management of fibrinogen replacement in acquired fibrinogen deficiency[7]. To estimate fibrinogen concentration, both techniques remove the effects of platelets on the developing clot; the resultant amplitudes (maximum amplitude (MA) for TEG® and maximum clot firmness (MCF) for ROTEM®) are well correlated with the Clauss fibrinogen concentration in a number of

clinical settings[16,17]. The functional fibrinogen assay for TEG® prevents platelet aggregation by inhibiting glycoprotein GPIIb/IIIa with a monoclonal antibody fragment[18]. In contrast, the FIBTEM assay of ROTEM® estimates fibrinogen by eliminating the effects of platelets on clot strength through the addition of a potent platelet inhibitor (cytochalasin D)[18,19]. The normal range for FIBTEM MCF is 9 to 25 mm[20]. Amplitudes at five minutes (A5) and 10 minutes (A10) have been shown to be closely correlated with MCF[16,21]; modern point-of-care based algorithms have thus moved to utilise the A5 or A10 to shorten the latency between blood sampling and decision-making regarding fibrinogen replacement[18].

The interpretation of clot strength on viscoelastic assays must take into consideration the presence of anaemia, which is a common finding in critical haemorrhage. In vivo, anaemia exacerbates microvascular bleeding, as erythrocytes facilitate platelet aggregation by releasing adenosine diphosphate[22,23]. However, anaemia enhances fibrin strand proximity and adherence in whole blood samples, which may lead to a spurious increase in clot strength on the ROTEM® assays[24]. Correlation with Clauss fibrinogen is reduced, as dilution of functional fibrinogen with a high red cell mass affects the viscoelastic properties to a greater degree than in separated plasma[16,25,26].

CURRENTLY AVAILABLE SOURCES OF FIBRINOGEN

Traditionally, fibrinogen has been replaced by the administration of fresh frozen plasma (FFP) or cryoprecipitate.

Fresh Frozen Plasma (FFP)

FFP is an allogenic blood product requiring ABO compatibility testing and thawing prior to use. It is produced from pooled whole blood donations or single donor apheresis and contains all components of human plasma at or below physiological concentrations[7]. Single donor FFP has significant inter-individual variability in the concentration of fibrinogen (median 2 g/L, range 0.9-3.2 g/L)[27].

Cryoprecipitate

Cryoprecipitate is extracted from FFP by centrifugation after a process of precipitation. It is a concentrated source of fibrinogen, factor VIII, factor XIII and von Willebrand factor (vWF)[7]. One apheresis dose contains approximately 800 mg of fibrinogen in 60 mL[28]. As an allogenic blood product, it requires ABO compatibility typing and thawing; however, there are no processes for viral inactivation, which pose a potential risk of pathogen transmission. Many European countries have ceased production of cryoprecipitate from FFP, due in part to these safety concerns[7,29].

Fibrinogen concentrate (FC)

Fibrinogen concentrate products, such as RiaSTAP® (CSL Behring, Australia), are a highly refined source of fibrinogen from multiple human plasma donors. They are heat-treated, lyophilised and virally inactivated. One vial contains 900-1300 mg of fibrinogen, as well as albumin, L-arginine and sodium citrate[30].

FC has several theoretical advantages over both FFP and cryoprecipitate[4], notably:

1. Universal compatibility: It does not require cross matching or ABO compatibility testing as it lacks ABO antigens and cellular components.
2. Storage: FC is present in a lyophilised form that can be stored at room temperature for up to five years.
3. Administration: FC is easily reconstituted with warm sterile water and administered over several minutes. In the context of critical bleeding, a delay in intervention has been identified as a major risk factor for poor patient outcome[31]. A low infusion volume and room temperature storage facilitate rapid administration of FC[7].
4. Risks: FC is pasteurised, enabling the inactivation of viruses. It is further purified to remove antigens and antibodies, reducing the risk of immunological or allergic reaction (e.g. transfusion related acute lung injury, TRALI) when compared to alternative products[7,32].
5. Potency: FC has a higher concentration of fibrinogen (20 g/L) than cryoprecipitate (16-18 g/L) or FFP (2 g/L). As FFP contains relatively low concentrations of fibrinogen, large volumes are required to provide a substantial increase in fibrinogen plasma concentration[7]. By contrast, a lower intravenous volume of FC can be transfused, mitigating the risk of transfusion associated circulatory overload (TACO)[5,32].

COMPARISON OF CRYOPRECIPITATE AND FC

Cryoprecipitate is widely available in the United States, United Kingdom and Australia for first-line replacement of fibrinogen[33]. In Europe, FC is administered “off label”, promoted by guidelines such the Management of Severe Perioperative Bleeding by the European Society of Anaesthesiology[34].

Cryoprecipitate contains several additional haemostatic factors, which are not present in FC as a purified product[7].

1. Factor VIII is a cofactor in the intrinsic tenase reaction, combining with FIXa and activating FX. Deficiencies, such as seen in haemophilia A, are associated with severe bleeding[35].

2. Factor XIII increases the mechanical stability of the clot by cross-linking fibrin chains[36]. In addition, FXIII has anti-fibrinolytic properties which protect the clot from premature degradation by the fibrinolytic system[37].
3. vWF is a glycoprotein which binds, stabilises and increases the half-life of factor VIII in circulation, while mediating platelet adhesion and aggregation in damaged vascular endothelium[38].

A systematic review of studies comparing FC and cryoprecipitate found a high risk of bias and a paucity of evidence favouring either product[33]. Nevertheless, the authors concluded there was equivalent efficacy in fibrinogen replacement, although the cryoprecipitate-treated group generated a faster clotting time on the ROTEM® assay. The difference may be explained by the presence of FVIII, XIII and vWF in cryoprecipitate, while FC remains a single factor concentrate[33]. Additionally, there was no demonstrable difference in the efficacy in preventing perioperative blood loss, thromboembolic complications or reduction in allogenic transfusion. A pilot randomised control trial (RCT) is underway in Queensland to compare the feasibility and efficacy of FC and cryoprecipitate in severe trauma (FEISTY)[39]. This will form the basis for a large multicentre trial.

CLINICAL INDICATIONS FOR FC

Congenital fibrinogen deficiency

Congenital afibrinogenemia and dysfibrinogenaemia are secondary to mutations in one or more of the genes coding for fibrinogen, resulting in absent, reduced or dysfunctional fibrinogen synthesis. Principal manifestations include spontaneous bleeding, haemorrhage after minor trauma and excessive bleeding during invasive procedures[40]. In patients with congenital fibrinogen deficiency, FC is effective for haemorrhage prophylaxis and in the treatment of spontaneous bleeding[40,41]. Guidelines from the United Kingdom recommend fibrinogen replacement to a plasma concentration of 1 g/L for haemostasis and 0.5 g/L for wound healing[42]. Supplementation with FC increases the plasma concentration of fibrinogen and enhances the strength and speed of clot formation[40]. Fibrinogen supplementation does not appear to confer any further benefit in patients with a plasma concentration greater than 1.5 g/L, providing additional factor deficiencies are not present[43]. Congenital fibrinogen deficiencies are predominantly associated with bleeding; however, there exists a greater risk of thrombotic complications in these patients. In these cases, the relative contributions of the underlying fibrinogen deficiency and fibrinogen replacement therapy have not yet been determined[43].

Trauma

In Australasia, trauma is the leading cause of death under the age of 45 years[44]. In severe trauma, the presence of consumptive and dilutional coagulopathy is associated with a three- to four-fold increase in mortality[5]. Despite surgical haemorrhage control, coagulopathy contributes to increased transfusion requirements, sepsis and multiple organ failure[45]. Plasma fibrinogen levels at presentation are an independent predictor of mortality in patients with severe trauma[46]. Optimising the treatment of coagulopathy via early fibrinogen replacement has been shown to improve outcomes and survival for severely injured trauma patients[5,6,47,48].

Trauma centres vary in their first line management of coagulopathy, with many administering FFP as the principal means of achieving haemostasis[49]. No conclusive evidence supports this treatment in trauma-induced coagulopathy and, importantly, the theoretical dilutional effect of FFP must be considered[50,51]. The potential for FC as a first line haemostatic agent has been demonstrated in retrospective analyses, which found that coagulopathy was corrected without the use of alternative products such as platelets or FFP[52,54]. Evidence suggests that the replacement of fibrinogen based on a point of care-guided algorithm with coagulation factor concentrates improves the outcomes for traumatic haemorrhage[50]. The RETIC (Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma) study compared the effects of fibrinogen replacement with either FFP or coagulation factor concentrates (combined FXIII, PCC and fibrinogen concentrate) on multi-organ failure and the need for massive transfusion[55]. The study was terminated early for safety reasons when a higher proportion of patients in the FFP arm required rescue treatment with fibrinogen than in the factor concentrates arm. Moreover, FFP was shown to be ineffective for haemostasis; its use was associated with ongoing bleeding, significantly increased transfusion requirements and risk of multi-organ failure. This finding has been supported by further retrospective studies; Schöchl et al reported that additional transfusion was required in 29 per cent fewer patients in a treatment cohort that received FC and prothrombin complex concentrate than an FFP group[53].

Pre-emptive administration of FC in patients with trauma-induced coagulopathy has been shown to enhance survival rates. One retrospective Japanese study demonstrated that 56 per cent of patients with severe traumatic injury had hypofibrinogenaemia, while 25 per cent had critical hypofibrinogenaemia (<1 g/L); pre-emptive administration of FC effectively increased plasma fibrinogen levels over an apparently critical threshold of 2 g/L, contributing to improved survival outcomes in this group despite no significant reduction in red cell transfusion volume[54]. A pilot RCT of pre-emptive FC in trauma is ongoing (PRooF-iTH), and may provide insight into the efficacy of early FC administration[56].

However, not all studies have reported positive findings. A retrospective study of 295 severely injured patients (Injury Severity Score >15) compared those who received FC in their initial resuscitation versus those who received alternative therapies, and demonstrated that although six hour mortality was significantly reduced in

the FC group, there was no difference in the overall mortality or red cell transfusion rates and there was an increase in the incidence of multi-organ failure[57]. This study had significant limitations; dosage, timing and the indications for FC were not recorded, while the administration of antifibrinolytic agents was not controlled for. Additionally, survivor bias may have contributed to the negative findings.

The European Guidelines for the Management of Major Bleeding and Coagulopathy Following Trauma recommend 3-4 g of fibrinogen replacement (FC or cryoprecipitate) if significant bleeding is accompanied by a fibrinogen deficit on point-of-care monitoring and/or Clauss fibrinogen is less than 1.5 g/L[48]. Repeat dosing is guided by viscoelastic testing and standard laboratory tests of coagulation.

Obstetrics

Obstetric haemorrhage (peri-partum blood loss of greater than 500 mL for vaginal delivery, or 1000 mL for Caesarean section) is a leading cause of maternal mortality worldwide. There is an increasing incidence of post-partum haemorrhage (PPH) in developed countries; in Australia, the rate of PPH rose from 6.1 per cent in 2003 to 8.3 per cent in 2011[58]. Normal physiological changes during pregnancy offer protection by inducing a pro-coagulable state with an increase in coagulation factors (particularly fibrinogen) and diminished fibrinolysis; additionally, blood volume and cardiac output increase late in the first trimester[59]. This is countered by the physiological anaemia of pregnancy and a relative thrombocytopaenia. Fibrinogen plasma levels rise antenatally to an average of 5 g/L, which normalises at four to eight weeks postpartum[60]. Antenatal plasma fibrinogen concentration was not associated with bleeding and did not differ significantly with post-partum samples in one large prospective observational study[61]. In contrast, a fibrinogen concentration of <2 g/L after the onset of PPH had a positive predictive value of 100 per cent in predicting the severity of PPH[11]. Fibrinogen concentration of <1.5 g/L and FIBTEM A5 threshold of 5 mm are closely correlated in pregnancy and enable early decision making regarding the transfusion of fibrinogen substrates[62].

A number of observational studies have demonstrated improved clinical outcomes in PPH with associated acquired hypofibrinogenaemia following the administration of FC[63,64]. One retrospective observational study identified that the use of FC in PPH was associated with significantly reduced blood loss and reduction in transfusion requirements of red blood cells (RBC), FFP and pooled platelet concentrates[64]. Additionally, following the institutional implementation of a ROTEM-based algorithm for PPH, Mallaiah et al reported that 3 g of FC resulted in reduced transfusion of allogenic blood products in patients with hypofibrinogenaemia[19].

The FIB–PPH trial assessed the efficacy and safety of pre-emptive FC administration (2g) in PPH[65]. No differences were found in transfusion or morbidity between the treatment or control arms. However, both groups had similar initial median fibrinogen concentrations of 4.5 g/L resulting in the conclusion that FC did not reduce allogenic blood transfusion in parturients with normofibrinogenaemia. The OBS2 group randomised 58 women with PPH to receive either FC or placebo[66]. In the subgroup of women with lower fibrinogen at enrolment (FIBTEM A5 <12 mm) there was reduced blood loss, lower allogenic blood product requirements, and a shorter duration of level 2/3 care postoperatively; however, in women with A5 >12 mm there was no apparent difference between the treatment arms. From this data it may be concluded, perhaps intuitively, that FC appears to have the greatest efficacy in severely hypofibrinogenaemic parturients, while providing little benefit in women with normal coagulation substrate.

Cardiothoracic surgery

Perioperative bleeding during cardiac surgery requiring transfusion is associated with increased morbidity and mortality[67]. Haemorrhage is multifactorial and includes patient-related factors, such as the perioperative use of antithrombotic medication, consumptive and dilutional coagulopathy, and fibrinolysis associated with cardio-pulmonary bypass (CPB)[68-70]. In particular, CPB impairs fibrin mesh formation to a greater degree than platelet function or thrombin generation[71].

A meta-analysis by Forminski et al demonstrated reduced perioperative bleeding and lower RBC transfusion requirements with the use of FC in cardiothoracic surgery[72]. Seminally, this meta-analysis demonstrated FC's potential benefit in reducing mortality[72]. The ZEPLAST (Zero Plasma Trial) showed that in high-risk cardiac surgery the use of an FC-based algorithm resulted in lower postoperative blood loss and reduced transfusion, when compared to the administration of FFP[73].

ROTEM®-guided FC replacement has been associated with a reduction in perioperative bleeding in cardiac surgery and reduced allogenic blood product transfusion[74-77]. FC has been demonstrated to be more effective than placebo, FFP or platelets in reducing intraoperative bleeding and resulted in fewer RBC transfusions in patients with coagulopathic bleeding undergoing elective cardiac surgery[10,78].

In the setting of cardiac surgery, low preoperative fibrinogen is considered a poor predictor of perioperative blood loss[79,80]. One meta-analysis of 20 studies found a weak correlation between pre- and postoperative plasma fibrinogen concentration and postoperative bleeding[81]. Moreover, preoperative fibrinogen replacement with 2 g of FC was not shown to influence postoperative bleeding in patients with normal plasma fibrinogen undergoing Coronary Artery Bypass Grafting (CABG) when compared with placebo[68]. Therefore, routine prophylactic fibrinogen concentrate replacement in hypofibrinogenaemic patients undergoing cardiac surgery cannot be recommended.

The administration of FC has been associated with adverse outcomes in some patient groups[82]. In their randomised controlled trial, Rahe-Meyer et al compared FC to placebo for the treatment of bleeding following complex elective aortic arch surgery. Patients randomised to the FC arm had higher requirements for allogenic products and a greater "return to theatre" rate for the management of bleeding[71]. This may have been due to variability in adherence to the complex transfusion study algorithm, or it may be that patients had plasma fibrinogen levels that would not normally be augmented in routine clinical practice[71].

Thrombocytopaenia

Thrombocytopaenia is a risk factor for major bleeding, particularly in association with cardiac surgery[83]. Traditionally, platelet transfusion has been the first-line haemostatic agent in patients with thrombocytopaenia or platelet dysfunction[84]. However, platelet transfusion is associated with significant risks, including bacterial transmission, non-haemolytic or allergic transfusion reactions and TRALI[85-87]. Additionally, platelet concentrates have a relatively short shelf-life (five days), limiting their storage and use in smaller centres[83]. In-vitro studies demonstrated that the addition of FC to patient samples with thrombocytopaenia significantly increased MCF on ROTEM®, comparable to platelet transfusion[83]. Low ROTEM® amplitudes are closely correlated with bleeding and FC may compensate for thrombocytopaenia by increasing the density of the fibrin network and establishing fibrinogen mediated platelet aggregation[88]. However, caution must be used when extrapolating these findings to the clinical setting.

TRIGGER AND TARGETS FOR TREATMENT WITH FIBRINOGEN

The target fibrinogen plasma concentration and the threshold at which fibrinogen replacement is indicated is contentious and, very likely, context specific (table 1). Fibrinogen replacement to above 2 g/L has been shown to improve the rate of fibrin polymerisation[89]. Fibrinogen supplementation improves in vitro clot strength linearly, even at fibrinogen levels above those observed in normal plasma.

The European Guidelines for Trauma recommend maintaining plasma fibrinogen concentration above 1.5 g/L to improve haemorrhage control[48]. Recent data show that at fibrinogen levels below 1.5 g/L there is an increased risk of perioperative bleeding[6]. Protocols from the American College of Surgeons Trauma Quality Improvement Program recommend replacement of fibrinogen at a FIBTEM MCF <8 mm[90]. Conversely, the definitions utilised by the RETIC study for trauma-induced coagulopathy associated with low fibrin polymerisation and prolonged initiation of coagulation were FIBTEM A10 <9 mm and EXTEM >90 sec respectively[55]. Ponschab et al used a cut-off of A10 <7 mm to trigger replacement with FC for management of trauma-related haemorrhage[91].

During pregnancy, physiological changes influenced by oestrogen and progesterone result in a hypercoagulable state with a shorter clotting time and a significantly increased MCF. While this is thought to provide a physiological buffer for partuition rather than being an absolute requirement for haemostasis, many algorithms retain higher thresholds for fibrinogen replacement in obstetrics to reflect the greater concentrations of fibrinogen at term. ROTEM® parameters were assessed intrapartum and one-hour postpartum and were found to be analogous, leading to the conclusion that uncomplicated labour in itself does not induce haemostatic changes[17]. An observational study found that FIBTEM A5 <5 mm had 100 per cent sensitivity and 85 per cent specificity to detect Clauss fibrinogen <1.5 g/L in PPH[62], while Mallaiah used a FIBTEM A5 <12 mm as indicative of a plasma fibrinogen level of 2 g/L to prompt replacement[19]. This was confirmed by subgroup analyses of the OBS2 study which demonstrated that a FIBTEM A5 >12 mm or Clauss fibrinogen >2 g/L reflected a concentration adequate to enable haemostasis in obstetric haemorrhage[66].

The threshold for fibrinogen replacement in cardiac surgery remains controversial; in particular, uncertainty exists as to the benefits and potential risks of FC in this cohort[82]. Historically, a Clauss fibrinogen of <1 g/L was recommended as the trigger for replacement[2]. In contrast, Bilecen et al did not demonstrate a significant difference in the intraoperative blood loss compared with placebo when plasma fibrinogen levels were maintained at greater than 2.5 g/L with FC in patients with intraoperative bleeding[70]. In the ZEPLAST trial the negative predictive value for severe bleeding was 100 per cent for a plasma fibrinogen of 2.8 g/L and 98 per cent for a FIBTEM MCF of 14 mm[77]. For high-risk cardiac surgery, such as aortic replacement, a high normal fibrinogen concentration of 22 mm on MCF was proposed by Rahe-Meyer and showed significantly fewer transfusions in the FC group when compared with placebo[78].

In our institution, fibrinogen supplementation in critical bleeding is recommended at a FIBTEM A5 of 10 mm. This figure correlates to a Clauss fibrinogen of 2 g/L and reflects a single pragmatic threshold across a range of perioperative settings (figure 1).

DOSING OF FIBRINOGEN CONCENTRATE

Product information for RiaSTAP® recommends an initial dose of 70 mg/kg of ideal body weight, prior to establishing a baseline plasma fibrinogen level[30]. European trauma guidelines advocate initial replacement with 3 to 4g of fibrinogen concentrate in traumatic haemorrhage[48]. Repeat dosing is guided by clinical response, viscoelastic monitoring and laboratory assessment of fibrinogen levels.

The ROTEM® MCF has been widely used to calculate an individualised dose of FC via the formula[10]:

Fibrinogen concentrate dose (g) = [target FIBTEM MCF (mm) – actual FIBTEM MCF (mm)] x [body weight (kg)/70] x 0.5 g/mm

A simplified fibrinogen dosing guide (figure 2) adapted from the King Edward Memorial Hospital (KEMH) ROTEM® algorithm for critical bleeding provides stratified dosing recommendations, and prompts fibrinogen replacement at FIBTEM A5 <10 mm. FC is administered in preference to cryoprecipitate if the FIBTEM A5 <7 mm, or if there is a high suspicion of coagulopathy in life threatening or time critical haemorrhage[92]. While there is a limited evidence base to guide exact FC dosing in acquired hypofibrinogenaemia, unpublished local data in postpartum haemorrhage suggests 2 g of FC increases the FIBTEM A5 by 2 to 3 mm, with a 5 g dose leading to an increase of >9 mm.

ADMINISTRATION

One ampoule of RiaSTAP® contains approximately 1 g of lyophilised fibrinogen[30]. Fifty millilitres of sterile water for injection (ideally warmed to 37 degrees Celsius) is transferred into the ampoule for reconstitution. The product is dissolved with a gentle swirling action; shaking the vial will cause foaming and difficulty in administering the product. Rapid reconstitution takes approximately five minutes, after which time the solution should be transparent and colourless with no particulate matter[93]. The manufacturer recommends administering RiaSTAP® at room temperature at a maximum rate of 5 mL/minute[30]. In critical bleeding, FC may be given via a syringe driver over 2-4 minutes per gram[30]. A ROTEM® should be performed 10 minutes after administration of the solution as additional fibrinogen replacement may be required.

SAFETY

FC has a favourable safety profile; compared with cryoprecipitate there is no reported increase in thromboembolic events or viral transmission. Extensive post marketing surveillance (1986-2013) of FC found a low incidence of thromboembolic events (28 reports) at a rate of one event per 23,300 standard doses[94]. Although an increase in the plasma fibrinogen concentration and clot firmness immediately following administration of FC in aortic surgery has been demonstrated, this effect was not seen in the first postoperative week[95]. Other data suggest that following FC administration in severe trauma, plasma fibrinogen levels over the ensuing seven days are not higher than that of a control group, irrespective of the dose of FC given[96]; moreover, FC administration does not down-regulate hepatic fibrinogen synthesis[97]. Thus, the use of FC is unlikely to enhance the pro-thrombotic state in the perioperative period, beyond that occurring naturally due to the acute phase reaction[96].

ECONOMIC EVALUATION

In Australia, the funding source for blood products varies between states. In Western Australia, cryoprecipitate is provided by the Australian Red Cross Blood Service at no cost to individual hospitals, One unit of apheresis cryoprecipitate (containing 790 mg of fibrinogen) costs $A325, while 1 g of FC is $A750[28,98]. A typical adult dose of five apheresis bags (4 g) is thus cheaper than the equivalent dose of FC ($1625 versus $3000). FC is not covered under the National Blood Authority funding model and must be provided at the hospital's expense.

A cost-minimisation model developed by Okerberg et al was developed to analyse the economic aspects of administering FC or cryoprecipitate[99]. The model did not include non-transfusion service expenses such as nursing time or consumables. They concluded that FC remains more expensive than cryoprecipitate in spite of the inevitable product wastage and transfusion costs associated with the latter[99]. In order for FC to become more economically competitive, it would need to either reduce in price by 44 per cent ($750/g to $414/g) or show tangible additional benefits, such as a reduction in overall blood product use or intensive care unit stay[99].

Although the current cost of FC is higher than cryoprecipitate, the difference may not be as pronounced when clinical efficacy is taken into consideration. In one study, the average dose of FC (2 g) raised plasma fibrinogen by a median of 1 g/L in a 60 kg patient[100]. In an analogous study, 1 g of FC ($750 AUD) increased plasma levels by approximately the same amount as ten units of whole blood cryoprecipitate ($A780)[101].

CONCLUSION

Fibrinogen concentrate is a promising alternative to cryoprecipitate, with increasing use in Australasia for treatment of acquired hypofibrinogenaemia. Robust prospective data demonstrating its efficacy alongside cryoprecipitate is eagerly awaited. While the current evidence base fails to establish superiority over cryoprecipitate, FC has a number of theoretical advantages, most importantly the rapidity with which it can be used to treat hypofibrinogenaemia in time-critical scenarios without input from transfusion laboratories. Despite these advantages, funding constraints and licensing issues may limit routine uptake of FC in Australasia. The utility of FC as a bridge to cryoprecipitate in the exsanguinating patient, while awaiting cross-match and thawing of fractionated products, remains significant despite these limitations. Its role in the management of haemorrhage in settings where cost and logistics limit the provision of frozen products, such as in the rural, prehospital and transport space should also be considered.

Figure 1. Fiona Stanley Hospital ROTEM algorithm for critical bleeding (reproduced with permission)

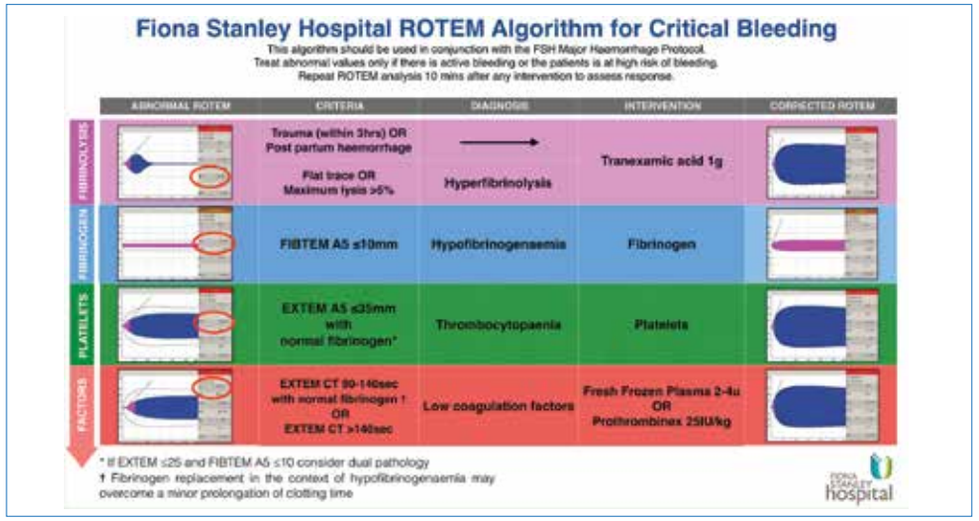

Figure 2. King Edward Memorial Hospital fibrinogen dosing guide (reproduced with permission)

FIBRINOGEN DOSING GUIDE

FIBTEM A5 Target: ≥12mm

FIBTEM A5	Increase required	Cryoprecipitate*	Fibrinogen Concentrate
9-10 mm	2-3 mm	10 Units	2g
7-8 mm	4-5 mm	15 Units	3g
4-6 mm	6-8 mm	20 Units	4g
<4 mm	≥9 mm	25 Units	5g

*Cryoprecipitate dosing is for standard adult units

(Cryo 5 units / Fib Conc 1g = Fibtem A5 increase of approx 2mm)

Table 1. Normal values for fibrinogen; thresholds and targets for treatment of hypofibrinogenaemia

	NON-PREGNANT	PREGNANT	THRESHOLD	TARGET
Fibrinogen plasma concentration	2.0-4.5 g/L[4]	5.0-6.0 g/L[17,60]	<1.5 to 2.0 g/L[102] Pregnant: <2 g/L[11] Cardiac >2.8 g/L[77]	Pregnancy: >2 g/L[11]
MCF	9-25 mm[20]	15-19 mm[103]	Trauma: <8 mm[90] Cardiac <14 mm[77]	High normal for aortic surgery: 22 mm[76]
A10	7-23 mm[20]	20-25 mm[17]	Trauma: <7 mm[91] Cardiac: <8 mm[104]	>15 mm[105] >8 mm[16] Trauma: 10-12 mm[91]
A5			Trauma: <10 mm[39] Pregnant: <5 mm[62], <12 mm[19]	

REFERENCES

1. Bolliger D, Tanaka KA. Fibrinogen - is it a universal haemostatic agent? Br J Anaesth. 2016;117(5):548-550.
2. Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion. 2014;54(5):1389-1405.
3. Litvinov RI, Weisel JW. What is the biological and clinical relevance of fibrin? Semin Thromb Hemost. 2016;42(4):333-343.
4. Kreuz W, Meili E, Peter-Salonen K, Dobrkovska A, Devay J, Haertel S, et al. Pharmacokinetic properties of a pasteurised fibrinogen concentrate. Transfus Apher Sci. 2005;32(3):239-246.
5. Aubron C, Reade MC, Fraser JF, Cooper DJ. Efficacy and safety of fibrinogen concentrate in trauma patients – a systematic review. J Crit Care. 2014;29(3):471, e11-e17.
6. Fries D, Martini WZ. Role of fibrinogen in trauma-induced coagulopathy. Br J Anaesth. 2010;105(2):116-121.
7. Rahe-Meyer N, Sorensen B. For: Fibrinogen concentrate for management of bleeding. J Thromb Haemost. 2011;9(1):1-5.
8. Cardenas JC, Matijevic N, Baer LA, Holcomb JB, Cotton BA, Wade CE. Elevated tissue plasminogen activator and reduced plasminogen activator inhibitor promote hyperfibrinolysis in trauma patients. Shock. 2014;41(6):514-521.
9. Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg. 1995;81(2):360-365.
10. Rahe-Meyer N, Solomon C, Hanke A, Schmidt DS, Knoerzer D, Hochleitner G, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. Anesthesiology. 2013;118(1):40-50.
11. Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost. 2007;5(2):266-273.
12. Tan V, Doyle CJ, Budzynski AZ. Comparison of the kinetic fibrinogen assay with the von Clauss method and the clot recovery method in plasma of patients with conditions affecting fibrinogen coagulability. Am J Clin Pathol. 1995;104(4): 455-462.
13. Fenger-Eriksen C, Moore GW, Rangarajan S, Ingerslev J, Sorensen B. Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. Transfusion. 2010;50(12):2571-2576.
14. Mackie IJ, Kitchen S, Machin SJ, Lowe GD, Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. Guidelines on fibrinogen assays. Br J Haematol. 2003;121(3):396-404.
15. Ekelund K, Hanke G, Stensballe J, Wikkelsoe A, Albrechtsen CK, Afshari A. Hemostatic resuscitation in postpartum hemorrhage - a supplement to surgery. Acta Obstet Gynecol Scand. 2015;94(7):680-692.
16. Mace H, Lightfoot N, McCluskey S, Selby R, Roy D, Timoumi T, et al. Validity of thromboelastometry for rapid assessment of fibrinogen levels in heparinized samples during cardiac surgery: a retrospective, single-center, observational study. J Cardiothorac Vasc Anesth. 2016;30(1):90-95.
17. de Lange NM, van Rheenen-Flach LE, Lance MD, Mooyman L, Woiski M, van Pampus EC, et al. Peri-partum reference ranges for ROTEM® thromboelastometry. Br J Anaesth. 2014;112(5):852-859.
18. Gill R. Practical management of major blood loss. Anaesthesia. 2015;70 (Suppl 1):54-57, e19-e20.
19. Mallaiah S, Barclay P, Harrod I, Chevannes C, Bhalla A. Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage. Anaesthesia. 2015;70(2):166-175.
20. Lang T, Bauters A, Braun SL, Potzsch B, von Pape KW, Kolde HJ, et al. Multi-centre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis. 2005;16(4):301-310.
21. Gorlinger K, Dirkmann D, Solomon C, Hanke AA. Fast interpretation of thromboelastometry in non-cardiac surgery: reliability in patients with hypo-, normo-, and hypercoagulability. Br J Anaesth. 2013;110(2):222-230.
22. Joist JH, Bauman JE, Sutera SP. Platelet adhesion and aggregation in pulsatile shear flow: effects of red blood cells. Thromb Res. 1998;92(6 Suppl 2):S47-S52.
23. Blajchman MA, Bordin JO, Bardossy L, Heddle NM. The contribution of the haematocrit to thrombocytopenic bleeding in experimental animals. Br J Haematol. 1994;86(2):347-350.
24. Kawasaki J, Katori N, Kodaka M, Miyao H, Tanaka KA. Electron microscopic evaluations of clot morphology during thrombelastography. Anesth Analg. 2004;99(5):1440-1444.
25. Spiezia L, Radu C, Marchioro P, Bertini D, Rossetto V, Castelli M, et al. Peculiar whole blood rotation thromboelastometry (ROTEM) profile in 40 sideropenic anaemia patients. Thromb Haemost. 2008;100(6):1106-1110.
26. Ogawa S, Szlam F, Bolliger D, Nishimura T, Chen EP, Tanaka KA. The impact of hematocrit on fibrin clot formation assessed by rotational thromboelastometry. Anesth Analg. 2012;115(1):16-21.
27. Theusinger O, Baulig W, Seifert B, Emmert M, Spahn D, Asmis L. Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. Br J Anaesth. 2011;106(4):505-511.
28. Service ARCB. Cryoprecipitate 2016 [Internet]. From: https://transfusion.com.au/blood_products/components/cryoprecipitate. Accessed 31 August 2017.
29. Sorensen B, Bevan D. A critical evaluation of cryoprecipitate for replacement of fibrinogen. Br J Haematol. 2010;149(6): 834-843.
30. Ltd CBAP. RiaSTAP® Australia and New Zealand: Product Information/ Data Sheet [Internet]. From: http://www.csl.com.au/docs/304/921/Riastap%20AU%20PI%20v7.00.pdf. Accessed 31 August 2017.
31. Riskin DJ, Tsai TC, Riskin L, Hernandez-Boussard T, Purtill M, Maggio PM, et al. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. J Am Coll Surg. 2009;209(2):198-205.
32. Elliott BM, Aledort LM. Restoring hemostasis: fibrinogen concentrate versus cryoprecipitate. Expert Rev Hematol. 2013;6(3):277-286.
33. Jensen NH, Stensballe J, Afshari A. Comparing efficacy and safety of fibrinogen concentrate to cryoprecipitate in bleeding patients: a systematic review. Acta Anaesthesiol Scand. 2016;60(8):1033-1042.

34. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol. 2017;34(6):332-395.
35. Plug I, Mauser-Bunschoten EP, Bröcker-Vriends AH, van Amstel HKP, van der Bom JG, van Diemen-Homan JE, et al. Bleeding in carriers of hemophilia. Blood. 2006;108(1):52-56.
36. Lord ST. Molecular mechanisms affecting fibrin structure and stability. Arterioscler Thromb Vasc Biol. 2011;31(3):494-499.
37. Fraser SR, Booth NA, Mutch NJ. The antifibrinolytic function of factor XIII is exclusively expressed through alpha(2)-antiplasmin cross-linking. Blood. 2011;117(23):6371-6374.
38. Peyvandi F, Garagiola I, Baronciani L. Role of von Willebrand factor in the haemostasis. Blood Transfus. 2011;9 (Suppl 2):s3-s8.
39. Winearls J. Fibrinogen early in severe trauma study [Internet]. From: http://www.feisty.org.au/information-for-investigators/. Accessed 28 May 2017.
40. Kreuz W, Meili E, Peter-Salonen K, Haertel S, Devay J, Krzensk U, et al. Efficacy and tolerability of a pasteurised human fibrinogen concentrate in patients with congenital fibrinogen deficiency. Transfus Apher Sci. 2005;32(3):247-253.
41. Franchini M, Lippi G. Fibrinogen replacement therapy: a critical review of the literature. Blood Transfus. 2012;10(1):23-27.
42. Bolton-Maggs PH, Perry DJ, Chalmers EA, Parapia LA, Wilde JT, Williams MD, et al. The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. Haemophilia. 2004;10(5):593-628.
43. Bornikova L, Peyvandi F, Allen G, Bernstein J, Manco-Johnson MJ. Fibrinogen replacement therapy for congenital fibrinogen deficiency. J Thromb Haemost. 2011;9(9):1687-1704.
44. Curtis K, Caldwell E, Delprado A, Munroe B. Traumatic injury in Australia and New Zealand. Australas Emerg Nurs J. 2012;15(1):45-54.
45. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, et al. Epidemiology of trauma deaths: a reassessment. J Trauma. 1995;38(2):185-193.
46. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost. 2012;10(7):1342-1351.
47. Stinger HK, Spinella PC, Perkins JG, Grathwohl KW, Salinas J, Martini WZ, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma. 2008;64(2 Suppl):S79-S85.
48. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care. 2016;20:100.
49. Grottke O, Rossaint R. Coagulation factor concentrates and point-of-care coagulation monitoring: both might be essential for optimal treatment of trauma-induced coagulopathy. Lancet Haematol. 2017;4(6):e246-e247.
50. Khan S, Davenport R, Raza I, Glasgow S, De'Ath HD, Johansson PI, et al. Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage. Intensive Care Med. 2015;41(2):239-247.
51. Collins PW, Solomon C, Sutor K, Crispin D, Hochleitner G, Rizoli S, et al. Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate. Br J Anaesth. 2014;113(4):585-595.
52. Schöchl H, Forster L, Woidke R, Solomon C, Voelckel W. Use of rotation thromboelastometry (ROTEM®) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. Anaesthesia. 2010;65(2):199-203.
53. Schöchl H, Nienaber U, Maegele M, Hochleitner G, Primavesi F, Steitz B, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care. 2011;15(2):R83.
54. Yamamoto K, Yamaguchi A, Sawano M, Matsuda M, Anan M, Inokuchi K, et al. Pre-emptive administration of fibrinogen concentrate contributes to improved prognosis in patients with severe trauma. Trauma Surg Acute Care Open Dec. 2016;1(1):e000037.
55. Innerhofer P, Fries D, Mittermayr M, Innerhofer N, von Langen D, Hell T, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol. 2017; 4(6):e258-e271.
56. Steinmetz J, Sorensen AM, Henriksen HH, Lange T, Larsen CF, Johansson PI, et al. Pilot Randomized trial of Fibrinogen in Trauma Haemorrhage (PRooF-iTH): study protocol for a randomized controlled trial. Trials. 2016;17(1):327.
57. Wafaisade A, Lefering R, Maegele M, Brockamp T, Mutschler M, Lendemans S, et al. Administration of fibrinogen concentrate in exsanguinating trauma patients is associated with improved survival at 6 hours but not at discharge. J Trauma Acute Care Surg. 2013;74(2):387-383.
58. Ford JB, Patterson JA, Seeho SK, Roberts CL. Trends and outcomes of postpartum haemorrhage, 2003-2011. BMC Pregnancy Childbirth. 2015;15:334.
59. Paidas MJ, Hossain N, Shamsi TS, Rodger MA, Langhoff-Roos J, Lockwood CJ, editors. Hemostasis and thrombosis in obstetrics & gynecology. Oxford: Wiley- Blackwell; 2011.
60. Huissoud C, Carrabin N, Benchaib M, Fontaine O, Levrat A, Massignon D, et al. Coagulation assessment by rotation thrombelastometry in normal pregnancy. Thromb Haemost. 2009;101(4):755-761.
61. Karlsson O, Jeppsson A, Thornemo M, Lafrenz H, Rådström M, Hellgren M. Fibrinogen plasma concentration before delivery is not associated with postpartum haemorrhage: a prospective observational study. Br J Anaesth. 2015;115(1):99-104.
62. Huissoud C, Carrabin N, Audibert F, Levrat A, Massignon D, Berland M, et al. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. BJOG. 2009;116(8):1097-1102.

63. Bell SF, Rayment R, Collins PW, Collis RE. The use of fibrinogen concentrate to correct hypofibrinogenaemia rapidly during obstetric haemorrhage. Int J Obstet Anesth. 2010;19(2):218-223.
64. Fenger-Eriksen C, Lindberg-Larsen M, Christensen AQ, Ingerslev J, Sorensen B. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. Br J Anaesth. 2008;101(6): 769-773.
65. Wikkelso AJ, Edwards HM, Afshari A, Stensballe J, Langhoff-Roos J, Albrechtsen C, et al. Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. Br J Anaesth. 2015;114(4):623-633.
66. Collins P. Cardiff University Centre of Trials Research: OBS2 2013. [Internet]. From: http://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/obs2. Accessed 31 August 2017.
67. Ranucci M, Baryshnikova E, Castelvecchio S, Pelissero G, Surgical and Clinical Outcome Research (SCORE) Group. Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. Ann Thorac Surg. 2013;96(2):478-485.
68. Jeppsson A, Walden K, Roman-Emanuel C, Thimour-Bergstrom L, Karlsson M. Preoperative supplementation with fibrinogen concentrate in cardiac surgery: a randomized controlled study. Br J Anaesth. 2016;116(2):208-214.
69. Besser MW, Ortmann E, Klein AA. Haemostatic management of cardiac surgical haemorrhage. Anaesthesia. 2015;70 (Suppl 1):87-95, e29-e31.
70. Bilecen S, de Groot JA, Kalkman CJ, Spanjersberg AJ, Brandon Bravo Bruinsma GJ, Moons KG, et al. Effect of fibrinogen concentrate on intraoperative blood loss among patients with intraoperative bleeding during high-risk cardiac surgery: a randomized clinical trial. JAMA. 2017;317(7):738-747.
71. Rahe-Meyer N, Levy JH, Mazer CD, Schramko A, Klein AA, Brat R, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. Br J Anaesth. 2016;117(1):41-51.
72. Fominskiy E, Nepomniashchikh VA, Lomivorotov VV, Monaco F, Vitiello C, Zangrillo A, et al. Efficacy and safety of fibrinogen concentrate in surgical patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2016;30(5):1196-1204.
73. Ranucci M, Baryshnikova E, Crapelli GB, Rahe-Meyer N, Menicanti L, Frigiola A, et al. Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. J Am Heart Assoc. 2015;4(6):e002066.
74. Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, Winterhalter M, Piepenbrock S, et al. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. Br J Anaesth. 2009;102(6):785-792.
75. Solomon C, Pichlmaier U, Schoechl H, Hagl C, Raymondos K, Scheinichen D, et al. Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. Br J Anaesth. 2010;104(5):555-562.
76. Rahe-Meyer N, Solomon C, Winterhalter M, Piepenbrock S, Tanaka K, Haverich A, et al. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. J Thorac Cardiovasc Surg. 2009;138(3):694-702.
77. Ranucci M, Baryshnikova E. Fibrinogen supplementation after cardiac surgery: insights from the Zero-Plasma trial (ZEPLAST). Br J Anaesth. 2016;116(5):618-623.
78. Rahe-Meyer N, Hanke A, Schmidt DS, Hagl C, Pichlmaier M. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: results from a randomized, placebo-controlled trial. J Thorac Cardiovasc Surg. 2013;145(3 Suppl):S178-S185.
79. Ranucci M, Jeppsson A, Baryshnikova E. Pre-operative fibrinogen supplementation in cardiac surgery patients: an evaluation of different trigger values. Acta Anaesthesiol Scand. 2015;59(4):427-433.
80. Bolliger D, Gonsahn M, Levy JH, Williams WH, Tanaka KA. Is preoperative fibrinogen predictive for postoperative bleeding after coronary artery bypass grafting surgery? Transfusion. 2009;49(9):2006-2007.
81. Gielen C, Dekkers O, Stijnen T, Schoones J, Brand A, Klautz R, et al. The effects of pre- and postoperative fibrinogen levels on blood loss after cardiac surgery: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2014;18(3):292-298.
82. Davis AK. When more is less efficacious: fibrinogen concentrate in complex cardiac surgery. Br J Anaesth. 2016;117(4): 415-417.
83. Schenk B, Lindner AK, Treichl B, Bachler M, Hermann M, Larsen OH, et al. Fibrinogen supplementation ex vivo increases clot firmness comparable to platelet transfusion in thrombocytopenia. Br J Anaesth. 2016;117(5):576-582.
84. Samama CM, Djoudi R, Lecompte T, Nathan-Denizot N, Schved JF, Agence Francaise de Securite Sanitaire des Produits de Sante expert group. Perioperative platelet transfusion: recommendations of the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSaPS) 2003. Can J Anaesth. 2005;52(1):30-37.
85. Bux J. Transfusion-related acute lung injury (TRALI): a serious adverse event of blood transfusion. Vox Sang. 2005;89(1):1-10.
86. Blajchman MA. Incidence and significance of the bacterial contamination of blood components. Dev Biol (Basel). 2002;108:59-67.
87. Perrotta PL, Snyder EL. Non-infectious complications of transfusion therapy. Blood Rev. 2001;15(2):69-83.
88. Lang T, Johanning K, Metzler H, Piepenbrock S, Solomon C, Rahe-Meyer N, et al. The effects of fibrinogen levels on thromboelastometric variables in the presence of thrombocytopenia. Anesth Analg. 2009;108(3):751-758.
89. Bolliger D, Szlam F, Molinaro RJ, Rahe-Meyer N, Levy JH, Tanaka KA. Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. Br J Anaesth. 2009;102(6):793-799.
90. Camazine MN, Hemmila MR, Leonard JC, Jacobs RA, Horst JA, Kozar RA, et al. Massive transfusion policies at trauma centers participating in the American College of Surgeons Trauma Quality Improvement Program. J Trauma Acute Care Surg. 2015;78(6 Suppl 1):S48-S53.

91. Ponschab M, Voelckel W, Pavelka M, Schlimp CJ, Schochl H. Effect of coagulation factor concentrate administration on ROTEM® parameters in major trauma. Scand J Trauma Resusc Emerg Med. 2015;23:84.
92. Department of Anaesthesia and Pain Medicine and the Hospital Transfusion Committee. KEMH ROTEM algorithm for critical bleeding [Internet] 2016. From: http://kemh.health.wa.gov.au/services/blood_transfusion/documents/WNHS.HAEM.ROTEMAlgorithm.pdf. Accessed 31 August 2017.
93. Karri JV, Cardenas JC, Johansson PI, Matijevic N, Cotton BA, Wade CE, et al. Invitro efficacy of RiaSTAP after rapid reconstitution. J Surg Res. 2014;190(2):655-661.
94. Solomon C, Groner A, Ye J, Pendrak I. Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data. Thromb Haemost. 2015;113(4):759-771.
95. Solomon C, Hagl C, Rahe-Meyer N. Time course of haemostatic effects of fibrinogen concentrate administration in aortic surgery. Br J Anaesth. 2013;110(6):947-956.
96. Schlimp CJ, Ponschab M, Voelckel W, Treichl B, Maegele M, Schochl H. Fibrinogen levels in trauma patients during the first seven days after fibrinogen concentrate therapy: a retrospective study. Scand J Trauma Resusc Emerg Med. 2016;24:29.
97. Zentai C, Braunschweig T, Schnabel J, Rose M, Rossaint R, Grottke O. Fibrinogen concentrate does not suppress endogenous fibrinogen synthesis in a 24-hour porcine trauma model. Anesthesiology. 2014;121(4):753-764.
98. Australia NBA. National Product Price List 1 Jan 2017 [Internet]. From: https://www.blood.gov.au/national-product-list. Accessed 31 Agust 2017.
99. Okerberg CK, Williams LA 3rd, Kilgore ML, Kim CH, Marques MB, Schwartz J, et al. Cryoprecipitate AHF vs. fibrinogen concentrates for fibrinogen replacement in acquired bleeding patients - an economic evaluation. Vox Sang. 2016;111(3): 292-298.
100. Fenger-Eriksen C, Lindberg-Larsen M, Christensen A, Ingerslev J, Sørensen B. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. Br J Anaesth. 2008;101(6): 769-773.
101. Theodoulou A, Berryman J, Nathwani A, Scully M. Comparison of cryoprecipitate with fibrinogen concentrate for acquired hypofibrinogenaemia. Transfus Apher Sci. 2012;46(2):159-162.
102. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2013;30(6): 270-382.
103. Armstrong S, Fernando R, Ashpole K, Simons R, Columb M. Assessment of coagulation in the obstetric population using ROTEM® thromboelastometry. Int J Obstet Anesth. 2011;20(4):293-298.
104. Weber CF, Zacharowski K, Meybohm P, Adam EH, Hofer S, Brun K, et al. Hemotherapy algorithms for coagulopathic cardiac surgery patients. Clin Lab. 2014;60(6):1059-1063.
105. Gorlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology. 2011;115(6):1179-1191.

Evidence, new methods and current practice of point-of-care coagulation testing in major haemorrhage

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INTRODUCTION

Major haemorrhage causes coagulopathy, although the proportion of patients who become coagulopathic by standard laboratory indices [prothrombin time (PT), activated partial thromboplastin time (APTT), platelet count and fibrinogen concentration] depends heavily on resuscitation practice. For example, coagulopathy developed in >70 per cent of trauma patients given >10 units of PRBC and crystalloid (in an era when plasma and platelets were only transfused after coagulopathy developed)[1], while whole blood transfused to Vietnam War casualties resulted in only mild coagulopathy an no observable coagulopathic bleeding[2]. However, in major bleeding (due to trauma), coagulopathy occurs in around 25-28 per cent of patients in the absence of dilution[3,4]. This trauma-induced coagulopathy (TIC) is thought instead to be caused by hypoperfusion, thrombomodulin induced activation of the protein C pathway, causing deactivation of factors Va and VIIIa and initiation of fibrinolysis[5]. Hypoperfusion from non-traumatic major haemorrhage possibly activates similar mechanisms. At clinically relevant levels, patient features traditionally hypothesised to cause coagulopathy (acidemia and hypothermia) are most likely no more than non-causative associations[6].

Coagulopathy in trauma[3,4] and other forms of major haemorrhage[7,8] is clearly associated with a higher case fatality rate. While most studies statistically isolate an independent effect of coagulopathy from underlying severity of illness, the superficially attractive notion that coagulopathy causes more bleeding and so more death is in reality questionable[9]. Most deaths due to haemorrhage are not due to uncontrolled microvascular bleeding. Nonetheless, resuscitation strategies that avoid or correct coagulopathy are so appealing that they should not really be questioned. The relevant question is how best to achieve expansion of the circulating blood volume and improve coagulopathy rapidly, economically, and without introducing adverse effects from therapy.

RATIO-BASED RESUSCITATION

Resuscitation thinking in major haemorrhage was fundamentally altered by a US military retrospective observational study showing higher transfused ratios of plasma to red blood cell units were associated with dramatically lower mortality[10]. Disappointingly, most of this effect is now recognised to be due to survivor bias (patients had to live long enough to receive plasma)[11]. A high-plasma-ratio resuscitation strategy seems unable to prevent coagulopathy after trauma[12], and a plasma:platelet:red cell ratio of 1:1:2 versus 1:1:1 resulted in no observable difference in 24-hour or 30-day mortality[13]. Observational studies have found high ratios of platelet administration to be beneficial[14,15], but the possibility of confounding remains. Paradoxically, a large observational study found high ratio plasma to red cell transfusions in major haemorrhage in medical and general surgical patients seems detrimental[16]. Notwithstanding all the above concerns, unlike resuscitation that omits clotting factors, plasma- and platelet-ratio based resuscitation seems at least not to make coagulopathy worse and so is the default strategy to which alternatives should be compared.

The concern with ratio-based protocols is that they might not achieve the four goals (efficacy, safety, speed, economy) as well as alternatives. Coagulopathy in major haemorrhage varies between patients, so fixed ratios will deliver plasma and platelets to some patients who do not need them. Further, the fibrinogen content of thawed fresh frozen plasma is low, suggesting either cryoprecipitate or fibrinogen concentrate should be added – but there is little evidence to guide their appropriate ratio. Fibrinogen concentrate is quicker to administer than either FFP or cryoprecipitate, and has a standardised fibrinogen concentration (although this advantage is moot if there is way to judge appropriate dosing). A diagnostic test that could show within minutes what clotting factors and platelets a particular patient requires would fix all of these problems.

POINT OF CARE VISCOELASTIC TESTING VERSUS STANDARD LABORATORY TESTS

Rapid identification of the key components of coagulation dysfunction associated with major haemorrhage has the potential to facilitate interventions to reduce blood loss, limit blood product transfusion and ultimately reduce mortality. Standard laboratory tests (SLT) have limited utility in the assessment of the complex, heterogeneous and multifactorial coagulopathy associated with major haemorrhage[17]. These tests are performed on platelet-poor plasma and are designed to assess single factor deficiencies and the effects of anticoagulant therapy, not complex multifactorial coagulopathies. Abnormal SLT can be associated with adverse outcomes but are poor predictors of bleeding, do not accurately define the various components of the coagulation system contributing to coagulopathy and give no information on clot strength or stability[18]. Further, they do not assess platelet or endothelial function – both major contributors to traumatic and most likely other forms of coagulopathy in major haemorrhage. Thrombocytopenia undoubtedly worsens coagulopathy, but most major haemorrhage patients are not thrombocytopenic and abnormal platelet function is not quantified by numerical platelet count. The major drawback of utilising SLT in major active haemorrhage is the time taken for result availability, which limits their utility in guiding transfusion of actively bleeding patients[19]. Rapid, point-of-care Pro-thrombin time analysis can overcome this time delay issue, but reliability and clinical utility is controversial[20-22]. Many of these problems are potentially solved by point-of-care (POC) viscoelastic haemostatic assays (VHA). VHA are performed on whole blood and provide information on clot initiation, amplification, strength and stability. They potentially allow differentiation of the various components of the coagulation system contributing to clot kinetics and provide results more rapidly than SLT[23,24].

Current Australian NHMRC Patient Blood Management guidelines make no recommendation on POC VHA testing. Module 1 (Critical Bleeding Massive Transfusion)[25] notes increasing use of POC tests but specifically excludes them from its systematic review. Module 2 (Perioperative)[26] limited its review to TEG, concluding only that "in adult patients undergoing cardiac surgery, the use of TEG should be considered (Grade C recommendation – a body of evidence provides some support for the recommendation but care should be taken in its application)". A 2015 Cochrane review in trauma patients concluded the paucity of evidence "strongly suggests that at present these tests should only be used for research"[27]. Contrary to often-repeated claims, POC tests do not measure the "whole" of the clotting system. They take no account of endothelial function, and assay blood from large vessels rather than the more relevant microvasculature, where haematocrit is lower and acidaemia more profound[28]. In 2016, only 9 per cent of US trauma centres incorporated viscoelastic testing into their massive transfusion protocols[29]. Nonetheless, anyone claiming lack of evidence for POC testing must also concede a similar lack of evidence supporting improved patient outcomes with standard laboratory coagulation tests in this context. Despite the lack of evidence to support the use of VHA in terms of mortality, their use is endorsed by several international guidelines[30,31]. As the implementation and use of VHA becomes more widespread in everyday anaesthetic practice it is of critical importance that we are aware of the potential benefits and drawbacks associated with this technology.

POINT-OF-CARE COAGULATION TESTING: WHAT NEW TECHNOLOGY IS AVAILABLE?

This review will predominantly focus on viscoelastic whole blood POC assays. One of the major drawbacks of the currently available viscoelastic devices is the inability to differentiate fully the effects of platelet dysfunction and its contribution to coagulopathic bleeding. Multiple electrode impedance aggregometry devices (for example, Multiplate; Roche, Basel, Switzerland) can potentially identify abnormal platelet function associated with increased bleeding and mortality[32,33]. However, there is limited data to support the routine use of platelet function analysis in guiding platelet transfusion[34]. The HemoSonics Quantra Platform (HemoSonics LLC, Charlottesville, VA, US) is a new viscoelastic device that assays clot formation from vibration in response to ultrasound. However, only two manufacturers currently dominate this market: TEM International GmBH, Munich, Germany (maker of the ROTEM device) and Haemonetics, Braintree, MA, USA (makers of the TEG device). The physical cup/pin principles of the original ROTEM Delta and TEG 5000 devices currently in widespread use are described well elsewhere. The test reagents differ and so indices of clot formation are not interchangeable. Each device uses various clot initiators and inhibitors allow assessment of platelet, fibrinogen, fibrinolytic and heparin effects on clotting. Both manufacturers recently introduced automated devices that claim to provide the same results: the ROTEM Sigma (figure 1) and the TEG 6S (figure 2). The ROTEM Sigma provides two cartridge choices (table 1) for use with citrated whole blood. The TEG 6S is also a cartridge-based device that offers the options listed in table 2. Unlike the TEG 5000, the TEG 6S can use citrated whole blood samples (for the global haemostasis cartridge) or heparinised whole blood (for the platelet mapping cartridge).

Figure 1. ROTEM Sigma

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Figure 2. TEG 6S

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Table 1. ROTEM Sigma Tests

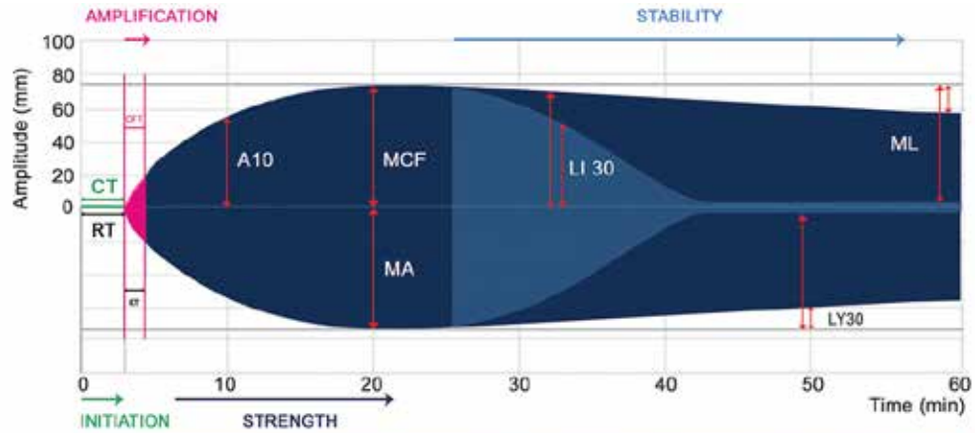
	INTEM C	EXTEM C	FIBTEM C	APTEM C	HEPTEM C
	Intrinsic clotting pathway (factors VIII-XII) (affected by heparin; also measured by APTT)	Extrinsic clotting pathway (factor VII) (affected by warfarin; also measured by PT)	Removes the effect of platelets from clot formation, consequently identifying the isolated effect of fibrinogen	Inhibits fibrinolysis in the sample, therefore identifying the effect of antifibrinolytic drugs	Neutralises heparin effect in the intrinsic pathway, identifying how much clotting inhibition is due to heparin
ROTEM Sigma complete	X	X	X	X	-
ROTEM Sigma complete + hep	X	X	X	-	X

Both the ROTEM Sigma and TEG 6s produce traces with the same appearance as the older-generation pin/cup devices (figure 3). The ROTEM Sigma cartridge (figure 4) uses a miniature version of the rotating pin and fixed cup used in the ROTEM Delta. In contrast, the TEG 6S measures shear stress changes during clot formation with a resonance frequency technique involving piezoelectric vibrations applied to the blood sample, with the resulting meniscus motion detected using a light passing to a photodetector (figure 5). Identical samples tested with the old/new TEG and ROTEM devices do not produce identical results, but agreement is considered satisfactory[35,36].

Table 2. TEG 6S Tests

	KAOLIN TEG	RAPID TEG	TEG FUNCTIONAL FIBRINOGEN	TEG PLATELET MAPPING	KAOLIN TEG WITH HEPARINASE
	Intrinsic clotting pathway (factors VIII-XII) (affected by heparin; also measured by APTT)	Simultaneously activates the intrinsic and extrinsic pathways to more rapidly assess coagulation properties	Removes the effect of platelets from clot formation, consequently identifying the isolated effect of fibrinogen	Includes thrombin generated and platelet-receptor specific tracings. Identifies platelet inhibition and aggregation using the Kaolin TEG as the control.	Neutralises heparin effect in the intrinsic pathway, identifying how much clotting inhibition is due to heparin
Global haemostasis cartridge	X	X	X	–	X
Platelet mapping cartridge	–	–	–	(includes four assays: maximum clotting potential, clot strength due to fibrinogen, and clot strength that would be inhibited by a. clopidogrel and b. aspirin.)	–

Figure 3. ROTEM and TEG Tracings



PHASE	TEG Parameter	ROTEM Parameter	Coagulation Factor
INITIATION	R – Reaction Time Measured in Seconds	CT - Clotting Time Measured in Seconds	Pro-Coagulant Factors Anti-Coagulant Factors
AMPLIFICATION / KINETICS	K – Kinetic Time Measured in Seconds	CFT - Clot Formation Time Measured in Seconds	Pro-Coagulant Factors Anti-Coagulant Factors Fibrinogen Platelets
PROPAGATION / STRENGTH	Amplitude after RT Measured in mm MA – Maximum Amplitude	Amplitude after CT Measured in mm A5 – Amplitude after 5 mins A10 – Amplitude after 10 mins MCF – Maximum Clot Firmness	Fibrinogen Platelets FXIII
STABILITY / LYSIS	LY – Lysis Measured in % of MA LY30 – 30 mins after MA	LI (Lysis Index/Residual Clot Firmness) Measured in % of MCF LI30 – 30 mins after CT ML – Maximum Lysis in % of MCF	Fibrinolytic Factors Fibrinolytic Inhibitors

Figure 4. ROTEM Sigma Cartridge

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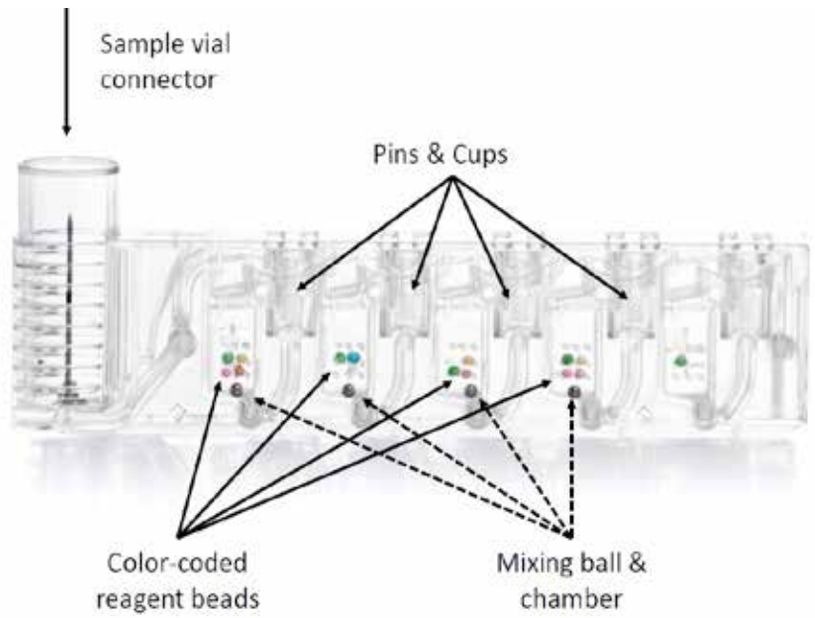

Figure 5. TEG 6S Cartridge and Mechanism

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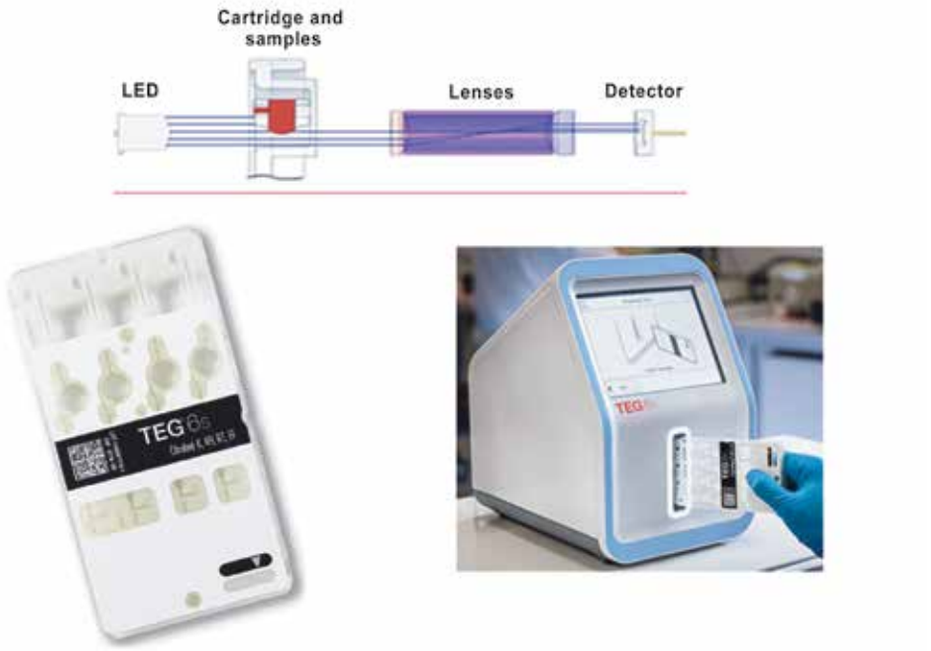


GOLD COAST UNIVERSITY HOSPITAL (GCUH) ROTEM GUIDED APPROACH

A ROTEM guided POC model was implemented at GCUH in 2014 initially in cardiac surgery and subsequently expanded to other forms of major haemorrhage including trauma, obstetrics, vascular surgery and incorporated into the GCUH Major Haemorrhage Protocol[37]. Devices are currently located in the ED, OR and ICU with results streamed to key clinical areas. During significant haemorrhage, ROTEM analysis is performed by a predetermined clinician, responsible for blood product transfusion and liaison with the blood bank. Strict training, education and competency policies are followed, as is participation in The Royal College of Pathologists of Australasia Quality Assurance Program. There are two algorithms in use at GCUH – cardiac surgery and general critical bleeding (figures 6 and 7). Both have been designed to be simple to teach, understand and follow, with tests run, interpreted and acted upon in a stepwise manner. The approach is highlighted by the following cases.

Figure 6. Cardiac surgery algorithm in use at Gold Coast University Hospital

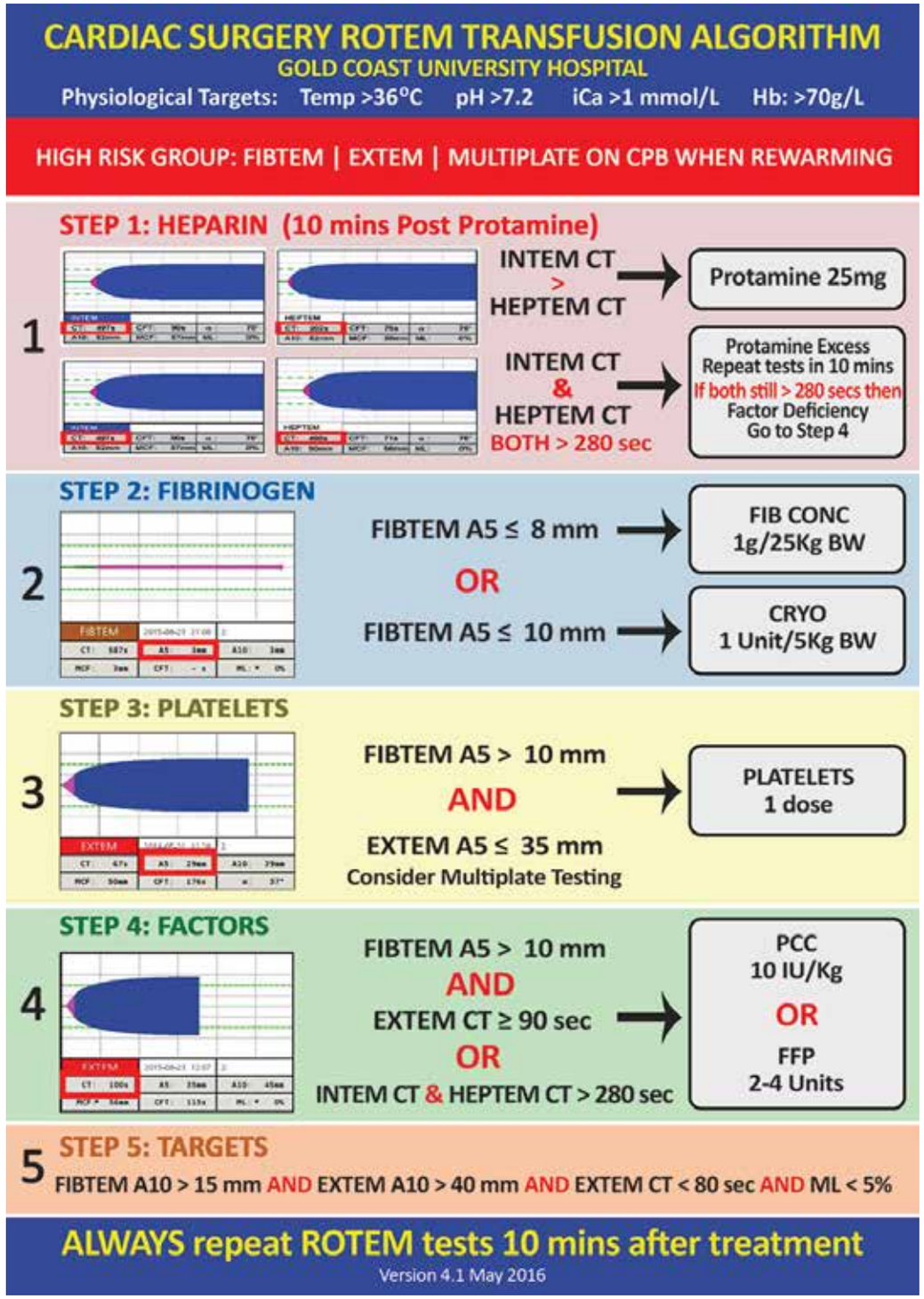
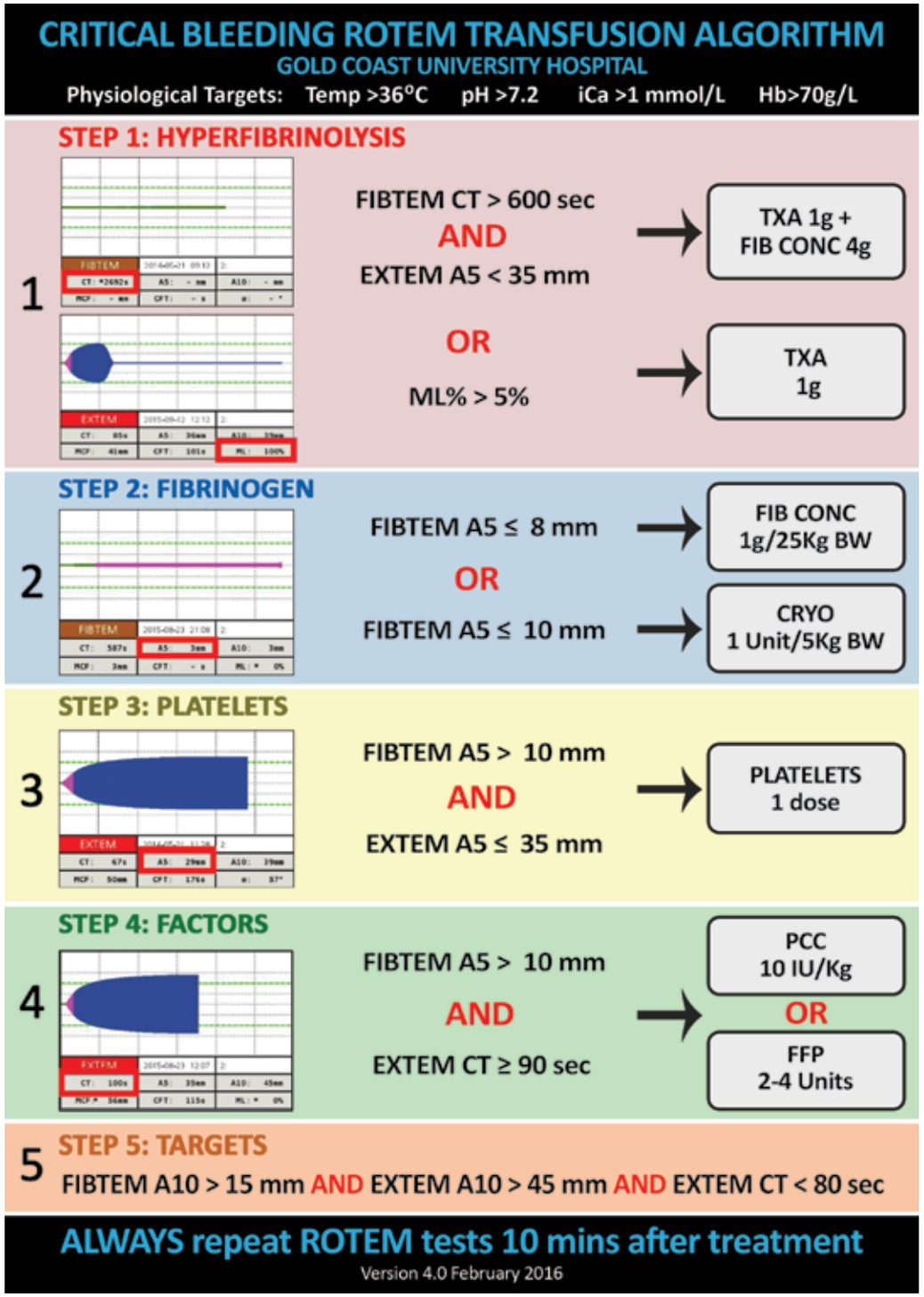


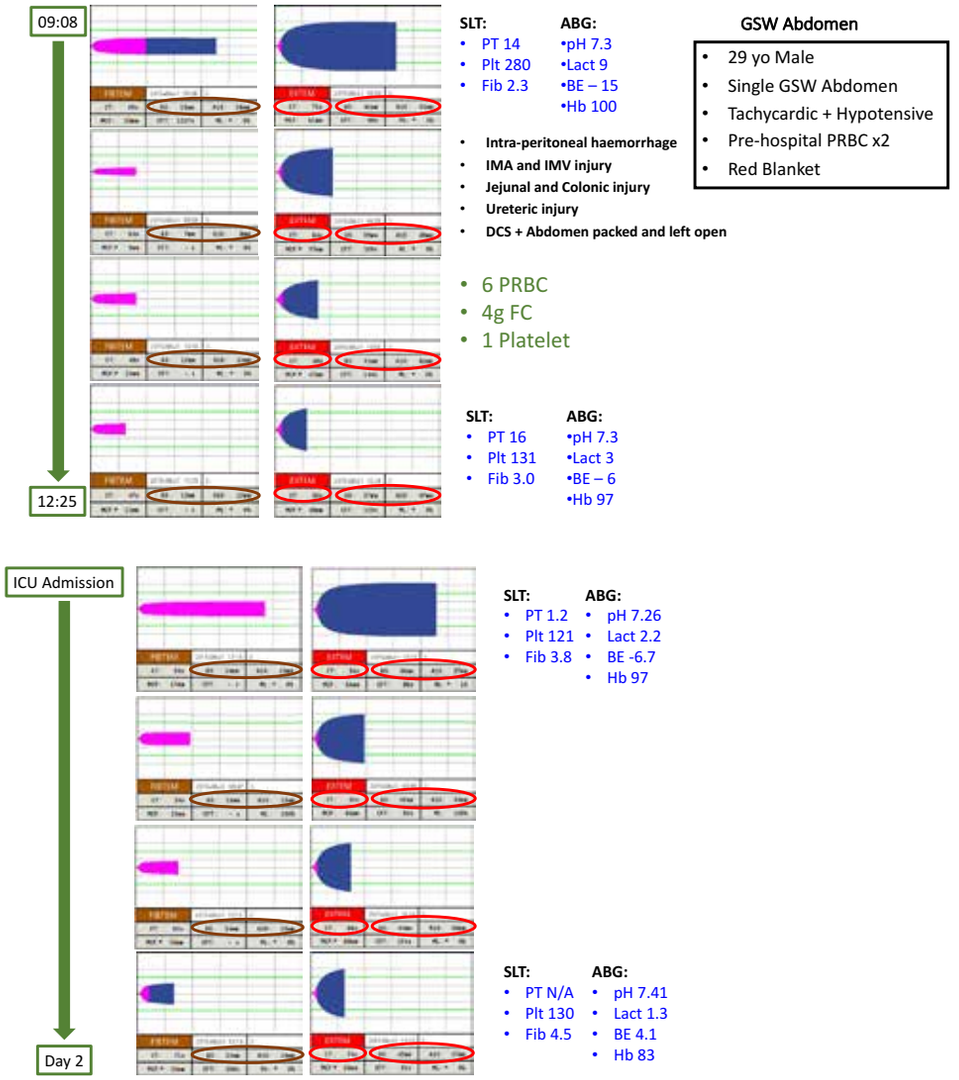
Figure 7. Clinical bleeding algorithmin in use at Gold Coast University Hospital



Trauma cases

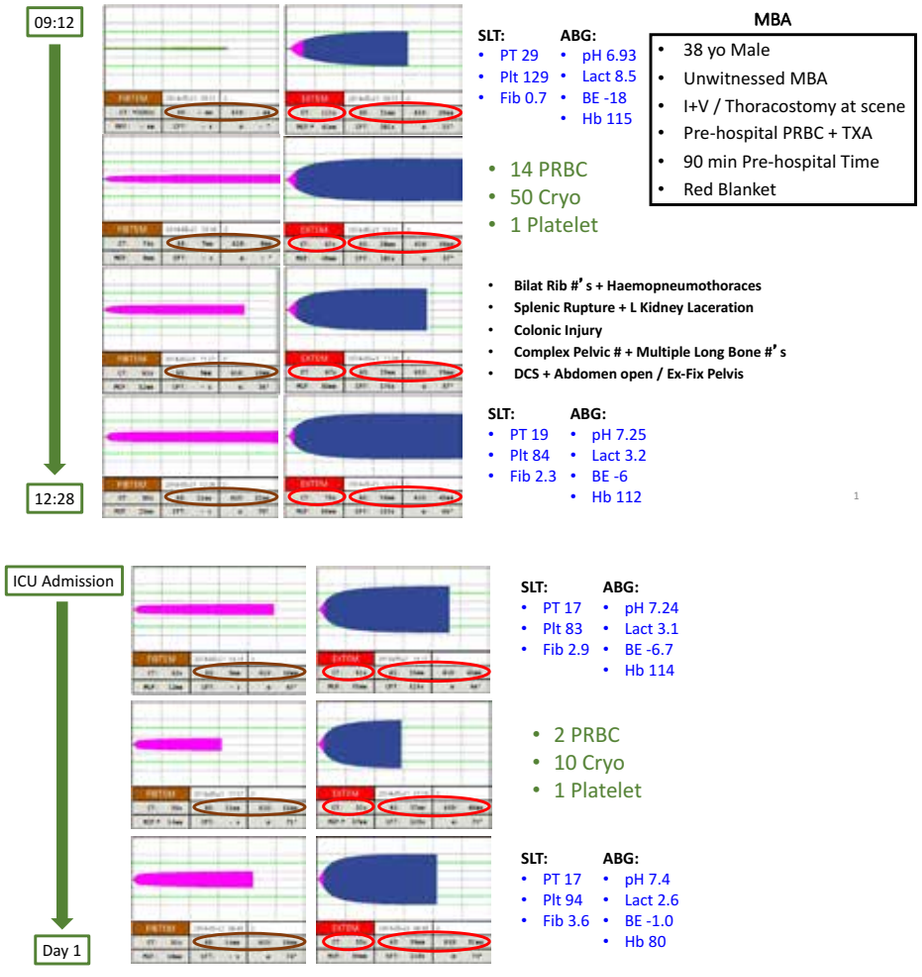
A 29-year-old male sustained a single gunshot wound to the abdomen at approximately 8.30am (figure 8). He was rapidly transported to GCUH and arrived at 9am, receiving two PRBC units and tranexamic acid (TXA) en route. On arrival, he was tachycardic and hypotensive and the "red blanket" protocol was activated, facilitating his immediate transfer to the operating theatre. His initial ROTEM on arrival to hospital revealed normal parameters in all tests and this was supported by the subsequent normal standard coagulation profile. Damage control laparotomy revealed significant intra-abdominal injuries. As per the GCUH ROTEM guided Major Haemorrhage Protocol (MHP), he received PRBC transfusion with repeat ROTEM analysis after four PRBC. Subsequent ROTEM demonstrated reduced clot amplitude in the FIBTEM test with a normal EXTEM CT, so he was given 4g FC. Further ROTEM analysis post fibrinogen replacement showed improved clot amplitude in the FIBTEM test but borderline reduced amplitude in the EXTEM test. In view of on-going bleeding he was transfused one unit of pooled platelets. At completion of laparotomy, haemorrhage control was achieved with normalisation of ROTEM parameters and standard coagulation profile and improvement in metabolic disturbance. Subsequent ROTEM analysis from ICU admission demonstrated the increased clot amplitude in both the FIBTEM and EXTEM tests that would be expected after significant trauma. It is our standard practice to monitor ROTEM parameters daily after major trauma and to initiate venous thromboembolism prophylaxis as soon as possible.

Figure 8. GSW Abdomen-3



A 38-year-old male was involved in an unwitnessed motorbike accident (figure 9). His trachea was intubated at the scene and bilateral finger thoracostomies were performed in the setting of clinically apparent significant chest injuries and hypotension. He was airlifted to GCUH and received PRBC and TXA transfusion en route. On arrival he was hypotensive, acidotic, coagulopathic and a red blanket protocol was activated. Initial FIBTEM analysis revealed no clot formation with markedly reduced clot amplitude in the EXTEM analysis. In tandem with damage control surgery and PRBC transfusion he was transfused 20 units cryoprecipitate (this was prior to FC availability) and further TXA. The prolonged EXTEM CT corrected with cryoprecipitate transfusion and no purified factor replacement was given. Throughout the resuscitation ROTEM analysis was performed and further cryoprecipitate and platelets were transfused in addition to 14 units PRBC. Major thoracic, abdominal, pelvic and long bone injuries were identified. At completion of damage control abdominal and orthopaedic surgery his ROTEM parameters and standard coagulation tests had normalised. After arrival in the ICU there was on-going diffuse bleeding from multiple operative and venepuncture sites. He was transfused further cryoprecipitate and platelets as per ROTEM analysis and the bleeding ceased; by day one his ROTEM analysis and standard coagulation profile had normalised.

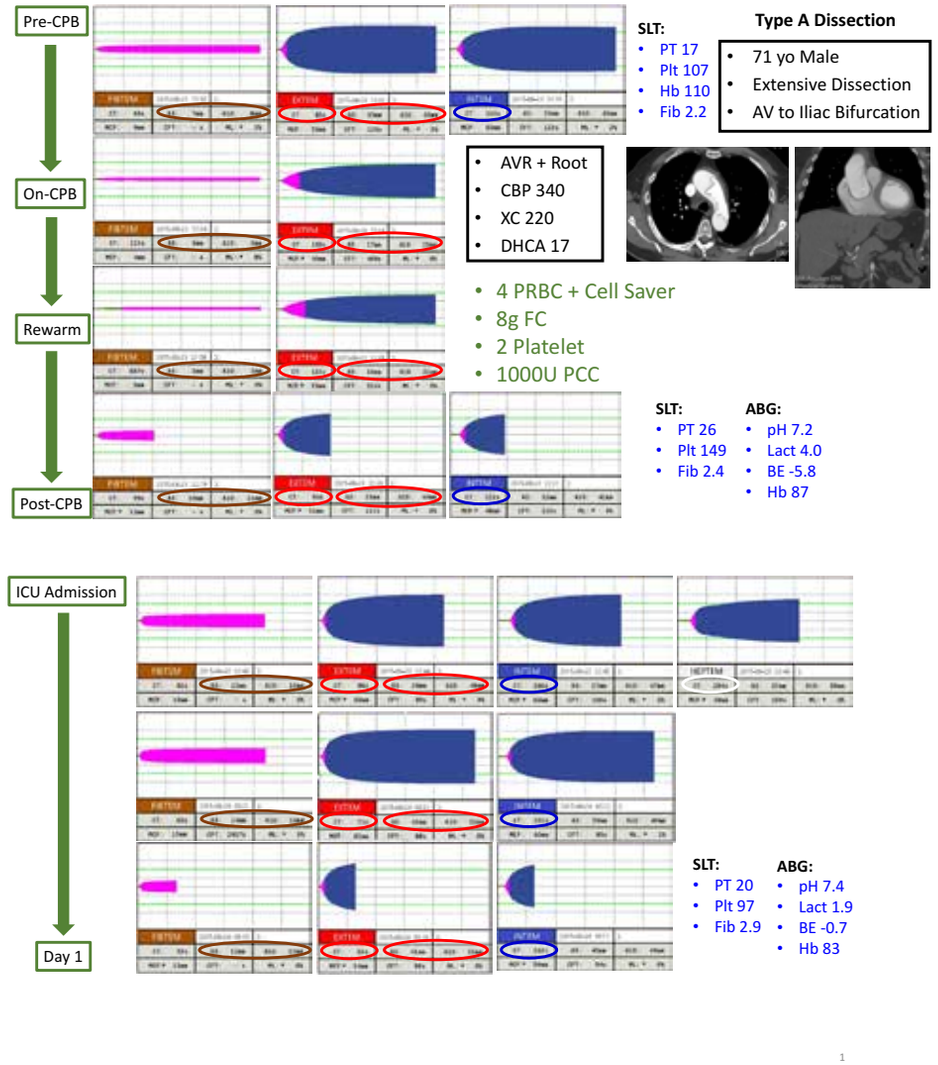
Figure 9. MBA-3



Cardiac surgical case

Blood product transfusion is common in cardiothoracic surgery, but only a small proportion of patients consume the majority of these blood products[38]. Blood product transfusion rates and clinical practice vary widely between centres; higher volume surgical units may have lower transfusion rates[39]. Excessive post-operative bleeding in the cardiac surgical patient is associated with worse outcomes and is a major focus for improving morbidity and mortality. Post-operative surgical bleeding can be surgical (most often requiring re-sternotomy), coagulopathic (multifactorial) or related to pre-operative anticoagulation and antiplatelet agents. One of the main challenges is to differentiate between the various causes to permit the appropriate and timely intervention. The coagulopathy associated with cardiac surgery is complex and multifactorial: large doses of heparin; exposure to an extracorporeal circuit; hypothermia; haemodilution; factor consumption; platelet dysfunction and fibrinolysis may all contribute. The exact pathophysiological mechanisms are beyond the scope of this article but what is clear is that the rapid identification of the different contributing components can permit timely intervention. The optimal blood product transfusion strategy in cardiac surgery remains elusive, however, there is increasing interest in the use of VHA[40]. Based on clinical information it is difficult to predict which patients require factor replacement. There can be little benefit to treating those patients that are not factor deficient, so it would seem logical to identify and treat only those patients in whom coagulopathy is contributing to on-going bleeding. The ROTEM guided approach to the management of post cardiac surgical bleeding at the GCUH is illustrated in the following case (figure 10).

Figure 10. Type A Dissection-2



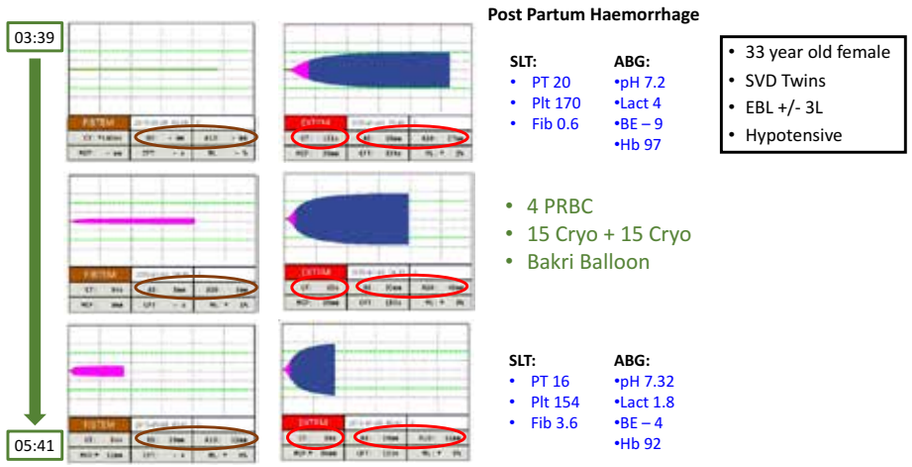
A 71-year-old male underwent emergency repair of a Type A dissection. Apart from hypertension, he had been previously well, on no anticoagulants or antiplatelet agents. The dissection extended from the aortic valve to the iliac bifurcation involving the brachiocephalic trunk, left subclavian artery, left renal artery and superior mesenteric artery. A pre-operative ROTEM demonstrated marginal clot strength in the FIBTEM test. Total cardio-pulmonary bypass (CPB) time was 300 minutes with 17 minutes of deep hypothermic cardiac arrest. The on-CPB and re-warm ROTEM demonstrate markedly reduced clot firmness in both the FIBTEM and EXTEM tests with a prolonged EXTEM CT. At separation from CPB he was transfused 6g FC and 2x Pool Platelets in addition to protamine, PRBC and cell saver blood. According to our algorithm we would usually replace fibrinogen first and subsequently platelets, after adequate clot strength is demonstrated in the FIBTEM test. However, in view of the long CPB time, complex proximal aortic surgery and high probability of coagulopathic bleeding associated with Type A dissection repair we instead gave platelets empirically. Subsequent ROTEM analysis post-CPB demonstrated a normal INTEM CT suggesting adequate reversal of heparin, marginal clot firmness in the FIBTEM test and a slightly prolonged EXTEM CT; in the context of microvascular bleeding further FC and PCC were transfused. On return to the ICU the ROTEM parameters had returned to normal with minimal drain losses.

Major obstetric haemorrhage case

Major obstetric haemorrhage is a significant cause of morbidity and mortality. Rates of post partum haemorrhage have remained unchanged despite advances in obstetric management[41,42]. Causes of obstetric haemorrhage are heterogeneous; with each aetiology having different patterns of severity and subsequent coagulopathy. As such it is difficult to rationalise how a fixed ratio empiric approach to blood product management in major obstetric haemorrhage would be appropriate for all patients. The ROTEM guided approach to the management of major obstetric haemorrhage at the Gold Coast University Hospital is shown in the following case (figure 11).

A previously well 33-year-old female developed significant post-partum haemorrhage after normal vaginal delivery of healthy twins at 33 weeks' gestation. After urgent transfer to the operating theatre, a ROTEM analysis demonstrated significant fibrinogen deficiency in addition to prolonged EXTEM CT and reduced EXTEM amplitude. Resuscitation in tandem with surgical control was performed. Based on the initial ROTEM at 3.39am 15 units of cryoprecipitate were transfused in addition to PRBC and TXA. We would administer TXA in the pregnant patient population if there were VHA signs of hyperfibrinolysis or in the absence of VHA availability empiric TXA as per the results of the recently published WOMAN Trial[43]. The initial ROTEM at 3.39am also showed a prolonged EXTEM CT of 151 seconds, which could potentially signify a factor deficiency. However, in this situation with significant fibrinogen deficiency we would replace fibrinogen prior to factors and then reassess. Frequently a prolonged EXTEM CT (in the absence of anticoagulants) can be corrected with fibrinogen replacement alone. The ROTEM analysis performed at 04:38 demonstrated an increment in the FIBTEM amplitude but despite cryoprecipitate remained low at 5mm. The EXTEM CT had normalised after fibrinogen replacement. There was on-going haemorrhage with PRBC requirements and a Bakri balloon was inserted after removal of retained products. A further 15 units of cryoprecipitate were transfused with normalisation of ROTEM parameters, and surgical haemorrhage control was achieved.

Figure 11. PPH



Validation of POC testing

In an insightful discussion[44], Solomon et al discuss the concept of "validation" of clinical tests. They note regulatory approval requires only that a test has acceptable accuracy, precision, and reproducibility, and that the interpretation of the results with reference to a "gold standard" has acceptable sensitivity, specificity and predictive value. TEG and ROTEM both meet these requirements and so are CE-marked and FDA approved. However, "clinical validation" implies that a test is relevant to clinical practice. This is more contentious.

Evidence supporting the use of point-of-care testing +/- factor concentrates in major haemorrhage

POC viscoelastic testing has been studied most extensively in the context of cardiac surgery. A 2017 meta-analysis of 15 trials in 8737 patients found no evidence for any effect of routine TEG/ROTEM use on mortality, reoperation for bleeding, stroke, ventilation time or hospital length of stay[45]. However, the incidence of red blood cell (Risk Ratio 0.88, 95 per cent Confidence Interval 0.79-0.97) and platelet transfusion (Risk Ratio 0.78, 95 per cent Confidence Interval 0.66-0.93) were both reduced. The quality of evidence for these findings was classed as low to very low.

The use of factor concentrates guided by VHA in cardiac surgery remains controversial. Some small studies have suggested reduced blood product requirements and improved mortality but this has not been confirmed by large scale robust clinical trials[46]. The recently published REPLACE Trial reported no benefit from empiric Fibrinogen Concentrate (FC) use in bleeding post cardiac surgery[47]. The FIBRES Study (NCT03037424), a large multi-centre trial, is currently underway comparing FC to cryoprecipitate in cardiac surgery.

Avoiding transfusion of blood products would be expected to have associated patient-centred outcome benefit, given the adverse effects associated with transfusion. That no cardiac surgery study has found patient-centred outcome benefit, despite reduced transfusion, is intriguing. Of course, this may be a consequence of the low quality evidence. However, there is another possibility. An Australian before-and-after study[48] found POC testing associated with a 25 per cent increase in cryoprecipitate use but substantial decreases in FFP (-74 per cent), platelet (-63 per cent) and red blood cell (-36 per cent) transfusion in cardiac surgery. It is possible that any benefit from reduced overall blood product transfusion due to more fibrinogen administration is offset by targeting POC indices that are theoretically associated with better outcomes, but that in practice result in actions that are to the patient's detriment. Theoretical concerns include the possibility that FFP or platelet transfusion might have benefits, aside from increasing platelet and factor concentrations, that are lost if POC tests indicate fibrinogen administration alone. Platelet transfusions deactivate activated protein C[49], restore PAI1[50], and provide enough factor V to overcome any clinically relevant inhibition by activated protein C[51]. Unique among volume-expanding alternatives, FFP preserves the integrity of the endothelial glycocalyx[52]. Second, it is possible that normalisation of POC parameters (i.e. to levels seen in healthy patients) might not be optimal for a surgical patient who is at risk of pro-thrombotic complications as well as bleeding.

POC testing is more sensitive than standard laboratory tests in detecting TIC[24]. Worse POC results clearly predict higher mortality in trauma[53]. However, the most important question for patient management is whether POC testing in guides treatment that reduces mortality. The "ideal" Major Haemorrhage Protocol and the composition of blood product transfusion is one of the most fiercely debated topics in contemporary trauma resuscitation, with widespread geographical and institutional variation in practice[54-57]. The incorporation of VHA-guided algorithms into a MHP might enable more rapid correction of specific coagulation abnormalities[24,58]. However, only one clinical trial has found patient-centred outcome benefit associated with POC testing. In this single-centre unblinded study involving 111 major trauma patients randomised to a massive transfusion protocol guided by either TEG or conventional clotting assays, patients in the TEG group had a significantly lower six hour (7.1 per cent versus 21.8 per cent, p=0.032) and 28 day (19.6 versus 36.4 per cent, p=0.049) mortality[59]. This study is remarkable, as trauma is often considered too heterogeneous to allow even effective interventions to be identified in conventionally designed randomised trials. Haemostasis management in severe trauma is widely accepted as a fundamental area where more research is required[60-62]. The currently recruiting STATA Trial (NCT02416817) and iTACTIC Trial (NCT02593877) will add to the evidence base regarding VHA use in severe trauma.

Factor concentrate administration guided by results of VHA as part of a MHP is another area of significant controversy in trauma. There are several theoretical advantages to the use of factor concentrates but to date there is limited high-level evidence to support their use[63-65]. The FiiRST Trial recently reported that early Fibrinogen Concentrate (FC) use is feasible and increases fibrinogen levels during traumatic haemorrhage[66]. A number of other trials investigating early FC use have recently completed or are currently recruiting; E-FIT (ISRCT67540073), PRooF-iTH[67], FEISTY (NCT02745041)[68]. Additionally, the recently published RETIC Trial reported improved patient outcomes with a factor concentrate based resuscitation strategy[69].

In obstetric haemorrhage, there is very little evidence-based consensus to guide clinical practice[70]. Most patients are significantly pro-thrombotic at term, and by the time standard laboratory tests of coagulation become abnormal there has been significant blood loss, and coagulopathy is profound[71,72]. There is increasing recognition of the key role hypofibrinogenaemia plays in the coagulopathy in obstetric haemorrhage. Fibrinogen is the first coagulation factor to fall in obstetric haemorrhage, and hypofibrinogenaemia (FibC <2 g/L) is associated with

severity of haemorrhage and worse outcomes[73,74]. The use of VHA (TEG and ROTEM) has been studied in the obstetric population and although reference ranges differ from the non-pregnant patient population they are able to identify rapidly fibrinogen deficiency[74-77]. As is a recurring theme in the management of major haemorrhage there is limited high-level evidence to support the use of a VHA guided transfusion strategy in obstetric haemorrhage. Empiric transfusion of plasma as part of fixed ratio MHP in obstetric patients might be detrimental in terms of fibrinogen replacement as the fibrinogen content of plasma is dilute compared to that of the patient[78]. A single centre study from the Liverpool Women's Hospital reported significant reduction in blood product transfusion after the implementation of a ROTEM-guided fibrinogen concentrate-based transfusion strategy in severe obstetric haemorrhage[79]. However, the blind administration of fibrinogen concentrate in the setting of obstetric haemorrhage cannot be supported after the publication of the Fib-PPH trial[80]. Additionally, the OBS 2 trial demonstrated that supplementation of fibrinogen at or to what could be considered supra-therapeutic levels (FibC 2-3 g/L) is ineffective in reducing haemorrhage[81]. If a VHA guided algorithm is to be utilised we would suggest that there is no need to have specific obstetric treatment triggers for the transfusion of fibrinogen.

Two 2017 systematic reviews[82,83] examined POC testing in all forms of major bleeding, finding no overall or subgroup evidence for any patient-centred outcome benefit, but ongoing uncertainty regarding mortality. Further, they confirmed evidence of reduced overall product usage (with resultant cost-effectiveness[84]), and no suggestion of increased mortality.

RECOMMENDATIONS

All trials of POC viscoelastic tests to date have been performed with older-generation devices. It is likely that the new automated devices will increase the number of patients, and the number of tests per patient, that feasibly can be performed. Consequently, evidence-guiding practice is likely to evolve rapidly. In the meantime, evidence of reduced product usage, greater cost-effectiveness, and no suggestion of worse patient outcomes, all argue POC testing in tandem with an appropriate treatment algorithm should become part of routine care. This paper describes what we think are examples of the sensible use to which this recommendation might be put.

REFERENCES

1. Faringer PD, Mullins RJ, Johnson RL, Trunkey DD. Blood component supplementation during massive transfusion of AS-1 red cells in trauma patients. J Trauma. 1993;34(4):481–485;discussion 485–487.
2. Simmons RL, Collins JA, Heisterkamp CA, Mills DE, Andren R, Phillips LL. Coagulation disorders in combat casualties. I. Acute changes after wounding. II. Effects of massive transfusion. III. Post-resuscitative changes. Ann Surg. 1969;169(4):455–482.
3. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003;54(6):1127–1130.
4. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma. 2003;55(1):39–44.
5. Davenport RA, Brohi K. Cause of trauma-induced coagulopathy. Curr Opin Anaesthesiol. 2016;29(2):212–219.
6. Reade MC, Holley AD. A new understanding of coagulopathy in trauma. In: Vincent JL, editor. Annual update in intensive care medicine. Berlin: Spinger-Verlag, 2012. pp. 689–698.
7. Klebl F, Bregenzer N, Schöfer L, Tamme W, Langgartner J, Schölmerich J. Risk factors for mortality in severe upper gastrointestinal bleeding. Int J Colorectal Dis. 2005;20(1):49–56.
8. Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion. 2004;44(10):1453–1462.
9. Poole D. Coagulopathy and transfusion strategies in trauma. Overwhelmed by literature, supported by weak evidence. Blood Transfus. 2016;14(1):3–7.
10. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007;63(4):805–813.
11. Ho AM, Dion PW, Yeung JH, Holcomb JB, Critchley LA, Ng CS. Prevalence of survivor bias in observational studies on fresh frozen plasma: erythrocyte ratios in trauma requiring massive transfusion. Anesthesiology. 2012;116(3):716–728.
12. Khan S, Brohi K, Chana M, Raza I, Stanworth S, Gaarder C. Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage. J Trauma Acute Care Surg. 2014;76(3):561–567.
13. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313(5):471–482.
14. Zink KA, Sambasivan CN, Holcomb JB, Chisholm G, Schreiber MA. A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. Am J Surg. 2009;197(5):565–570.
15. Shaz BH, Dente CJ, Nicholas J, MacLeod JB, Young AN, Easley K, et al. Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. Transfusion. 2010;50(2):493–500.
16. Mesar T, Larentzakis A, Dzik W, Chang Y, Velmahos G, Yeh DD. Association between ratio of fresh frozen plasma to red blood cells during massive transfusion and survival among patients without traumatic injury. JAMA Surg. 2017;152(6):574–580.
17. Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schöchl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence?. Br J Anaesth. 2014;114(2):217–224.

18. Hoffman M, Cichon LJ. Practical coagulation for the blood banker. Transfusion. 2013;53(7):1594–1602.
19. Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, et al. Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med. 2011;39:2652–2658.
20. Goodman MD, Makley AT, Hanseman DJ, Pritts TA, Robinson BR. All the bang without the bucks: defining essential point-of-care testing for traumatic coagulopathy. J Trauma Acute Care Surg. 2015;79(1):117–124;discussion 124.
21. Mitra B, O'Reilly G, Collecutt M, Cameron PA, Phillips L, Davis A. Prospective comparison of point-of-care international normalised ratio measurement versus plasma international normalised ratio for acute traumatic coagulopathy. Emerg Med Australas. 2012;24(4):363–368.
22. Mistral T, Boue Y, Bosson JL, Manhes P, Greze J, Brun J. Performance of point-of-care international normalized ratio measurement to diagnose trauma-induced coagulopathy. Scand J Trauma Resusc Emerg Med. 2017;25:59.
23. Cotton BA, Faz G, Hatch QM, Radwan ZA, Podbielski J, Wade C. Rapid thrombelastography delivers real-time results that predict transfusion within one hour of admission. J Trauma. 2011;71(2):407–414;discussion 414–417.
24. Holcomb JB, Minei KM, Scerbo ML, Radwan ZA, Wade CE, Kozar RA. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. Ann Surg. 2012;256(2):476–486.
25. National Blood Authority. Patient blood management guidelines module 1: critical bleeding / massive transfusion. Canberra: National Health and Medical Research Council, 2011.
26. National Blood Authority. Patient blood management guidelines module 2: perioperative. Canberra: National Health and Medical Research Council, 2012.
27. Hunt H, Stanworth S, Curry N, Woolley T, Cooper C, Ukoumunne O, et al. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. Cochrane Database Syst Rev. 2015:2;CD010438.
28. Campbell JE, Aden JK, Cap AP. Acute traumatic coagulopathy: whole blood thrombelastography measures the tip of the iceberg. J Trauma Acute Care Surg. 2015;78(5):955–961.
29. Etchill E, Sperry J, Zuckerbraun B, Alarcon L, Brown J, Schuster K. The confusion continues: results from an American Association for the Surgery of Trauma survey on massive transfusion practices among United States trauma centers. Transfusion. 2016;56(10):2478–2486.
30. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. Anesthesiology. 2015;122(2):241–275.
31. Rossaint R, Bouillon B, Cerny V, Coats T, Duranteau J, Fernández-Mondéjar E, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care. 2016;20:100.
32. Kutcher ME, Redick BJ, McCreery RC, Crane IM, Greenberg MD, Cachola LM et al. Characterization of platelet dysfunction after trauma. J Trauma Acute Care Surg. 2012;73(1):13–19.
33. Petricevic M, Konosic S, Biocina B, Dirkmann D, White A, Mihaljevic MZ, et al. Bleeding risk assessment in patients undergoing elective cardiac surgery using ROTEM(®) platelet and Multiplate(®) impedance aggregometry. Anaesthesia. 2016;71(6):636–647.
34. Paniccia R, Priora R, Liotta AA, Abbate R. Platelet function tests: a comparative review. Vasc Health Risk Manag. 2015;11:133–148.
35. Gurbel PA, Bliden KP, Tantry US, Monroe AL, Muresan AA, Brunner NE, et al. First report of the point-of-care TEG: a technical validation study of the TEG-6S system. Platelets. 2016; 27(7):642–649.
36. Johansson PI. Next generation viscoelastic haemostatic assays and platelets function testing. Paper presented at: International Symposium on Critical Bleeding; 2015 August 31–September 1; Copenhagen, Denmark.
37. Winearls J, Reade M, Miles H, Bulmer A, Campbell D, Görlinger K, et al. Targeted coagulation management in severe trauma: the controversies and the evidence. Anesth Analg. 2016;123(4):910–924.
38. Besser MW, Ortmann E, Klein AA. Haemostatic management of cardiac surgical haemorrhage. Anaesthesia. 2015;70(Suppl 1):87–95;e29–e31.
39. Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson TB Jr, Peterson ED, Gammie JS, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. JAMA. 2010;304(14):1568–1575.
40. Görlinger K, Dirkmann D, Hanke AA. Potential value of transfusion protocols in cardiac surgery. Curr Opin Anaesthesiol. 2013;26(2):230–243.
41. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–e333.
42. Kramer MS, Berg C, Abenhaim H, Dahhou M, Rouleau J, Mehrabadi A, et al. Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. Am J Obstet Gynecol. 2013;209(5):449;e441–e447.
43. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017; 389(10084):2105–2116.
44. Solomon C, Asmis LM, Spahn DR. Is viscoelastic coagulation monitoring with ROTEM or TEG validated?. Scand J Clin Lab Invest. 2016;76(6):503–507.
45. Serraino GF, Murphy GJ. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis. Br J Anaesth. 2017;118(6):823–833.
46. Görlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology. 2011;115(6):1179–1191.

47. Rahe-Meyer N, Levy JH, Mazer CD, Schramko A, Klein AA, Brat R, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. Br J Anaesth. 2016;117(1):41–51.
48. National Blood Authority. Point of care coagulation testing case study: The Prince Charles Hospital Brisbane. Canberra: National Health and Medical Research Council, 2014.
49. Jane SM, Mitchell CA, Hau L, Salem HH. Inhibition of activated protein C by platelets. J Clin Invest. 1989;83(1):222–226.
50. Vulliamy P, Gillespie S, Gall LS, Green L, Brohi K, Davenport RA. Platelet transfusions reduce fibrinolysis but do not restore platelet function during trauma hemorrhage. J Trauma Acute Care Surg. 2017;83(3):388–397.
51. Campbell JE, Meledeo MA, Cap AP. Comparative response of platelet fV and plasma fV to activated protein C and relevance to a model of acute traumatic coagulopathy. PLoS One. 2014; 9(6):e99181.
52. Torres LN, Sondeen JL, Ji L, Dubick MA, Torres Filho I. Evaluation of resuscitation fluids on endothelial glycocalyx, venular blood flow, and coagulation function after hemorrhagic shock in rats. J Trauma Acute Care Surg. 2013;75(5):759–766.
53. Da Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NK. Effect of thromboelastography (TEG(®) and rotational thromboelastometry (ROTEM(®) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. Crit Care. 2014;18(5):518.
54. Winearls J, Mitra B, Reade MC. Haemotherapy algorithm for the management of trauma-induced coagulopathy: an Australian perspective. Curr Opin Anaesthesiol. 2017;30(2):265–276.
55. Dutton RP. Management of traumatic haemorrhage – the US perspective. Anaesthesia. 2015;70 (Suppl 1):108–111;e138.
56. Schäfer N, Driessen A, Fröhlich M, Stürmer EK, Maegele M, TACTIC partners. Diversity in clinical management and protocols for the treatment of major bleeding trauma patients across European level I Trauma Centres. Scand J Trauma Resusc Emerg Med. 2015;23:74.
57. Maegele M, Nardi G, Schöchl H. Hemotherapy algorithm for the management of trauma-induced coagulopathy: the German and European perspective. Curr Opin Anaesthesiol. 2017;30(2):257–264.
58. Schöchl H, Maegele M, Solomon C, Görlinger K, Voelckel W. Early and individualized goal-directed therapy for trauma-induced coagulopathy. Scand J Trauma Resusc Emerg Med. 2012;20:15.
59. Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. Ann Surg. 2016;263(6):1051–1059.
60. Veigas PV, Callum J, Rizoli S, Nascimento B, da Luzcorresponding LT. A systematic review on the rotational thrombelastometry (ROTEM(®)) values for the diagnosis of coagulopathy, prediction and guidance of blood transfusion and prediction of mortality in trauma patients. Scand J Trauma Resusc Emerg Med. 2016;24:114.
61. Hunt H, Stanworth S, Curry N, Woolley T, Cooper C, Ukoumunne O, et al. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. Cochrane Database Syst Rev. 2015;2:CD010438.
62. Asehnoune K, Balogh Z, Citerio G, Cap A, Billiar T, Stocchetti N, et al. The research agenda for trauma critical care. Intensive Care Med. 2017.
63. Aubron C, Reade MC, Fraser JF, Cooper DJ. Efficacy and safety of fibrinogen concentrate in trauma patients–a systematic review. J Crit Care. 2014;29(3):471;e11–e17.
64. Jensen NH, Stensballe J, Afshari A. Comparing efficacy and safety of fibrinogen concentrate to cryoprecipitate in bleeding patients: a systematic review. Acta Anaesthesiol Scand. 2016;60(8):1033–1042.
65. Innerhofer P, Westermann I, Tauber H, Breitkopf R, Fries D, Kastenberger T, et al. The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Injury. 2013;44(2):209–216.
66. Nascimento B, Callum J, Tien H, Peng H, Rizoli S, Karanicolas P. Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial. Br J Anaesth. 2016;117(6):775–782.
67. Steinmetz J, Sørensen AM, Henriksen HH, Lange T, Larsen CF, Johansson PI, et al. Pilot randomized trial of fibrinogen in trauma haemorrhage (PRooF-iTH): study protocol for a randomized controlled trial. Trials. 2016;17:327.
68. Winearls J, Wullschleger M, Wake E, Hurn C, Furyk J, Ryan G. Fibrinogen early in severe trauma study (FEISTY): study protocol for a randomised controlled trial. Trials. 2017;18:241.
69. Innerhofer P, Fries D, Mittermayr M, Innerhofer N, von Langen D, Hell T, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol. 2017;4(6):e258–e271.
70. Allard S, Green L, Hunt BJ. How we manage the haematological aspects of major obstetric haemorrhage. Br J Haematology. 2014;164(2):177–188.
71. O'Riordan MN, Higgins JR. Haemostasis in normal and abnormal pregnancy. Best Pract Res Clin Obstet Gynaecol. 2003;17(3):385–396.
72. de Lloyd L, Bovington R, Kaye A, Collis RE, Rayment R, Sanders J. Standard haemostatic tests following major obstetric haemorrhage. Int J Obstet Anesth. 2011;20(2):135–141.
73. Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost. 2007;5(2):266–273.
74. Collins PW, Lilley G, Bruynseels D, Laurent DB, Cannings-John R, Precious E, et al. Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. Blood. 2014;124(11):1727–1736.
75. Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. Br J Anaesth. 2012;109(6):851–863.
76. Hill JS, Devenie G, Powell M. Point-of-care testing of coagulation and fibrinolytic status during postpartum haemorrhage: developing a thrombelastography®-guided transfusion algorithm. Anaesth Intensive Care. 2012;40(2):1007–1015.

77. de Lange NM, Lancé MD, de Groot R, Beckers EA, Henskens YM, Scheepers HC. Obstetric hemorrhage and coagulation: an update. Thromboelastography, thromboelastometry, and conventional coagulation tests in the diagnosis and prediction of postpartum hemorrhage. Obstet Gynecol Surv. 2012;67(7):426–435.
78. Collis RE, Collins PW. Haemostatic management of obstetric haemorrhage. Anaesthesia. 2015;70(Suppl 1):78–86; e27–e78.
79. Mallaiah S, Barclay P, Harrod I , Chevannes C, Bhalla A. Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage. Anaesthesia. 2015; 70(2):166–175.
80. Wikkelsø AJ, Edwards HM, Afshari A, Stensballe J, Langhoff-Roos J, Albrechtsen C, et al. Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. Br J Anaesth. 2015;114(4):623–633.
81. Aawar N, Alikhan R, Bruynseels D, Cannings-John R, Collis R, Dick J, et al. Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial. Trials. 2015;16:169.
82. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. Anaesthesia. 2017;72(4):519–531.
83. Fahrendorff M, Oliveri RS, Johansson PI. The use of viscoelastic haemostatic assays in goal-directing treatment with allogeneic blood products – a systematic review and meta-analysis. Scand J Trauma Resusc Emerg Med. 2017;25:39.
84. Whiting P, Al M, Westwood M, Ramos IC, Ryder S, Armstrong N, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2015;19(58):1–228;v–vi.

Intraoperative cell salvage

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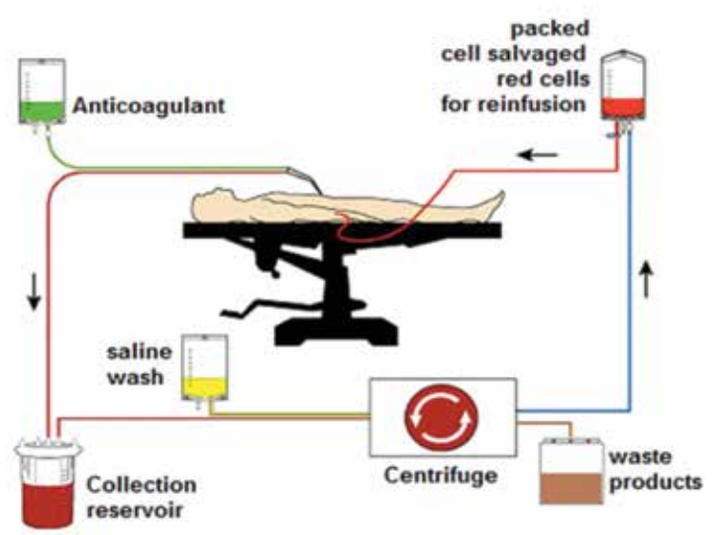
INTRODUCTION

Intraoperative cell salvage (ICS) is a process in which blood lost during a surgical procedure is collected, anticoagulated, washed, filtered and returned to the patient (figure 1). The surgeon collects the blood via suction, where it is anticoagulated, before passing into a reservoir where large clots and debris are removed. If blood loss is low and processing is not required it is possible to use only the collecting part of the consumable set. If blood loss is significant then processing of the blood occurs where the blood is washed to remove any contaminants and other blood components (free Hb, platelets, plasma) leaving concentrated red cells suspended in saline with a haematocrit of 50-70 per cent. The red cells can then be returned to the patient. The salvaged blood can be reinfused in the theatre, or kept and reinfused within four hours. Some Jehovah's Witness patients may accept the use of a continuous reinfusion circuit.

Figure 1. Reproduced from the National Blood Authority (Australia)[1]



The cell salvage device is operated by an "autotransfusionist". This can be an anaesthetist, anaesthetist technician/nurse, perfusionist, or a contractor as long as they have appropriate training in the operation of the device. The manufacturer normally conducts initial training and following this, the National Blood Authority recommend that the operator completes a minimum number of cases per year once accredited to remain competent in its operation[1]. An online autotransfusion course has also been developed by the Australian and New Zealand Perfusion College.

The history of cell salvage
The first suggestion about the possibility of cell salvage and autologous transfusion was in 1818, when Blundell treated patients with post-partum haemorrhage[2]. The first autotransfusion occurred in 1874 when Hueter transfused 350 mls of autologous blood into a patient with frost gangrene, in an attempt to re-perfuse the foot[3]. The first successful surgical use of autotransfusion was published by Duncan in 1886 who used the technique during the amputation of a leg[4]. HJ Thies, a German obstetrician, described autotransfusion in 1914 after autologous blood was given to three women with ruptured ectopic pregnancy[5]. The first large case series came from the University of Louisville in 1943, where 100 consecutive cases of autotransfusion occurred in patients with trauma or ruptured ectopic pregnancy[5].

By the 1940s there had been a substantial improvement in both blood donation and storage practices, and autotransfusion was largely ignored until the AIDS epidemic in the mid-1980s reignited an interest in autologous blood transfusion as a means of avoiding donor blood[5,6]. Autologous blood was considered invaluable and intraoperative cell salvage (ICS) became part of a paradigm shift in transfusion medicine[7].

Recently there has been a significant focus on perioperative blood management in patients undergoing major surgical procedures. Patient blood management (PBM) is an evidence-based, patient-centered, multi-disciplinary approach aiming to reduce the need for allogeneic transfusion[8]. The three-pillar concept of PBM was introduced to allow optimisation and preservation of the patients own red blood cell mass[9,10]. It also forms part of Standard 7 of the National Safety and Quality Health Service Standards in Australia. ICS is considered an integral part of the second pillar and has now become a well-accepted and safe modality aiming at the reduction or avoidance of allogeneic blood transfusion (ABT)[11,12]. In the Cochrane analysis published in 2010 there was a 38 per cent reduction in ABT when ICS was used[12].

Where can it be used?
ICS is indicated in surgery with:

- Anticipated blood loss of >750 mL or >20 per cent estimated blood volume.
- Blood loss great enough to induce anaemia.
- A surgery where >10 per cent of the patients having that procedure in that institution require transfusion.
- Patients with a low haemoglobin or increased risk factors for bleeding.
- Patients with multiple antibodies or rare blood types.
- Patients with objections to receiving allogeneic (donor) blood.

ICS should be considered in:

- Cases where blood loss is potentially unpredictable.

In what type of surgery should ICS be considered?
ICS can be used in a number of surgical specialties. Common areas for use are listed below.

Table 1. Suggested uses for ICS

CARDIOTHORACICS	ALL MAJOR SURGERY
Trauma	Multi trauma (caution when bowel perforation and faecal contamination)
Gynaecology	Ruptured ectopic
	Total abdominal hysterectomy
	Uterine myomectomy
Obstetrics	LSCS (particularly accreta, increta, percreta)
	Laparotomy for PPH
Orthopaedics	Revision hip
	Pelvic surgery
	Long bone fracture lower extremities
	Resection bony tumours
Spinal	Multilevel instrumented spinal surgery (particularly posterior fusion and scoliosis surgery)
	Resection tumours
Liver and spleen	Hemihepatectomy
	Transplant
	Whipples procedure
	Ruptured spleen
Vascular	Abdominal or thoraco-abdominal aneurysm
	Aorto-bifemoral grafts
Urology	Open nephrectomy
	Radical prostatectomy
	Cystectomy
Plastics	Major flaps

Who should not have cell salvage?
The manufacturers contraindicate the use of ICS in the presence of bowel contamination unless there is catastrophic haemorrhage. A number of studies have shown however that postoperative infection rates after abdominal injury was equal in patients who received allogeneic or cell salvaged blood[13,14]. While salvage from grossly contaminated fields should be avoided, procedures involving bowel resection should be able to use ICS for part of the procedure. These patients should have a leukodepletion filter used and receive broad-spectrum antibiotics[14]. There is some evidence however that with increasing bacterial load the leukodepletion filter may be overcome[15], so each case must be individually evaluated by the surgeon and anaesthetist for risks and benefits of proceeding with ICS.

ICS should be temporarily discontinued when substances not licensed for IV use are present in the surgical field. These include iodine, topical clotting agents and orthopaedic cement. The area should be washed with 0.9 per cent sodium chloride before resuming ICS[14].

Debate continues as to whether patients with Sickle cell disease or trait should have ICS. There remains some concern about the possibility that cell salvaged blood returned to the patient may sickle, causing significant haemolysis and further reduce oxygen carrying capacity, as well as adverse outcomes related to free haemoglobin. Studies have shown a rate of 15-50 per cent sickling with processing[11]. ICS has been used successfully without complications in a few instances, but should be discussed with a haematologist on a case by case basis.

ICS should also be avoided during pheochromocytoma surgery, as the vasoactive molecules are still active on reinfusion, and may result in hypertension[11].

Advantages and disadvantages of intraoperative cell salvage
Some of the advantages and disadvantages of ICS are listed in table 2.

Table 2. Advantages and disadvantages of ICS

ADVANTAGES	DISADVANTAGES
Higher levels of 2,3-diphosphoglycerate	Possible hypotension on reinfusion (increased risk if a leukodepletion filter and ACD is used)
Red cells maintain their flexibility in the microcirculation	Pyrexia
Immediately active in tissue oxygenation	With large blood loss other blood components may still be needed (for example, platelets, clotting factors)
Normal pH	Unavailability of trained staff
Normal ATP levels	
Increased mean erythrocyte viability and membrane activity	
Provide a ready source of red cells that are available and proportional to losses	
Reduces transfusion associated risks (ABO incompatibility, transmission of blood borne infections, haemolytic transfusion reactions, immunosuppression)	
Avoids or limits allogeneic transfusion and its associated risks (see table 3)	
Acceptable to the majority of patients who may decline allogeneic blood	
Cheaper	

Table 3. Reported adverse outcomes associated with allogeneic blood transfusion

INFECTION	CARDIAC ARREST
Septicaemia	Renal failure
Transfusion-related acute lung injury (TRALI)	Stroke
Multisystem organ failure (MOF)	Thromboembolism
Systemic inflammatory response syndrome (SIRS)	Diminished postoperative functional recovery
Acute respiratory distress syndrome (ARDS)	Bleeding requiring re-operation
Prolonged mechanical ventilation	Increased admission to ICU
Vasospasm	Increased ICU length of stay
Low-output heart failure	Increased hospital length of stay
Atrial fibrillation	Increased hospital readmission

Source: National Blood Authority[1]

Is cell salvage safe?

A recent study published in *Transfusion* reviewed the use of cell salvage in nine hospitals over an 11-year period[16]. They found 43,198 patients had ICS for their procedure, and 33,531 had blood returned. There was found to be two patient adverse events, both of which made a complete recovery. This resulted in an adverse events rate of 0.006 per cent. There were 12 equipment malfunctions.

Historical concerns about amniotic fluid embolism are no longer a contraindication in current practice due to a lack of strong evidence[17]. CMACH, NICE, AAGBI and the Australian National Patient Blood management Guidelines (module 5 Obstetrics) have endorsed cell salvage in obstetric surgery.

Why not just transfuse?

We are all aware that blood is a finite resource, and relies on the generosity of blood donors. There is now also increasing evidence of harm from transfusion of blood products. A study looking at 48,000 post-op non-cardiac surgery patients found 4.6 per cent received a transfusion post operatively. Of those transfused there was increased 30-day mortality, all cause mortality, and rate of postoperative infections. Hospitals with liberal practices were two times more likely to transfuse patients, and had higher risk adjusted mortality rates than restrictive hospitals[18].

Even with a single unit transfusion of donor red cells there is increased odds of mortality, morbidity, perioperative ischaemic stroke and/or myocardial infarction, wound problems, pulmonary complications, postoperative renal dysfunction, systemic sepsis and postoperative length of stay[19,20]. Rates of morbidity and mortality increased in a dose dependent manner with further transfusion of donor red cells[20]. With an ageing population with increasing co-morbidities, there is an even greater need to try and avoid donor blood wherever possible.

Despite the known risks associated with allogeneic blood transfusion (ABT), it remains the default position for many clinicians. Ten per cent of patients admitted to hospital will receive a blood transfusion. ABT has been identified as one of the five most over prescribed medical treatment modalities[21].

Cost

The machine routinely used at our institution is the Continuous Auto Transfusion System (CATS) by Fresenius. Other ICS providers within Australia include Haemonetics and LivaNova. The initial set-up cost involves the purchase of the machine, and ongoing costs include disposables, training of staff, and maintenance.

A business case and considerations for implementation are available within the National Blood Authority's "Guidance for the provision of Intraoperative cell salvage document and appendixes"[1].

For the Fresenius Kabi product the cost of the collection system is $85 per patient. This includes the reservoir, suction tubing, and the heparinised saline. If processing of the collected blood occurs, then the cost increases to $283 per patient, or $320 if a leukodepletion filter is also required. Currently, the Australian Red Cross Blood Service costs a unit of red blood cells at $346.87[22]. This, however, only reflects the manufacturing cost. The total cost of a unit of blood when considering all direct and indirect costs is likely closer to $733[1]. The indirect cost of allogeneic blood transfusion is as high as five times that of the direct cost[23].

The cost of blood is increasing as there is an increased demand for blood, costs of collection storage and processing have increased, and there is more stringent testing of blood for viruses[24]. According to the National Blood Authority the estimated cost associated with blood transfusion in Australia is over $1 billion per year[25].

A cell salvage program was established at a hospital in Cleveland with an economic analysis conducted. Based on collected data ICS was used in as many as 2500 cases per year. Prior to implementation of ICS the hospital paid for each unit of donor blood administered to patients. They concluded that they were able to break even in terms of initial outlay costs (machine purchase, disposables, training, and wages for the technician) in 1.93 months[24].

A further study showed from the UK showed that they were able to recover the purchase cost of the ICS machine within 20 cases when it was used for open radical prostatectomy[26].

In the Australian context, there has been a significant change in regard to costs associated with blood product administration. While previously the expense was absorbed by the individual states, there is a now a shift of costs to the individual health network in almost all states except South Australia and Western Australia. With this shifting of costs there may be increased interest by hospital administrators on ways to reduce expenditure related to blood products. The National Blood Authority has an extensive document on business case guidance for hospitals looking to implement a cell salvage service[1].

ICS in specific surgical subspecialities

Orthopaedic surgery

A Cochrane review in 2010 found that when ICS was used for orthopaedic procedures there was a relative risk reduction of 54 per cent of receiving allogeneic blood. This was a larger relative risk reduction than for cardiac surgery[12].

Revision hip arthroplasty is known to be associated with high blood loss. In a study by Herd et al, the use of ICS for revision hips was investigated[27]. One group had ICS for their revision hip replacement surgery, while a control group did not. There was a 55 per cent reduction in the transfusion rate in the ICS group, with an average of 0.4 units per patient transfused, versus 3.5 units in the control group.

ICS should be considered in patients undergoing hip fracture repair if they are anaemic preoperatively, or inadequately reversed from their anticoagulation.

Cancer surgery

The use of ICS for cancer surgery has been controversial for many years. In 1986 the American Medical Council stated ICS was contraindicated for cancer surgery[8]. This was because of fear of recurrence or distant metastases secondary to reinfusion. Early studies that investigated whether this idea had merit were non-reinfusion studies,

where blood was collected and washed, but not returned to the patient and instead analysed for the presence of cancer cells. Non-reinfusion studies demonstrated that blood salvaged and passed through a leukodepletion filter contained only non-nucleated cell fragments of tumour cells that were unable to cause metastases[8]. Leukodepletion filters (LDF) are highly effective (around 99.9 per cent) in removing contaminating tumour cells from cell-salvaged blood[11].

Following the results of these studies, reinfusion studies were commenced. The first group to adopt ICS was urology for patients undergoing radical prostatectomies. In two groups undergoing radical prostatectomy they found no evidence of increased risk of recurrence or metastases[26]. Group A had standard care, whereas Group B had ICS. There was a significant decrease in the number of units of RBC prescribed (69 versus 16). In the ICS group there was also no increased risk of early biochemical relapse, and a decreased recurrence rate at three year. A similar study confirmed these results in 2005[28].

The benefit of using ICS for oesophagectomy has also been shown. Only 3 per cent of patients received allogeneic blood when ICS was used, versus 33.7 per cent in the control group. There was also a lower rate of postoperative infection in the ICS group[29].

A meta-analysis conducted in 2011 that looked at 10 studies where ICS had been used versus a control group. The primary end point was a comparison of the odds ratio for cancer recurrence, or the development of metastases in the group who received autologous blood. In most studies there was no significant difference in cancer recurrence rates in patients who received autologous blood from ICS, and several studies showed a lower recurrence rate. The studies included in the meta-analysis were retrospective or case control studies, and they have suggested that a prospective trial is warranted to demonstrate the superiority of intraoperative allogeneic transfusion[30] (see figure 2).

Figure 2. Literature review comparing research related to cell salvage and cancer recurrence[30]

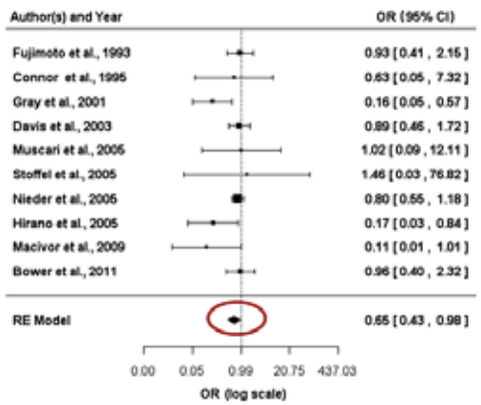


Fig. 1. Forest plot for all studies of cancer recurrence after IBS use versus control. Values less than 1 favor the group of patients who received IBS during their cancer surgeries.

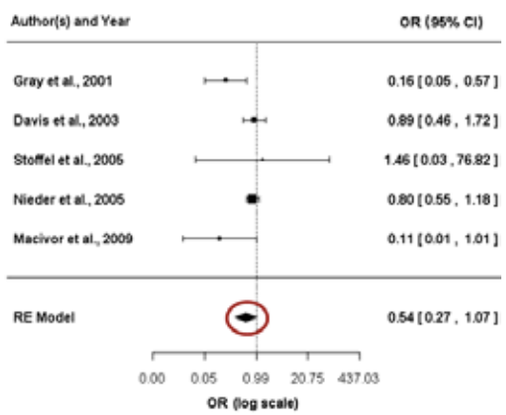


Fig. 2. Forest plot for studies of prostate cancer recurrence. Values less than 1 favor the group of patients who received IBS during their cancer surgeries.

A further meta-analysis published in 2014 in *The Lancet Oncology* journal[31] reviewed 30 studies where patients had cancer surgery for a wide variety of primaries. One thousand nine hundred and ninety three patients had ICS used during their procedures. In only two cases was there any evidence of tumour cells after processing and use of a LDF. These were both in patients who had hepatocellular carcinoma that ruptured during resection. All studies showed either equivalent or better results in the ICS group, with no evidence of worse long term outcomes[31].

The spine is the most common place for skeletal metastases. In 2014 a study was conducted looking at 24 patients who had metastatic spinal disease secondary to varied primaries[32]. Blood samples were taken and tested for the presence of cancer cells at three different points along the collection system. Cancer cells were located in 8/24 samples at the operative site, 3/24 samples before the LDF, and 0/24 sample post filter. Spinal surgery is associated with significant blood loss, and substantial intraoperative blood loss is associated with increased morbidity and mortality. Given there is no evidence of increased risk of metastatic disease or recurrence, there should be increased use in this area.

NICE now recommends the use of ICS for urological malignancies, and the evidence would suggest that it can be safely used in all malignancy surgery[33]. They stated that they did not consider it likely that further long-term research would identify metastases that might have been caused by reinfusion of malignant cells. A leukodepletion filter should always be used.

Immunological changes in donor blood

ABT (allogeneic blood transfusion) is known to promote tumour growth via immunosuppression. Transfusion related immune modulation (TRIM) occurs after transfusion of allogeneic blood. This involves a decrease in the function of natural killer cells, a decrease in the proliferation of T and B lymphocytes, induction of T regulatory cells, and decreased maturation and antigen presenting activity of dendritic cells[34]. In contrast autologous blood results in increased TNFα and complement C3 levels, which strengthen immune ability against infection[35].

Ectopic pregnancy

Ectopic pregnancy occurs at a rate of 11 per 1000 pregnancies[36]. Around 15 per cent of women with ectopic pregnancy will present to hospital with evidence of hypovolaemic shock[37]. The reported transfusion rate for ectopic pregnancy is quoted between nine and 29 per cent[38,39].

In a retrospective audit conducted at the Lyell McEwin Hospital of cases of ruptured ectopic pregnancies over a one year period found 26 cases that underwent surgical intervention. On 10 occasions ICS was set up, and in six of those cases there was enough blood collected to allow for reinfusion. These six women all had evidence of shock prior to induction, and were all found to have significant haemoperitoneum. The mean volume infused in these cases was 526 mls (min 290 – max 800). In total 3157 mls of autologous blood was returned to the patients, the equivalent of 13 units of RBCs.

The cell salvage collection suction tubing can be directly connected to the laparoscopic suction outlet, with studies showing no difference in the quality of the red cells with collection via this method, versus the standard Yankauer sucker[40].

Obstetrics

Blood loss is notoriously difficult to predict in obstetric patients. Maternal haemorrhage remains the third most likely cause of direct maternal deaths in Australia[41]. LSCS is reported to have a transfusion rate of five per cent[42]. There has been a recent shift towards the use of ICS for LSCS in high-risk patients. In the 2005-2006 year 38 per cent of obstetric units in Britain were using ICS for obstetrics[14]. The use of ICS in obstetrics is now supported by AAGBI, RANZCOG, RCOG, NICE and the National Blood Authority Australia.

Previously it was thought that cell salvage could not be used due to the theoretical risk of amniotic fluid embolus (AFE). However, in a series of 400 cases, there was no increased risk of AFE, and no adverse events. There have been two case reports of hypotension after reinfusion through a LDF[16].

The majority of the early research on this topic has come from the Liverpool Women's Hospital in the UK[43]. They established a protocol where all women undergoing LSCS had ICS set up unless they were considered low risk. This included women who were having a LSCS for breech presentation, because of a previous vaginal tear, who had only one previous LSCS, or for maternal request. They found that enough blood was collected for reinfusion in 1/6 cases (A reinfusion rate of 16 per cent). When ICS was used for only "high risk" patients (for example, abnormal placentation) their reinfusion rates were 23.3 per cent[43].

In 2010 King Edward Memorial Hospital published their experience of the introduction of an intraoperative cell salvage program. They chose to target women at high risk of bleeding, and those women who would not accept donor blood. ICS was used 51 times in just over a two-year period. Twenty-one women had blood reinfused (41 per cent), with a median volume of 359 mls. Seven of these 21 women had only salvaged blood reinfused[42]. They also noted that 66 per cent of the women who were transfused started with haemoglobin of less than 120 g/L. For the 30 women who did not receive salvaged blood, the estimated median blood loss was 750 mls.

In a Japanese case series 50 high-risk parturients had ICS used for their LSCS. All 50 women had blood reinfused. Thirty per cent had ICS blood alone receiving a median volume of 315 mls (range 80-939 mL)[44].

Using the Liverpool data we set up a similar pilot study at the Lyell McEwin Hospital, with more restrictive criteria around who was eligible for ICS. Over a three month period in 2015 we found our reinfusion rates to be around 10 per cent, and noticed a significant decrease in the number of women transfused in the perioperative period (2.2 to 1.1 per cent). Interestingly our study also showed that the number of women who lost >750 mls at their LSCS was almost split equally between emergency and elective caesareans despite our eligibility criteria targeting "high risk" women. Therefore, many women were excluded who may have benefited from ICS.

In our institution it is routine to use a single suction system. All amniotic fluid is collected in the reservoir. The amniotic fluid is removed during processing, and the collected blood is returned via a leukodepletion filter to further aid removal. These filters have a small pore microfiber web and a negative surface charge and remove foetal squamous cells, amniotic fluid, vernix, tissue factor and alpha fetoprotein. A number of these factors have been implicated as playing a role in the development of an amniotic fluid embolus syndrome[45]. Many hospitals still use a separate suction device to collect amniotic fluid and then another to collect blood. However, the international movement currently is towards using one suction device as a result of safety evidence available.

One caveat concerning the use of ICS in LSCS is that foetal red cells are not removed with washing or using a filter, as the machine is unable to differentiate foetal and maternal red cells[14]. Rhesus negative mothers require a Kleinhauer to be sent if reinfusion occurs to aid with determining the dose of Anti-D required to prevent alloimmunisation.

Currently we are awaiting the full results of the SALVO trial. This RCT conducted in the UK studied 3050 women undergoing LSCS who were at risk of bleeding. One group received ICS, whereas the other had standard care, including donor transfusion if required[46]. The study's outcomes are to review differences in transfusion rates, morbidity and mortality, and blood loss between the groups. One thousand four hundred and ninety eight women had ICS used for their LSCS with a reinfusion rate of 50.8 per cent (mean 259.9 ml). Donor blood rates were lower in the ICS group (2.5 versus 3.5 per cent). The full results should be published by the end of 2017.

CONCLUSION

Patient blood management involves a multidisciplinary approach, with the anaesthetist playing a vital role. Intraoperative cell salvage is a clinically safe and cost effective intervention. It has been clearly demonstrated to limit allogeneic transfusion, and the risks associated with donor blood. It has very few adverse effects associated with its use, and can be used in a wide range of surgical specialties. Its use in clinical practice should be embraced, and will hopefully form part of a routine care for patients where it is indicated.

ICS should ideally be discussed with the patient before their surgery, and consent obtained. Information sheets can be downloaded for distribution from the National Blood Authority Australia website. As part of the WHO recommended "time out" prior to surgery beginning the surgeon is asked to estimate the expected blood loss. Cell salvage should be implemented for anyone who is likely to lose >750 mL of blood, or is at moderate or high risk of requiring a blood transfusion in their perioperative course.

REFERENCES

1. National Blood Authority. Guidance for the provision of intraoperative cell salvage [Internet]. 2014. From: https://www.blood.gov.au/ics. Accessed 10 October 2017.
2. Blundell J. Experiments on the transfusion of blood by the syringe. Med Chir Trans. 1818;9(Part 1):56–92.
3. Peters E. Die arterielle Transfusion and ihre Anwendung bei erfrierung [dissertation]. Greifswald, DE: Greifwald Univ.; 1874.
4. Duncan J. On re-infusion of blood in primary and other amputations. Br Med J. 1886;1(1309):192-193.
5. Konig G, Waters JH. Washing and filtering of cell-salvaged blood – does it make autotransfusion safer?. Transfus Altern Transfus Med. 2012;12(3–4):78–87.
6. Vanderlinde ES, Heal JM, Blumberg N. Autologous transfusion. BMJ. 2002;324(7340):772–775.
7. Isbister JP. The paradigm shift in blood transfusion. Med J Aust. 1988;148(6):306–308.
8. Zaw AS, Bangalore Kantharajanna S, Kumar N. Is autologous salvaged blood a viable option for patient blood management in oncologic surgery?. Transfus Med Rev. 2017;31(1):56–61.
9. Isbister JP. The three-pillar matrix of patient blood management – an overview. Best Pract Res Clin Anaesth. 2013;27(1):69–84.
10. Clevenger B, Mallett SV, Klein AA, Richards T. Patient blood management to reduce surgical risk. Br J Surg. 2015;102(11):1325–1337.
11. Esper SA, Waters JH. Intraoperative cell salvage: a fresh look at the indications and contraindications. Blood Transfus. 2011;9(2):139–147.
12. Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2010:14(4):CD001888.
13. Ashworth A, Klein AA. Cell salvage as part of a blood conservation strategy in anaesthesia. Br J Anaesth. 2010;105(4):401–416.
14. The Association of Anaesthetists of Great Britain & Ireland. AAGBI Safety Guideline. Blood transfusion and the anaesthetist – intraoperative cell salvage [Internet]. 2009. From: https://www.aagbi.org/sites/default/files/cell%20_salvage_2009_amended.pdf Accessed 15 October 2017.
15. Waters JH, Tuohy MJ, Hobson DF, Procop G. Bacterial reduction by cell salvage washing and leukocyte depletion filtration. Anesthesiology. 2003;99(3):652–655.
16. DeAndrade D, Waters JH, Triulzi DJ, Alarcon L, Wisniewski MK, Dyga R, et al. Very low rate of patient-related adverse events associated with the use of intraoperative cell salvage. Transfusion. 2016;56(11):2768–2772.
17. National Institute for Health and Care Excellence. NICE Interventional procedures guidance [IPG144]. Intraoperative blood cell salvage in obstetrics [Internet]. 2005. From: https://www.nice.org.uk/guidance/IPG144. Accessed 15 October 2017.
18. Abdelsattar Z, Hendren S, Wong SL, Campbell DA Jr, Henke P. Variation in transfusion practices and the effect on outcomes after noncardiac surgery. Ann Surg. 2015;262(1):1–6.
19. Whitlock E, Kim H, Auerbach A. Harms associated with single unit perioperative transfusion: retrospective population based analysis. BMJ. 2015:350:h3037.
20. Ferraris V, Davenport D, Saha SP, Austin PC, Zwischenberger JB. Surgical outcomes and transfusion of minimal amounts of blood in the operating room. Arch Surg. 2012;147(1):49–55.
21. Goodnough L. Blood management: transfusion medicine comes of age. Lancet. 2013;381(9880):1791–1792.
22. National Blood Authority Australia [Internet]. 2017. From: https://www.blood.gov.au/national-product-list. Accessed 15 October 2017.
23. Sapere Research Group. Analysis of cost drivers and trends in the blood sector: for the Department of Health and Ageing. 2011. From: https://www.health.gov.au/internet/main/publishing.nsf/Content/foi-disc-log-2012-13/$File/COSTS%20AND%20TRENDS%20-%20FINAL%2030%20August%2011.pdf. Accessed 23 November 2017.
24. Waters JR, Meier HH, Waters JH. An economic analysis of costs associated with development of a cell salvage program. Anesth Analg. 2007;104(4):869–875.

25. National Blood Authority. National blood research and development strategic priorities: 2013–2016, version 4.1 [Internet].2013.From: https://www.blood.gov.au/system/files/documents/nba-research-and- developmentpriorities-2013-16.pdf. Accessed 15 October 2017; p. 3.
26. Ubee S, Kumar M, Athmanathan N, Singh G, Vesey S. Intraoperative red blood cell salvage and autologous transfusion during open radical retropubic prostatectomy: a cost-benefit analysis. Ann R Coll Surg Engl. 2011;93(2):157–161.
27. Herd J, Joseph J, McGarvey M, Tsimbouri P, Bennett A, Meek RM, Morrison A. Intraoperative cell salvage in revision hip surgery. Ann Med Surg. 2014;3(1):8–12.
28. Muscari F, Suc B, Vigouroux D, Duffas JP, Migueres I, Mathieu A, et al. Blood salvage autotransfusion during transplantation for hepatocarcinoma: does it increase the risk of neoplastic recurrence?. Transplant Int. 2005;18(11):1236–1239.
29. Kinoshita Y, Udagawa H, Tsutsumi K, Ueno M, Nakamura T, Akiyama H, et al. Usefulness of autologous blood transfusion for avoiding allogenic transfusion and infectious complications after esophageal cancer resection. Surgery. 2000;127(2):185–192.
30. Waters J, Yazer M, Chen YF, Kloke J. Blood salvage and cancer surgery: a meta analysis of available studies. Transfusion. 2012;52(10):2167–2173.
31. Kumar N, Chen Y, Zaw AS, Nayak D, Ahmed Q, Soong R, et al. Use of intraoperative cell-salvage for autologous blood transfusions in metastatic spinal surgery: a systematic review. Lancet Oncol. 2014;15(1):e33–41.
32. Kumar N, Ahmed Q, Lee VK, Chen Y, Zaw AS, Goy R, et al. Can there be a place for intraoperative salvaged blood in spine tumor surgery?. Ann Surg Oncol. 2014;21(7):2436–2443.
33. National Institute for Health and Care Excellence. NICE Interventional procedures guidance [IPG258]. Intraoperative red blood cell salvage during radical prostatectomy or radical cystectomy [Internet]. 2008. From: https://www.nice.org.uk/guidance/ipg258. Access 15 October 2017.
34. Cata J, Wang H, Gottumukkala V, Reuben J, Sessler DI. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. Br J Anaesth. 2013;110(5):690–701.
35. Long M, Liu Z, Zhu JG. Comparative analysis of autologous blood transfusion and allogeneic blood transfusion in surgical patients. Int J Clin Exp Med. 2014;7(9):2889–2894.
36. Newbatt E, Beckles Z, Ullman R, Lumsden MA, Guideline Development Group. Ectopic pregnancy and miscarriage: summary of NICE guidance. BMJ. 2012;345:e8136.
37. Cohen A, Almog B, Satel A, Lessing JB, Tsafrir Z, Levin I. Laparoscopy versus laparotomy in the management of ectopic pregnancy with massive haemoperitoneum. Int J Gynaecol Obstet. 2013;123(2):139–142.
38. Hendrix N, Chauhan S, Mobley J, Devoe LD, Smith RP. Risk factors associated with blood transfusion in ectopic pregnancy. J Reproductive Med. 1999;44(5);433–440.
39. Hutton J, Narayan R. Is ectopic pregnancy too often diagnosed too late?. NZ Med J. 1986;99(794):3–5.
40. Nagarsheth N, Fenske S, Shah A, Moshier E, Stahl R, Shander A. In vitro analysis of cell salvaged blood collection with a laparoscopic suction device. J Minim Invasive Gynaecol. 2013;20(1):104–106.
41. Australian Institute of Health and Welfare. Maternal deaths in Australia 2008–2012 [Internet]. 2015. From: https://www.aihw.gov.au/reports/mothers-babies/maternal-deaths-in-australia-2008-2012/contents/table-of-contents. Accessed 15 October 2017.
42. McDonnell N, Kennedy D, Long LJ, Gallagher-Swann MC, Paech MJ. The development and implementation of an obstetric cell salvage service. Anaesth Intensive Care. 2010;38(3):492–499.
43. Brearton C, Bhalla A, Mallaiah S, Barclay P. The economic benefits of cell salvage in obstetric haemorrhage. Int J Obstet Anesth. 2012;21(4):329–333.
44. Morikawa M, Kuramoto A, Nakayama M, Oguchi H, Hasegawa M, Funakoshi T. Intraoperative cell salvage during obstetric surgery in 50 Japanese women. Int J Gynaecol Obstet. 2015;128(3):256–259.
45. Sullivan I, Faulds J, Ralph, C. Contamination of salvaged maternal blood by amniotic fluid and fetal red cells during elective caesarean section. Br J Anaesth. 2008;101(2):225–229.
46. Dhariwal S, Khan K, Allard S, Wilson M, Moore P, SALVO study group. Does current evidence support the use of intraoperative cell salvage in reducing the need for blood transfusion in caesarean section?. Curr Opin Obstet Gynecol. 2014;26(6):425–430.

Regional

What is the role of thoracic epidural analgesia in contemporary anaesthesia practice?

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INTRODUCTION

Thoracic epidural analgesia (TEA) is an established technique to provide perioperative analgesia to patients undergoing major surgery of the thorax and abdomen. The continued and welcome expansion of minimally invasive surgery has seen a decline in the number of procedures for which thoracic epidural analgesia is indicated. Further, alternative regional anaesthesia techniques have increased in use e.g. paravertebral blocks, Transversus Abdominis Plane blocks and wound infusion catheters. The relative benefits of thoracic epidural analgesia compared to alternate techniques are not well established in the literature. These factors have lead to regional and generational differences in practice, reflected by the removal of thoracic epidural insertion from the volume of practice requirements for ANZCA training. This article aims to provide a narrative review of thoracic epidural analgesia in today's anaesthesia practice and suggest ways in which the technique's efficacy can be optimised.

WHAT IS THE EVIDENCE REGARDING THE EFFICACY OF PERIOPERATIVE THORACIC EPIDURAL ANALGESIA?

Interpreting the literature in regards to the efficacy of TEA is problematic, and pivotal papers are cited by both those in favour and those against. Like all areas of anaesthesia, there exists an abundance of small, single centre trials in favour based on a studied endpoint. These trials are typically underpowered to detect other clinically important differences. Single centre trials are more likely to have positive findings and caution should be used in their interpretation[1]. Further, meta-analyses that suggest the use of TEA reduces mortality and morbidity[2–5], should not be cited as definitive evidence due to the poor agreement between positive meta-analysis and subsequent large randomised trials[6].

The MASTER trial[7] is a good example of the problems of interpreting the TEA literature. The MASTER trial was a randomised, multi-centre trial comparing TEA to IV opiate analgesia in high-risk patients undergoing open abdominal surgery. It showed a statistically significant improvement in pain scores with coughing and a decrease in respiratory failure in patients receiving TEA. This is an important finding, as pain with movement compromises coughing and postoperative mobilisation. The MASTER trial also found a non-significant 3.6 per cent absolute risk reduction in a composite endpoint of major morbidity and mortality. The sample size for the trial was calculated on the basis of an expected 10 per cent absolute risk reduction of a composite endpoint of mortality and major morbidity. If the 3.6 per cent reduction was real, the MASTER trial was underpowered to detect it (n=888) and a sample size of 6000 would be required to detect a combined mortality and morbidity benefit of this size, and 55,000 for a mortality benefit[8]. It is unlikely that a sufficiently large randomised controlled trial will ever be conducted to answer this question.

Although an absolute risk reduction of 3.6 per cent sounds small, it is a similar effect size to other important medical therapies e.g. aspirin for secondary prevention of myocardial infarction[9], tamoxifen in breast cancer and thrombolysis in acute myocardial infarction[7]. If the disease and therapy are common, this translates to a potentially large number of patients who benefit from the intervention.

INDICATIONS AND POTENTIAL BENEFITS

TEA is one of a number of techniques that can be used to manage acute pain following open thoracic and abdominal surgery, and traumatic rib fractures. The Enhanced Recovery After Surgery (ERAS) Society has published guidelines recommending the use of TEA for open gastrointestinal[10], open colonic[11] and open rectal/pelvic surgery[12], gastrectomy[13], radical cystectomy[14], and pancreaticoduodenectomy[15]. TEA is not recommended for routine use in minimally invasive surgery as the benefits (see below) are less pronounced compared to open procedures[16,17]. This is probably also true for open surgery with relatively short lengths of stay such as open general gynaecologic surgery[18]. ERAS guidelines have been shown to reduce recovery time, reduce the rate

of complications, and improve the quality of care at institutions which adopt them[19]. It may be that specific aspects of the "bundle" of changes such as TEA are less important than the process of standardisation itself. Some institutional ERAS protocols do not use TEA for open abdominal surgery. In a meta-analysis by Greco on ERAS for abdominal surgery, around one in four included studies did not use TEA yet found the introduction of protocolised care improved patient outcomes and length of stay[20].

The superiority of TEA over parenteral opioids for analgesia is well documented[21]. The potential benefits of TEA appear to be greater than improved analgesia alone however, as TEA has beneficial effects on multiple organ systems. This is potentially due to a modification of the postoperative neurohumoural stress response[22]. Compared to patients using systemic opioids, meta-analyses suggest patients with TEA have a lower incidence of nausea and vomiting, sedation, atrial fibrillation, supraventricular tachycardia, deep vein thrombosis, pulmonary complications including respiratory depression, atelectasis and pneumonia, ileus and improved bowel function, insulin resistance, and overall lower mortality[5,8]. The MASTER trial indicated a number needed to treat (NNT) of 15 to prevent one episode of respiratory failure in high-risk patients[7].

The benefits of TEA are probably procedure specific, and may be related to the level of the surgical incision. For example, although the benefits of TEA in open colonic resection appear clear, there may be less benefit in patients undergoing hysterectomy, radical prostatectomy, total hip replacement and lower limb vascular surgery[23,24]. These procedures require incisions below the umbilicus or outside of the abdomen, are typically less painful compared to incisions above the umbilicus, and some have relatively short lengths of stay.

TEA is also beneficial in patients with rib fractures following thoracic trauma. TEA decreases the duration of mechanical ventilation[25] and improves mortality in patients with three or more rib fractures[26,27]. The use of TEA in patients with fractured ribs is supported by the fourth edition of *Acute Pain Management: Scientific Evidence*[28].

Although a reduction in the neurohumoural stress response by using TEA should theoretically be beneficial in decreasing cancer recurrence, there is currently insufficient evidence to support its use for this indication[29-32].

POTENTIAL LIMITATIONS TO USE AND RISKS

Like any technique, there are limitations, risks and complications associated with the use of TEA. These relate to the procedure of epidural catheter insertion and certain patient and surgical considerations.

Most anaesthetists agree that contraindications to TEA are similar to spinal anaesthesia, and include patient refusal, infection at the site of injection, sepsis, coagulopathy, indeterminate neurological disease, or impaired mental state. Relative contraindications include infection in an area distant to the site of injection and hypovolaemia. Relative contraindications require balanced consideration of patient comorbidities and surgical risk versus the potential benefits of TEA. A discussion of coagulopathy and TEA is beyond the scope of this article, and is outlined by the American Society of Regional Anesthesia Practice Advisory 2010[33]. The use of TEA for patients undergoing liver resection and liver transplantation is controversial, primarily due to the potential for postoperative coagulopathy.

Hermanides and colleagues have reported rates of failure for TEA ranging from 13 to 32 per cent depending on the definition of failure used[34]. Considerations that influence epidural failure include: failure to localise the epidural space (approximately 3 per cent[7]), the insertion level not covering the surgical incision, complete failure of analgesia due to an incorrectly placed catheter, catheter migration and pump failure. Secondary migration of an epidural catheter is common and occurs during normal patient movement[35]. An imaging study of failed epidurals found approximately half were due to the catheter tip lying outside of the epidural space[36].

Adverse effects of TEA include hypotension (8.9 per cent for local anaesthetic and opioid containing solution versus 2.3 per cent IV opioid control, OR 4.19, 95 per cent CI 2.53–6.94), pruritus (OR 1.47 95 per cent CI 1.15–1.88), urinary retention (OR 1.60, 95 per cent CI 1.02–2.51), and motor block rarely[5]. Hypotension also has resource implications, as vasopressor use to treat hypotension typically requires higher nursing ratios such as an admission to ICU/HDU/Surgical Step Down.

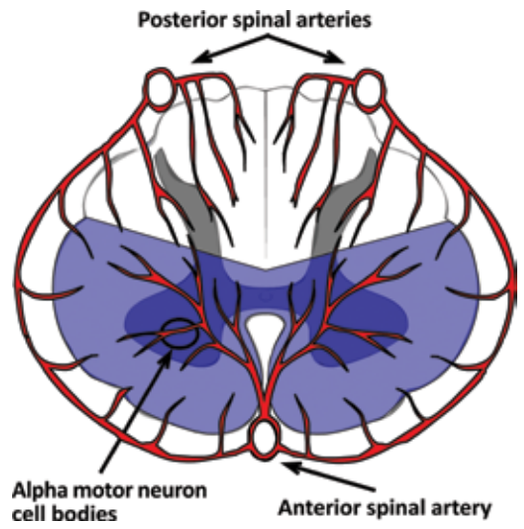
As mentioned above, urinary retention is a potential issue because prophylactic urinary catheterisation has been associated with urinary tract infections and increased length of stay[37]. There is no consensus as to how best to manage this issue. Zaouter et al showed that removing a urinary catheter the morning after surgery in patients at low risk of urinary retention did not result in an increased rate of re-catheterisation, and decreased the incidence of urinary tract infection and length of stay[37]. Hu et al however, showed that TEA after thoracotomy did increase the rate of urinary retention, though this could be managed with an algorithm that included bladder scanning for asymptomatic patients[38]. It would seem prudent that bladder scanning be used routinely in patients with TEA who have had a urinary catheter removed early in the postoperative period to screen for urinary retention.

TEA cannot block the multiple sensory afferents that transmit nociceptive stimuli after thoracotomy or laparotomy. TEA blocks thoracic spinal nociception only. The phrenic nerve (C3/4/5) innervating the diaphragm will not be blocked e.g. referred shoulder tip pain, nor will the vagus nerve innervating the mediastinum, oesophagus, gut and peritoneum e.g. localised peritonitic pain or central abdominal ache. Multimodal systemic analgesia is therefore often required in addition to TEA e.g. paracetamol, a non-steroidal anti-inflammatory drug (NSAID), tramadol, ketamine. There is concern that the concurrent administration of non-selective NSAIDs and prophylactic heparin may increase the risk of epidural haematoma. The American Society of Regional Anesthesia suggests COX-II NSAIDs in this situation as they have minimal effect on platelet function[33].

TEA leads to less motor block compared to lumbar epidural analgesia[39]. Unlike a lumbar epidural, motor block with TEA should not be considered normal and leg weakness occurring with a thoracic epidural always requires further review and possible investigation as it may indicate spinal cord ischemia[40]. Perfusion of the anterior spinal cord which contains the motor efferents is via the single anterior spinal artery (figure 1), and is at greater risk of compromise than the posterior cord. A space occupying lesion in the spinal canal therefore classically presents as lower limb motor block with preserved sensation and pain. Spinal cord ischemia lasting longer than four hours increases the risk of permanent neurological injury. Time to decompression is critical, with rapid diagnosis via MRI and subsequent neurosurgical decompression necessary for a good neurological outcome. An algorithm for management of leg weakness following a thoracic epidural is suggested at the end of this article (Appendix 1).

Permanent neurological injury may occur due to direct needle trauma at the time of insertion, epidural haematoma temporarily associated with an epidural catheter, or epidural abscess typically occurring in the days or weeks after TEA. The incidence of paraplegia or death was estimated to be between one in 5800 cases and one in 12,200[41].

Figure 1. Illustration of spinal cord perfusion (courtesy of Dr Benjamin Darby, MBBS). A single anterior spinal artery supplies the anterior horns which contains the cell bodies of alpha motor neurons



ALTERNATIVE REGIONAL AND IV ANALGESIC TECHNIQUES

Comparison of regional techniques with TEA for open thoracic and abdominal surgery is difficult due to the typically low quality of evidence with varying surgical procedures, control groups, small study sizes and abundance of single centre trials. An important factor to consider in comparing trials is pain on movement as this improves the ability to cough and participate in postoperative physiotherapy. Further, the contribution of systemically absorbed local anaesthetic rather than regional local anaesthetic blockade may explain the analgesic effects of some of these techniques[42].

Paravertebral block for thoracic surgery

Meta-analyses support the equivalence of analgesia of thoracic paravertebral block, with a lower incidence of hypotension, urinary retention, nausea and vomiting and pulmonary complications compared to TEA[43,44]. This block is an appealing alternative to TEA for single sided surgery and rib fractures, although a well conducted study examining patient outcomes is lacking.

Intrathecal morphine

Intrathecal morphine is an efficacious technique that provides early postoperative analgesia only. Compared to systemic opioids, the incidence of pruritus, urinary retention and respiratory depression (although rare) is increased[45]. The technique is appealing in low risk patients undergoing procedures which are likely to have short lengths of stay[10].

Transversus Abdominis Plane (TAP) block
TAP blocks can be performed by landmarks, US-guided, or by the surgeon prior to closure of the abdominal wall, administered either as a single shot or via catheter and continuous infusion. The block improves analgesia and opioid consumption compared to IV opioids[46,47], although a comparison to a postoperative intravenous lignocaine infusion is lacking. This technique is appealing in laparoscopic or laparoscopic assisted surgery[48], particularly in institutions where postoperative IV lignocaine cannot be administered easily.

Continuous systemic lignocaine infusions
Systemic lignocaine infusions improve postoperative analgesia compared to opiates alone, with reduced opioid consumption, nausea and vomiting and hospital length of stay, and faster ileus recovery[49]. Compared to TEA, intravenous lignocaine provides inferior analgesia and return of bowel function[50]. It is probably a worthwhile technique in reducing opioid consumption for minimally invasive surgery, or where regional or neuraxial analgesia is not used.

Continuous Wound Infusion (CWI)
There is conflicting evidence as to the utility of CWI of local anaesthetic after open surgery in improving postoperative analgesia and reducing opioid consumption[51-53]. Further, if CWI is efficacious, it is unclear if this analgesic effect is due to regional or systemic analgesic effects.

WHAT IS THE PLACE OF TEA IN CURRENT ANAESTHESIA PRACTICE?

The continued expansion of minimally invasive surgery (video assisted thoracoscopic surgery, laparoscopic and laparoscopic assisted abdominal surgery) has reduced the indications for TEA. However, older patients with greater perioperative morbidity are undergoing more extensive operations than in the past, increasing the need for excellent perioperative analgesia to assist recovery. Although there is currently high regional variability in the use of TEA, it is likely a new "middle-ground" will be found in which the use of perioperative TEA will expand for some surgical procedures e.g. open abdominal surgery, and no longer be used in others e.g. laparoscopic assisted general surgery, abdominal hysterectomy. The adoption of ERAS Society guidelines that promote TEA may facilitate this change.

A SUGGESTED APPROACH TO IMPROVE THE EFFICACY OF TEA

The number of epidurals inserted by a practitioner or an institution is typically fewer than it has been in the past. There is therefore the potential for practitioners to be unskilled at their insertion, uncertain about their management, unfamiliar with how to troubleshoot problems and unaware of important red flags such as motor block.

This unfamiliarity of thoracic epidural insertion in some institutions is a potential barrier to its increased use. There is concern among consultant anaesthetists that there are insufficient opportunities for trainees to achieve competence, and consultants to maintain it. This concern, and resulting lack of confidence, leads to decreased learning opportunities for trainees[54]. While there is some evidence for the number of lumbar epidural insertions required to attain competence, this has not yet been determined for thoracic epidural insertions, which is considered a more complex technique[55]. Simulation of thoracic epidural insertion learning for both midline and paramedian techniques may assist trainee's initial skill acquisition[56]. Reassuringly, Siddiqui et al[57] found no difference in epidural failure between consultants and trainees, while Heinink et al[58] found no difference between anaesthetists who inserted few epidurals per year and those who inserted many.

Institutions keen to adopt the ERAS society guidelines for open thoracic and abdominal surgery are likely to increase the use of TEA. To improve the efficacy and safety of TEA, institutional strategies promoting standardisation may compensate for this loss of individual and "corporate" knowledge. A suggested standard institutional approach is as follows;

- Fix the catheter following placement with a dedicated fixation device or tunnelling (figure 2). Fixation decreases epidural dislodgement and rate of failure[59-61].
- Standardise the solution. Surprisingly, the optimal concentration (high versus low) of local anaesthetic has not been found, with contradictory evidence about efficacy and incidence of side effects of varying doses of bupivacaine, ropivacaine and levobupivacaine[34]. Local anaesthetics combined with an opioid provide superior pain relief than either medication alone[62]. Further, the incidence of hypotension is reduced with a combined solution compared to local anaesthetic only[5], presumably due to the lower dose of local anaesthetic used. Opioids alone via the epidural route are of no analgesic benefit compared to systemic administration[63], although cause less constipation. The addition of adrenaline to the local anaesthetic and opioid solution further improves TEA[64], probably due to local vasoconstriction with delayed resorption of local anaesthetic and a direct antinociceptive action at the spinal cord. Adrenaline does not appear to cause spinal cord ischemia at doses used clinically[65]. Standardising the solution allows use of a pre-mixed solution, decreasing the risk of drug mixing errors and solution contamination.

- Standardise the prescription with use of a patient controlled epidural analgesia (PCEA) using an infusion rate and bolus volume based on the level of insertion (see Appendix 2 for an example PCEA prescription). A bolus of local anaesthetic containing the same total local anaesthetic dose results in greater spread in the spinal canal compared to an infusion, decreasing the probability of a differential block[66]. The efficacy and safety of a PCEA delivery system on the ward appears favourable[67,68]. Institutions in which TEA is rare are likely to have staff who are less familiar with clinician ordered boluses, potentially increasing the failure rate of TEA. A standardised PCEA order with infusion rates and boluses based on insertion level avoids this problem, allowing the patient to control the timing of boluses instead.
- Routine prescription of systemic analgesics including regular paracetamol and a COX-2 NSAID e.g. oral celecoxib twice daily for three days, unless there is a specific contraindication to a NSAID.
- Standardised algorithm for the management of excessive pain in the presence of TEA. A patient can still experience significant pain despite a working epidural due to nociceptive transmission via the un-blocked phrenic and vagus nerves. Appendix 3 outlines a suggested algorithm.
- Standardise the duration of placement depending on the surgery to avoid an excessively long period of use and the potential for epidural abscess formation[69].
- As serious complications of TEA e.g. epidural haematoma occur rarely, a standardised institutional algorithm for the management of motor block may aid rapid diagnosis and management. An example algorithm is included as Appendix 3.
- Early removal of urinary catheters in patients with TEA appears reasonable if bladder scanning to screen for urinary retention is available.
- A key message of the ANZCA *Acute Pain Management: Scientific Evidence* (fourth edition) is that more effective acute pain management results from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves[70]. Use of an acute pain management service to establish local protocols, follow patients during admission, and be available for consultation in the event of a complication will improve the efficacy and safety of TEA[71].

Figure 2. An example of a commercially available catheter fixation device (LOCKIT PLUS™ regional anesthesia catheter securement device, Smiths Medical, Bella Vista, NSW 2153, Australia, source: Dr Andrew Deacon)

CONCLUSION

Thoracic epidural analgesia is an established technique to provide perioperative analgesia. Its major advantage over systemic analgesia is the improvement in pain on movement, allowing coughing and participation in postoperative physiotherapy. Further, it is the only technique to have shown a decrease in respiratory complications in high-risk patients undergoing open abdominal surgery. Standardisation of management of thoracic epidural analgesia is likely to improve the effectiveness of the technique, and decision algorithms can assist the management of pain and leg weakness, which may be due to a rare complication such as epidural haematoma.

ACKNOWLEDGEMENTS

Thank you to the following people for their proof-reading and input into the article: Penny Deacon, Dr Benjamin Darby (Anaesthetic Registrar, Canberra Hospital, Canberra), Dr Vaughn Oerder (Cardiothoracic Anaesthetist, Canberra Hospital, Canberra), Dr Simon Robertson (Paediatric Anaesthetist and ICU physician, Canberra Hospital, Canberra), Professor Thomas Brussel (Professor of Anaesthesia, Canberra Hospital, Canberra), Dr Desmond McGlade (Cardiothoracic Anaesthetist, St Vincent's Hospital, Melbourne) and Professor Peter Slinger (Cardiothoracic Anaesthetist, Toronto General Hospital, Toronto, Canada).

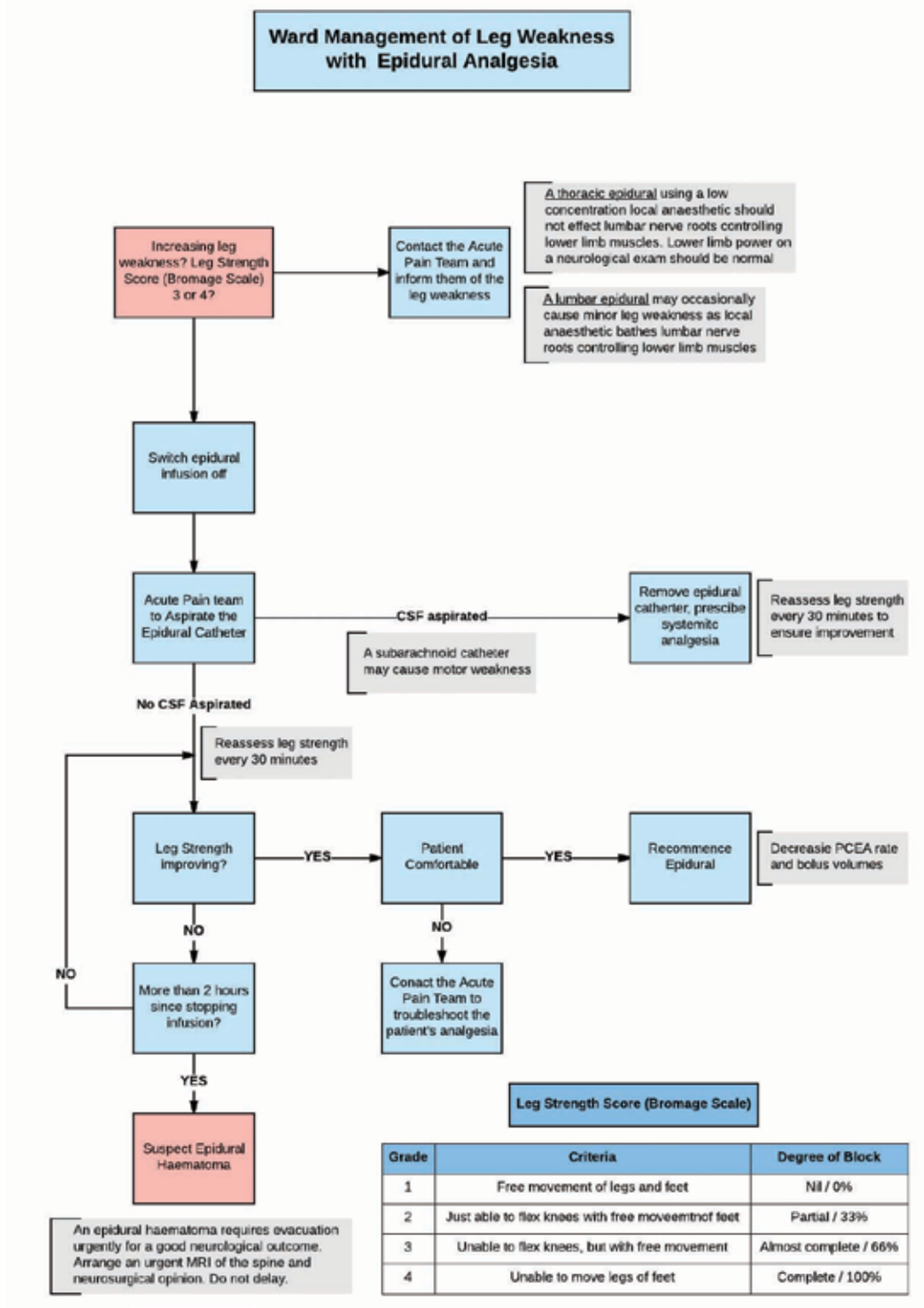
REFERENCES

1. Bellomo R, Warrillow SJ, Reade M. Why we should be wary of single-centre trials. Crit Care Med. 2009;37(12):3114–3119.
2. Beattie SW, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarctin: a meta-analysis. Anesth Analg. 2001;93(4):853–858.
3. Guay J. The benefits of adding epidural analgesia to general anesthesia: a metaanalysis. J Anesth. 2016;20(4):335–340.
4. Pöpping DM, Elia N, Marret E, Remy C, Tramer MR. Protective effect of epidural analgesia on pulmonary complications after abdominal and thoracic surgery – a meta-analysis. Arch Surg. 2008;143(10):990–999.
5. Pöpping DM, Elia NE, Van Aken HK, Marret E, Schug SA, Kranke P, et al. Impact of epidural analgesia on mortality and morbidity after surgery – systematic review and meta-analysis of randomised controlled trials. Ann Surg. 2014;259: 1056–1067.
6. Sivakumar H, Peyton PJ. Poor agreement in significant findings between meta-analyses and subsequent large randomised trials in perioperative medicine. Br J Anaesth. 2016;117(4):431–441.
7. Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet. 2002;359(9314):1276–1282.
8. Wijeysundera DN, Beattie SW, Austin PC, Hux JE, Laupacis A. Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. Lancet. 2008;372(9638):562–569.
9. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71–86.
10. Feldheiser A, Aziz O, Baldini G, Cox BPBW, Fearon KCH, Feldman LS, et al. Enhanced recovery after surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. Acta Anaesthesiol Scand. 2016;60(3):289–334.
11. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg. 2013;37(2):259–284.
12. Nygren J, Thacker J, Carli F, Fearon KCH, Norderval S, Lobo, DN, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg. 2013;37(2):285–305.
13. Mortensen K, Nilsson M, Slim K, Schafer M, Mariette C, Braga M, et al. Consensus guidelines for enhanced recovery after gastrectomy. Enhanced Recovery After Surgery (ERAS) Society recommendations. Br J Surg. 2014;101(10): 1209–1229.
14. Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS) society recommendations. Clin Nutr. 2013;32(6):879–887.
15. Lassen K, Coolsen MME, Slim K, Carli F, de Aguilar-Nascimento JE, Schäfer M, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg. 2013;37(2):240–258.
16. Khan SA, Khokhar HA, Nasr AR, Carton E, El-Masry S. Effect of epidural analgesia on bowel function in laparoscopic colorectal surgery: a systematic review and meta-analysis. Surg Endosc. 2013;27(7):2581–2891.
17. Liu H, Hu X, Duan X, Wu J . Thoracic epidural analgesia (TEA) vs. patient controlled analgesia (PCA) in laparoscopic colectomy: a meta-analysis. Hepatogastroenterology. 2014;61(133):1213–1219.
18. Nelson G, Altman AD, Nick A, Meyer LA, Ramirez PT, Achtari C, et al. Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations – part II. Gynecol Oncol. 2016;140(2):323–332.
19. Ljungqvist O, Scott M, Fearon K. Enhanced recovery after surgery: a review. JAMA Surg. 2017;152(3):292–298.
20. Greco M, Capretti G, Beratta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. World J Surg. 2014;38(6):1531–1541.
21. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J, APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence. 4th ed. Melbourne: ANZCA & FPM; 2015. 194 p.
22. Freise H, Van Aken HK. Risks and benefits of thoracic epidural anaesthesia. Br J Anesth. 2011;107(6):859–868.
23. Prospect Working Group. Prospect – procedure specific postoperative pain management [Internet]. 2015. From: http://www.postoppain.org. Accessed 30 May 2017.
24. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J, APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence. 4th ed. Melbourne: ANZCA & FPM; 2015. 197–198 p.
25. Carrier FM, Turgeon AF, Nicole PC, Trepanier CA, Fergusson DA, Thauvette D, et al. Effect of epidural analgesia in patients with traumatic rib fractures: a systematic review and meta-analysis of randomized controlled trials. Can J Anaesth. 2009;56(3):230–242.

26. Gage A, Rivara F, Wang J, Jurkovich GJ, Arbabi S. The effect of epidural placement in patients after blunt thoracic trauma. J Trauma Acute Care Surg. 2014;76(1):39–45.
27. Malekpour M, Hashmi A, Dove J, Torres D, Wild J. Analgesic choice in management of rib fractures: paravertebral block or epidural analgesia? Anesth Analg. 2017;124(6)1906–1911.
28. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J, APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence. 4th ed. Melbourne: ANZCA & FPM; 2015. xxxvii p.
29. Myles P, Peyton P, Silbert B, Hunt J, Rigg, JRA, Sessler DI. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. BMJ. 2011;342:d1491.
30. Chen WK, Miao CH. The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. PLoS One. 2013;8(2):e56540.
31. Cakmakkaya OS, Kolodzie K, Apfel CC, Pace NL. Anaesthetic techniques for risk of malignant tumour recurrence. Cochrane Database Syst Rev. 2014;11:CD008877.
32. Byrne K, Levins KJ, Buggy DJ. Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis?. Can J Anesth. 2016;63(2):184–192.
33. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (3rd Ed). Reg Anesth Pain Med. 2010;35(1);64–101.
34. Hermanides J, Hollmann MW, Stevens MF, Lirk P. Failed epidural: causes and management. Br J Anaesth. 2012;109(2):144–154.
35. Hamilton CL, Riley ET, Cohen SE. Changes in the position of epidural catheters associated with patient movement. Anesthesiology. 1997;86(4):778–784.
36. Motamed C, Farhat F, Rémérand F, Stéphanazzi J, Laplanche A, Jayr C. An analysis of postoperative epidural analgesia failure by computed tomography epidurography. Anesth Analg. 2006;103(4):1026–1032.
37. Zaouter C, Kaneva P, Carli F. Less urinary tract infection by earlier removal of bladder catheter in surgical patients receiving thoracic epidural analgesia. Reg Anesth Pain Med. 2009;34(6):542–548.
38. Hu Y, Craig SJ, Rowlingson JC, Morton SP, Thomas CJ, Persinger MB, et al. Early removal of urinary catheter after surgery requiring thoracic epidural: a prospective trial. J Cardiothorac Vasc Anesth. 2014;28(5):1302–1306.
39. Richman JM, Rowlingson AJ, Maine DN, Courpas G, Bristow RS, Liu SS, et al. The effects of epidural catheter location on outcomes in women undergoing gynaecologic surgery with an abdominal incision: a randomised clinical trial. Acute Pain. 2007;9(3):109–118.
40. The Royal College of Anaesthetists. 3rd national audit project (NAP3): national audit of major complications of central neuraxial block in the United Kingdom. London: The Royal College of Anaesthetists; 2009. pp.113.
41. The Royal College of Anaesthetists. 3rd national audit project (NAP3): national audit of major complications of central neuraxial block in the United Kingdom, London: The Royal College of Anaesthetists; 2009. pp.106.
42. Mokini Z, Vitale G. Blocks of the anterior abdominal wall: local or systemic effect?. Anesth Analg. 2015;120(6):1428.
43. Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy - a systematic review and meta-analysis of randomized trials. Br J Anaesth. 2006;96(4): 418–426.
44. Baidya DK, Khanna P, Maitra S. Analgesic efficacy and safety of thoracic paravertebral and epidural analgesia for thoracic surgery: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2014;18(5):626–635.
45. Meylan N, Elia N, Lysakowski C, Tramer MR. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. Br J Anaesth. 2009;102(2):156–167.
46. Siddiqui MR, Sajid MS, Uncles DR, Cheek L, Baig MK. A meta-analysis on the clinical effectiveness of transversus abdominis plane block. J Clin Anesth. 2011;23(1):7–14.
47. De Oliveira GS Jr, Castro-Alves LJ, Nader A, Kendall MC, McCarthy RJ. Transversus abdominis plane block to ameliorate postoperative pain outcomes after laparoscopic surgery: a meta-analysis of randomized controlled trials. Anesth Analg. 2014;118(2):454–463.
48. Niraj G, Kelkar A, Hart E, Horst C, Malik D, Yeow C, et al. Comparison of analgesic efficacy of four-quadrant transversus abdominis plane (TAP) block and continuous posterior TAP analgesia with epidural analgesia in patients undergoing laparoscopic colorectal surgery: an open-label, randomised, non-inferiority trial. Anaesthesia. 2014;69(4):348–355.
49. Vigneault L, Turgeon AF, Cote D, Lauzier F, Zarychanski, Moore L, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anesth. 2011;58(1):22–37.
50. Kuo CP, Jau SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, et al. Comparison of the effects of thoracic epidural analgesia and IV infusion with lidocaine and cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. Br J Anaesth. 2006;97(5):640–646.
51. Beaussier M, El'Ayoubi H, Schiffer E, Rollin M, Parc Y, Mazoit JX, et al. Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery: a randomized, double-blind, placebo-controlled study. Anesthesiology. 2007:107(3):461–468.
52. Karthikesalingam A, Walsh SR, Markar SR, Sadat U, Tang TY, Malata CM. Continuous wound infusion of local anaesthetic agents following colorectal surgery: systematic review and meta-analysis. World J Gastroenterol. 2008;14(34):5301–5305.
53. Gupta A, Favaios S, Perniola A, Magnuson A, Berggren L. A meta-analysis of the efficacy of wound catheters for post-operative pain management. Acta Anaesthesiol Scand. 2011;55(7):785–796.
54. Johnson T. Counterbalancing clinical supervision and independent practice: case studies in learning thoracic epidural catheter insertion. Br J Anaesth. 2010;105(6):772–776.
55. Konrad C, Schupfer G, Wietlisbach M, Berber H. Learning manual skills in anesthesiology: is there a recommended number of cases for anesthetic procedures?. Anesth Analg. 1998;86(3):635–639.

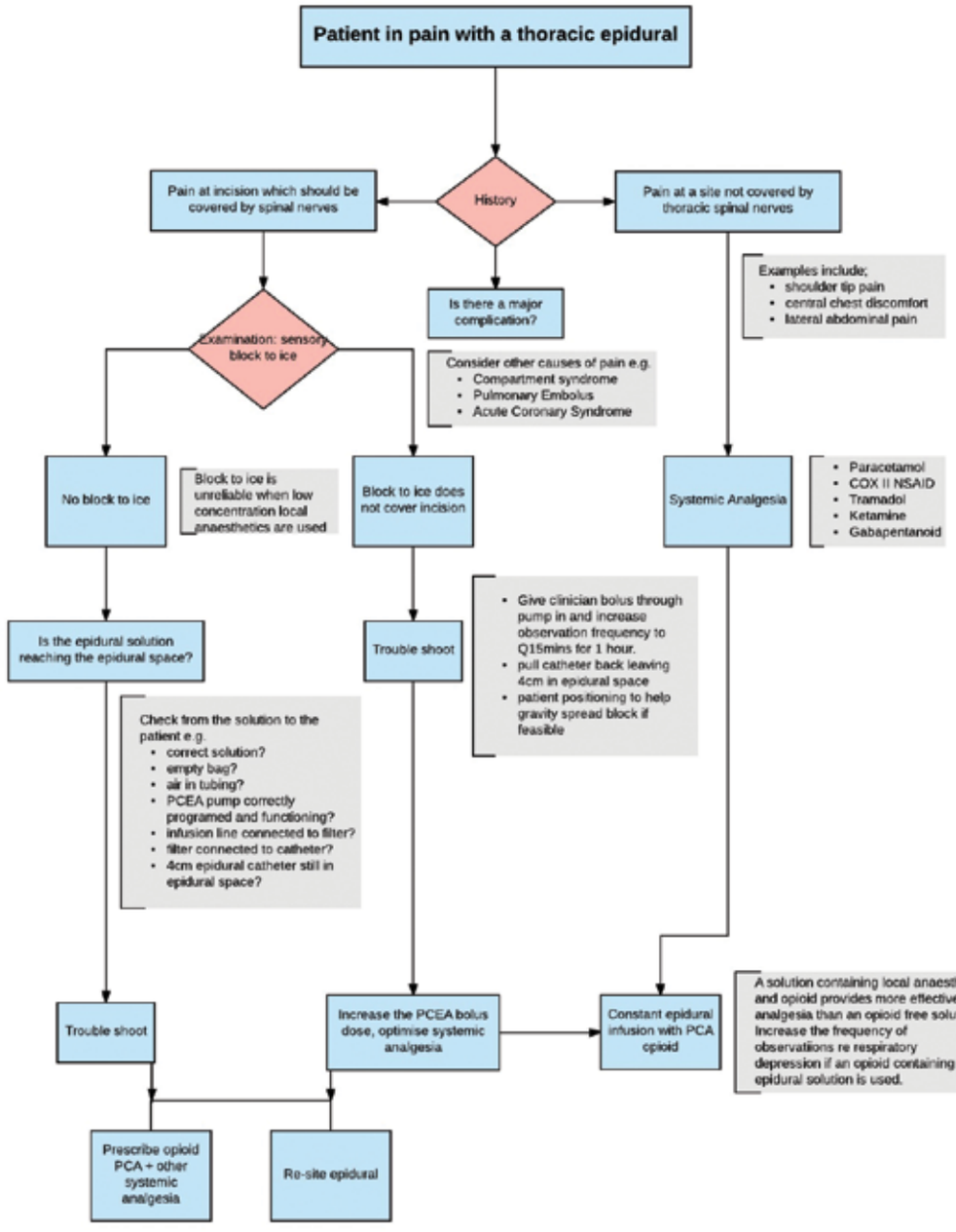
56. Castanelli DJ. The rise of simulation in technical skills teaching and the implications for training novices in anaesthesia. Anaesth Intensive Care. 2009;37(6):903–910.
57. Siddiqui S, Quek C, Prasad MM, Venkatesan. A 6-month audit of epidural analgesia in a teaching hospital. Indian J Pain. 2016;30(2):101–107.
58. Heinink TP, Baker BG, Yates VF, Addison DC, Williams JP. The effect of anaesthetist grade and frequency of insertion on epidural failure: a service evaluation in a United Kingdom teaching hospital. BMC Anesthesiology. 2015;15(5).
59. Clark MX, O'Hare K, Gorringe J, Oh T. The effect of the Lockit epidural catheter clamp on epidural migration: a controlled trial. Anaesthesia. 2001;56(9):865–870.
60. Sellmann T, Bierfischer V, Schmitz A, Weiss M, Rabenalt S, MacKenzie C, et al. Tunneling and suture of thoracic epidural catheters decrease the incidence of catheter dislodgement. Sci World J. 2014(2014):610635.
61. Sharma A, Parasa SK, Tejvath K, Ramachandran G. Epidural catheter fixation. A comparison of subcutaneous tunneling versus device fixation technique. J Anaesthesiol Clin Pharmacol. 2016;32(1):65–68.
62. Curatolo M, Petersen-Felix S, Scaramozzino P, Zbinden AM. Epidural fentanyl, adrenaline and clonidine as adjuvants to local anaesthetics for surgical analgesia: meta-analyses of analgesia and side-effects. Acta Anaesthesiol Scand. 1998;42(8):910–920.
63. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003;290(18):2455–2463.
64. Niemi G, Breivik H. The minimally effective concentration of adrenaline in a low-concentration thoracic epidural analgesic infusion of bupivacaine, fentanyl and adrenaline after major surgery, a randomised, double-blind, dose-finding study. Acta Anaesthesiol Scand. 2003;47(4):439–450.
65. Neal JM. Effects of epinephrine in local anesthetics on the central and peripheral nervous systems: neurotoxicity and neural blood flow. Reg Anesth Pain Med. 2003;28(2):124–134.
66. Christiaens F, Verborgh C, Dierick A, Camu F. Effects of diluent volume of a single dose of epidural bupivacaine in parturients during the first stage of labor. Reg Anesth Pain Med. 1998;23(2):134–141.
67. Tan T, Wilson D, Walsh A, Hu P, Power C. Audit of a ward-based patient-controlled epidural analgesia service in Ireland. Ir J Med Sci. 2011;180(2):417–421.
68. Golster M. Seven years of patient-controlled epidural analgesia in a Swedish hospital: a prospective survey. Eur J Anaesthesiol. 2014;31(11):589–596.
69. Horlocker TT, Bimback DJ, Connis RT, Nickinovich DG, Palmer CM, Pollock JE, et al. Practice advisory for the prevention, diagnosis and management of infectious complications associated with neuraxial techniques: a report by the American Society of Anesthesiologists Task Force on Infectious Complications Associated with Neuraxial Techniques. Anesthesia. 2010;112(3):1–15.
70. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J, APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence. 4th ed. Melbourne: ANZCA & FPM; 2015. pp. 61.
71. Faculty of Pain Medicine, Royal College of Anaesthetists. Best practice in the management of epidural analgesia in the hospital setting. London: Faculty of Pain Medicine, Royal College of Anaesthetists; 2010. pp. 3.

Appendix 1. Suggested Management of leg weakness with thoracic epidural analgesia
(Source: Modified by Dr Andrew Deacon, based on "Management of leg weakness with epidural analgesia" by Dr Iain Christie, Anaesthetist, Derriford Hospital, Plymouth, UK, as published in NAP 3, page 142, used with permission).



Appendix 2. Suggested management of pain in the presence of TEA

(Source: Dr Andrew Deacon, Department of Anaesthesia, The Canberra Hospital, Canberra, Australia. Reproduced with permission)



Appendix 3. A suggested PCEA prescription

The solution used is bupivacaine 0.125 per cent, fentanyl 5 mcg/mL and adrenaline 2 mcg/mL (premixed by BAXTER, Old Toongabbie, NSW 2146, Australia), lockout 20 minutes. The bottom line "other" allows for variation in unusual circumstances (Source: The Canberra Hospital, Canberra, Australia. Reproduced with permission).

INSERTION LEVEL	INFUSION (ML/HR)	BOLUS (ML)
T4–6	3	2
T7–11	4	3
T12–L4	6	3
Other		

Dissecting epidural failure in the obese parturient: Time to carefully consider the lumbar interspinous ligament

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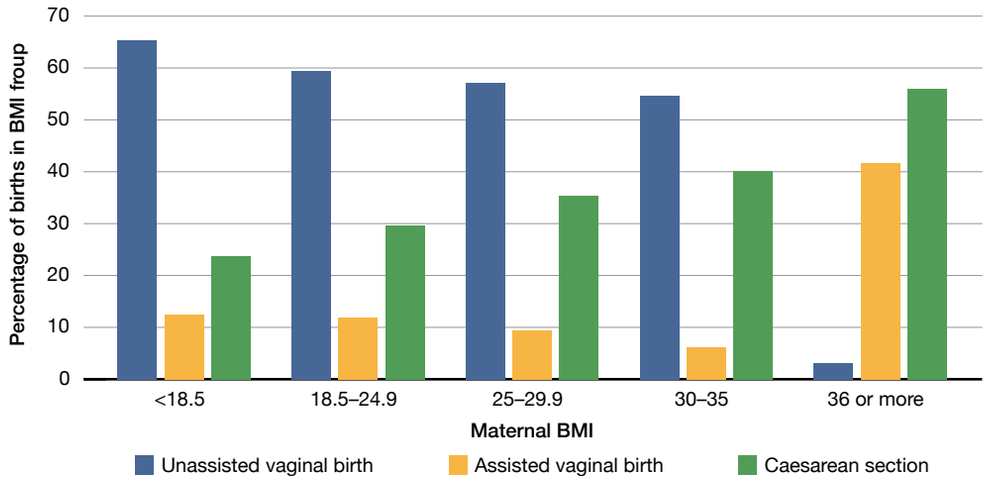
INTRODUCTION

Epidural and combined spinal epidural (CSE) techniques have become the mainstay of labour analgesia in developed countries, but incidence of epidural catheter failure remains around 5-10 per cent[1]. Studies indicate that increasing prevalence of morbid obesity has led to higher rates of Caesarean delivery in this population cohort. The reliability of epidural catheterisation in these patients is becoming increasingly important for patient safety. Problems concerning labour epidurals in the obese parturient include difficult insertion due to poorly defined landmarks, displacement of epidural catheters after insertion, higher failure rates and greater need to revise catheter placement[2].

Obesity rates in Australian and New Zealand are increasing. Almost one in three Australian and New Zealanders are obese, defined as body mass index (BMI) >30 kg/m^2. The population averaged BMI for adults is transitioning from the overweight (BMI 25-30 kg/m^2) and into the obese range[3, 4]. The rising prevalence of obesity is reflected in all age groups as well as the generalised rising prevalence of obesity with age[5-8]. These overall trends include women of child-bearing age.

Obesity has a dramatic impact on pregnancy outcome. Particularly increased prevalence of poor perinatal and neonatal outcomes, and increased risk of pregnancy complications such as postpartum anaemia, hypertension, pre-eclampsia, preterm delivery, emergency caesarean section, and gestational diabetes[9]. Epidural and combined spinal epidural (CSE) analgesia and anaesthesia is also commonly performed for the obstetric population. Sullivan and colleagues published on behalf of Australasian Maternity Outcomes Surveillance System (AMOSS) a 2010 cohort of "super-obese" pregnant women as defined by BMI >50 kg/m^2 or weight >140 kg. The Caesarean section rate was 51.6 per cent compared with 31.7 per cent in the comparison group ($p < 0.01$)[10]. Data from the Queensland Maternal and Perinatal Quality Council, demonstrate a trend toward assisted vaginal birth and caesarean section with increasing BMI (figure 1)[11]. This chapter aims to explore the challenges of epidural catheterisation in obese parturients. Potential contributions will be discussed, including the potential impact of obesity related anatomical changes.

Figure 1. Body Mass Index (BMI) versus mode of birth in Queensland 2009 to 2013. Used with permission from the Queensland Maternal and Perinatal Quality Council, a quality assurance functionary of Queensland Health, 2015 Report[12]



THE INFLUENCE OF OBESITY ON OBSTETRIC ANAESTHETIC MANAGEMENT

The prevalence of obese parturients impacts upon healthcare provision in several ways. Anaesthetic management is potentially associated with requirements for greater time allocation, access to anaesthetic expertise and equipment, as well as altered epidural catheter security.

Time management

Numerous studies confirm that anaesthetic management of the obese parturient demands a greater allocation of time. A retrospective study by Vricella and colleagues examined anaesthetic complications during elective Caesarean deliveries for morbidly obese women[13]. It was demonstrated that both the morbidly obese (BMI of ≥40 kg/m^2) and overweight or obese group had significantly longer total anaesthetic and surgical times compared to the normal BMI group. Additionally, it was noted that regional anaesthetic was significantly more difficult to place as measured by "attempts"[13]. At the Royal Brisbane and Women's Hospital, Eley and colleagues described similar results in a cohort of women with a booking BMI of ≥40 kg/m^2. In parturients receiving neuraxial analgesia in labour and then progressing to Caesarean section, anaesthetic case time was significantly longer than their case-control cohort (79 minutes (IQR 26.0) versus 66 minutes (IQR 17))[14]. The "MUM Size" study published this year also echoes these findings[15].

Anaesthetic expertise

Obesity has implications for anaesthetic staffing and availability of the appropriate expertise. Eley and colleagues document the presence of a senior anaesthetist at caesarean section more often in the obese population (40.0 per cent cf 11.1 per cent, p<0.001)[14]. Ellinas and colleagues conducted a prospective observational study to describe characteristics of parturients with BMI >35 kg/m^2 at time of neuraxial block insertion[16]. It was found that if the BMI was >35 kg/m^2 then an experienced physician was more likely to intervene and "take over" the procedure. This was associated with a significant decrease in the risk of block failure. Butcher and colleagues also warn that self-discrimination of back midline is less reliable in the obese parturient[17].

Equipment

Anaesthetic management of the obese parturient may require access to equipment that is less frequently used in routine practice.

Ultrasound

Neuraxial ultrasound is a promising adjunct to assist epidural placement. Studies suggest ultrasound-assisted epidural placement may increase the success rate, reduce the risk of traumatic procedures, and thus may possibly contribute to increase the safety of lumbar central neuraxial blocks[18]. The potential benefits of using ultrasound include improved pre-procedural mapping and identification of lumbar intervertebral levels, more accurate prediction of needle insertion depth, location of the midline and interspinous/interlaminar spaces, and decreasing the number of needle punctures.

Clinkscales and colleagues found that increased BMI was associated with an increase in depth of the L4/5 epidural space (R^2 = 0.3646; P <0.0001), but only when adjusted for maternal age, gestational age and vertebral interspace of epidural catheter placement. They found that all the lumbar interspaces above L4/5 vertebral level had no statistical difference in depth and the range of depth varied widely, even within BMI sub-groupings[19].

This is consistent with data published by Palmer and colleagues 24 years earlier and with fewer patients[20]. Both studies would have the majority of epidural catheters successfully sited using a standard 8 cm epidural needle.

Alternative needles

In a study of non-specialist hospital doctors, 78.4 per cent were unaware that lumbar puncture needles longer than nine centimetres were available and only 13.3 per cent had used one[21]. Varieties of epidural and combined spinal epidural sets are available for neuraxial anaesthesia and seem to be generally well appreciated by the anaesthetic community.

Epidural catheter security

The risk of epidural catheter dislodgement is increased in obese patients. Eappen and colleagues noted an epidural catheter failure rate of 13.1 per cent[22]. Hamilton, Riley and Cohen divided 255 patients into BMI <25 kg/m^2, 25-30 kg/m^2 and >30 kg/m^2 and found that distance to the epidural space and the magnitude of catheter movement with position change from a flexed to upright then lateral position was greater in obese parturients[23]. It is possible that the epidural catheter is subject to capture and relative fixation by the elastic nature of the ligamentum flavum; the observed movement of the epidural catheter into the patient with these staged movements was more likely explained by movement of the tissues overlying the interspinous space. They postulated that, if the epidural catheter was not fixed to the skin, the length of catheter in the epidural space was unchanged but if the catheter was fixed at the skin then the only way to accommodate the changes of tissue depth was a relative withdrawal of the catheter from the epidural space.

Archer formalises this concept of altering patient positioning prior to epidural catheter securement as the "Cohen Manoeuvre"[24]. An alternative management plan for accommodation of excessive epidural catheter movement leads other authors such as Bang and colleagues to recommend 10 cm of epidural catheter be left in the epidural space of severely morbidly obese parturient for labour analgesia[25].

THE LUMBAR INTERSPINOUS LIGAMENT

Neuraxial techniques are a fundamental component of anaesthetic management of the obese parturient. It is important to understand the tissues through which the epidural needle passes. Historical descriptions of the lumbar interspinous ligament (LISL) will be discussed before considering anatomical changes associated with obesity.

Historical descriptions

The gross anatomy of the spine outlining key bony, ligamentous, and neural elements was recognised very early and reflected in anatomical investigation across the globe. The earliest questioning regarding anatomy of this area referred to the explanation of posture and movement including a communication system enabling coordination of the musculoskeletal system[26]. The anatomical descriptions of the LISL by the 1800s usually stated the features outlined in table 1[27]. The basic anatomical understanding of the position and nature of the ligaments was established in exceptional detail as leading-edge technology at the time included advances in optical microscopy[28].

Table 1. Anatomical origins, arrangements and function of the interspinous ligaments

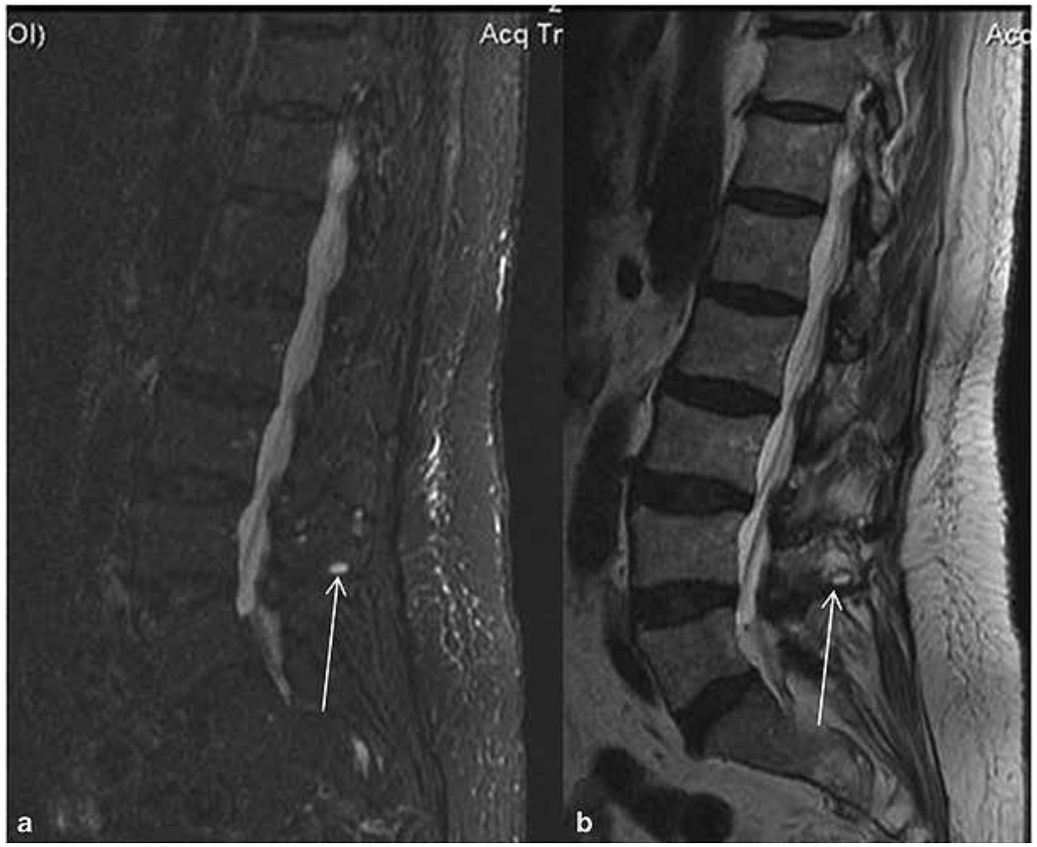
ORIGIN	Ligamenta flava, laminae, zygapophyseal aponeurosis and spinous process inferiorly
INSERTION	Spinous process superiorly and supraspinous ligament
FABRIC	Fibre bundles irregularly place with an overall arrangement of infero-anterior insertion and supero-posterior termination. Stronger and thicker the lower their situation is in the spine.
FUNCTION	Structural stability whilst allowing flexibility of the vertebral column and fixation for surrounding musculature

The study of anatomy has advanced the understanding of pathology and vice versa. In 1825 Professor Mayer proposed that here were two, yet to be acknowledged, joints of the spine. He described that when examining the LISLs; there was an articular cavity following the general fibre direction outlined in table 1. He claimed that it was lined by a synovial capsule and contained synovial fluid. Although he didn't link this proposed joint to changes with wear or age he does admit that it isn't universally present. He states it is most prominent between the third and fourth lumbar vertebrae, in people who in life had mobile and flexible spines, males, and adults[29].

His other proposed joint of the thoracic spine was not accepted by the anatomists at the time but in contrast Mayer's "diarthrosis interspinosa vertebrarum lumborum" has long been depicted as part of anatomical alteration with degenerative spine changes[30].

Baastrup, a Danish radiologist, continued this thread by linking localised lumbar pain to radiographic changes of the spinous processes[31]. It is now accepted that degenerative changes to the lumbar spine may result in the posterior portions of adjacent interspinous ligaments abutting each other and be associated with changes in the interspinous ligaments. A sagittal section MRI illustrating this posterior cystic change is included in figure 2.

Figure 2. Posterior cystic change demonstrated by a sagittal section MRI. Degenerative changes to the lumbar spine may result in the posterior portions of adjacent interspinous ligaments abutting each other and be associated with changes in the interspinous ligaments



Investigation into back pain, including the origins and possible treatments lead the next phase of anatomical enquiry. The LISL fibre direction debate started with this phase of study[32]. As summarised in table 2, descriptions of the LISL have been inconsistent. The currently accepted description of this small and insignificant ligament is that the LISL may be divided into distinct portions; anterior/ventral, middle/intermediate and posterior/dorsal. The fibres are agreed to be arranged as a combination of sheet and fibre bundles with the angle of fibre orientation slightly different in different zones; the fibres pass from infero-anterior to postero-superior in the style of an italicised “S” (table 2).

Table 2. The orientation of the fibre bundles of the interspinous ligaments is contentious[27,30,32-49]

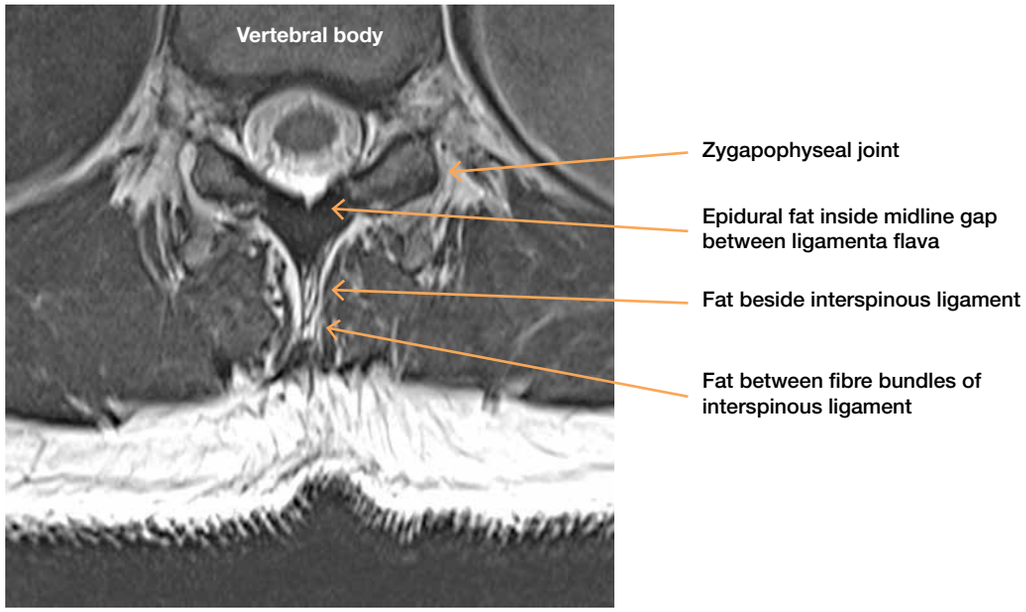
LUMBAR INTERSPINOUS LIGAMENT DIRECTION	AUTHOR	YEAR
Horizontal or multiple depictions	Ellis and colleagues	2014
Horizontal with reflected convexity anteriorly, “C”	Tandler	1919
Vertical	Kapandji	2008
Oblique antero-superior to postero-inferior	Fink	1904
	Aspden and colleagues	1987
	Cousins and Bridenbaugh	2009
Oblique antero-inferior to postero-superior, linear	Rissanen	1960
	Heylings	1978
	Sharrock	1979
	Bywaters and Evans	1982
	Netter	2011
	Bogduk	2012
	Paulsen and Waschke	2013
	Butt and colleagues	2015
	Standring	2016
Oblique antero-inferior to postero-superior but variable, complex, decussating or non-linear “S”	Knox (Cloquet)	1830
	Grant	1972
	Johnson	2002
	Scapinelli and colleagues	2006
	Agur and colleagues	2013
	Mahato	2013

Rissanen’s, and later Heyling’s, work describes a ventral gap in the anterior portion of the LISL. This is a function of the origin of this portion of the ligament as it arises from the bilateral ligamenta flava and zygapophyseal joint capsules[40,50]. Rissanen observed in infants and young children that this gap is populated by fat but in adult spines the fat had disappeared. He also observed that it was normal to have fatty lamella either side of the LISL in infants as well as islets of fat between fibre bundles. With the wider application of both electron and light microscopy, Yahia and colleagues stated that “occasional lipid droplets were found” but gives no indication of exact location or proportion of the nine LISLs displayed this feature[51,52].

Anatomical changes in the obese individual

This most recent anatomical work on the LISL precedes the change in our population toward a higher prevalence of obesity. An MRI set to maximise contrast fat with lipophobic and solid tissues is presented in figure 3. Early studies evaluating lumbar epidural steroid injections warned that the loss of resistance technique could be a false indicator of needle-tip position. Bartynski and colleagues concluded the position was inaccurate in 30 per cent of lumbar epidural injections by using the loss of resistance to air[53]. It was concluded that the probable cause of inaccuracy is loss of resistance while the needle tip is positioned within the fat overlying the ligamentum flavum. Loubert and colleagues refer to false positives when using the loss-of-resistance technique due to fat pockets in their descriptions of the difficulties and failures of neuraxial techniques in obese women having Caesarean section[54]. Hameed and colleagues noted that there was a midline fat density superficial to the ligamentum flavum in 25.8 per cent of the interspaces studied [BMI = 28.3 ± 5.0 (mean ± standard deviation)] when investigating anatomic impediments to interlaminar lumbar epidural steroid injection[55].

Figure 3. Epidural trajectory MRI. Image is of a modified transverse plane of a normal BMI adult low thoracic interspace that aligns with a trajectory of a midline epidural needle. It illustrates the following; epidural fat protruding through the midline gap in the ligamentum flavum, difference of structure of the anterior portion compared with the posterior portion of the interspinous ligament, fatty lamella outlining the interspinous ligament laterally and fat infiltration between fibre bundles creating a marbled effect. Used with permission from Dr DG Cowin, National Imaging Facility, Centre for Advanced Imaging, The University of Queensland[56]



THE FUTURE OF NEURAXIAL TECHNIQUES IN OBSTETRIC ANAESTHESIA

The technique of neuraxial anaesthesia is not new. A paper documenting a successful neuraxial block occurred as early as 1885 but it wasn't until the development of new drugs and delivery devices in the early 1900s that its use became more widespread in clinical anaesthesia[57]. Identification of needle entry into the epidural space using the loss of resistance technique, which was described in 1921, has largely remained unchanged[58]. Although further research is required, a number of directions could improve anaesthetic management of the obese parturient.

Improved anatomical understanding

The increasing rates of obesity and higher than average rates of Caesarean sections in this cohort require an accurate and up-to-date anatomical knowledge of the lumbar region in order to safely place and trouble shoot epidural anaesthesia. Typically, the proceduralist aims to pass through the dense ligamentous structures of the supraspinous ligament, interspinous ligament and ligamentum flavum. As the epidural needle orifice emerges anteriorly a "loss of resistance" to injection indicates the epidural needle tip has left the dense ligamentous structures. This generally means that either the epidural space has been entered or the needle tip has left anatomical midline. The notion that there could potentially be midline extra-epidural fat is not considered. The mistaken acceptance of inaccurate needle placement and strongly held unacceptability of an inadvertent dural tap may contribute to lower success rates for epidural analgesia in labour and conversion of labour epidural analgesia into epidural anaesthesia for Caesarean section in the obese parturient.

Alternative use of needles

An awareness of alternative needles should not imply the ability to use those needles. Combined spinal epidurals are usually performed with the goal of enjoying the benefits of the spinal block with the backup potential of using the epidural to extend the block height or duration. If loss of resistance has been sensed at a shallower depth than expected, either clinically or by ultrasound mapping, the clinician might choose to accept the shallower space and proceed with epidural placement. An alternative technique could use a needle through needle technique to test if cerebrospinal fluid (CSF) lies closely beyond the tip of the epidural needle. If no CSF is obtained through the seeking spinal needle, the epidural needle may then be advanced or re-directed towards the midline. Using the needle through needle technique appears to offer reassurance to the proceduralist that an inadvertent dural puncture is not imminent as the epidural needle may be progressed anteriorly within the zone tested by the spinal needle. The authors have found this clinically useful but intend further research before recommending this as mainstream practice.

New and future technologies

Over the past decade newer technologies have emerged to help proceduralists identify entry into the epidural space. These include ultrasound techniques that not only allow pre-procedural imaging of anatomical landmarks but allow real-time guidance through needle tracking and navigation tools. Ultrasound imaging is largely dependent on computer processing power and clinical applications are progressing rapidly. The high computational speed of modern machines allows rapid image acquisition in real time to generate three or four dimensional imaging, but currently the techniques are limited in the spine because of complex anatomy, artefacts, and varying bony shadows[59]. An alternate method is application of an ultrasound transducer to the tip of an epidural needle. This needle through ultrasound technique allows identification of the both the dura and ligamentum flavum. Although providing real time information on the needle tip special equipment is required and limited to spaces into which the needle fits[60].

Electromagnetic tracking systems also exist. These have established value in central line insertion, endovascular surgery and in radiofrequency ablation of liver tumours. Guidance systems, consisting of a transmitter and sensors, determine the position of the needle with respect to the ultrasound image, allowing a virtual image of the needle's trajectory[61]. Application to epidural catheter insertion are yet to be manifest and will be challenging within the constraints of the birthing suite.

Future technologies may include artificial intelligence based software to aid in correct identification of intervertebral levels, measuring acoustic or bio-impendence of tissues surrounding the epidural space or modifying the loss of resistance technique. Several adjuncts have been described which mostly rely on modification of the loss of resistance syringe or needle but most are not commercially available. Novel techniques including optical reflectance spectroscopy, optical coherence tomography or the optical analog of B-mode ultrasonography, electrocardiograph guiding, epidural pressure waveform analysis and near-infra red tracking hold promise but are currently confined to research applications[61].

SUMMARY

The practice of obstetric anaesthesia makes passing a needle through the LISL a work-a-day event. Epidurals are inserted with such frequency that an appreciation of the structural arrangement of the LISL is crucial so that anatomical variations may be predicted and accounted for.

Anatomical study of the lumbar spine was initially driven by the spirit of discovery. More recently, an understanding of stability, mobility and pain has been sought. The next step must include application of modern imaging techniques, inclusion of anatomical alterations with morbid obesity and the perspective neuraxial axis access using minimally invasive techniques. The incremental gains of improved understanding of anatomy paired with alternative use of needles and techniques, including ultrasound, will hopefully translate into improved performance of epidural analgesia. This should be realised in terms of both efficacy and safety.

REFERENCES

1. Arendt K, Segal S. Why epidurals do not always work. Rev Obstet Gynecol. 2008;1(2):49-55.
2. Abenhaim HA, Benjamin A. Higher caesarean section rates in women with higher body mass index: are we managing labour differently? J Obstet Gynaecol Can. 2011;33(5):443-448.
3. World Health Organisation. Prevalence of obesity [Internet]. 2016. From: http://gamapserver.who.int/gho/interactive_charts/ncd/risk_factors/obesity/atlas.html. Accessed 28 May 2017.
4. World Health Organisation. Mean body mass index trends [Internet]. 2016. From: http://gamapserver.who.int/gho/interactive_charts/ncd/risk_factors/bmi/atlas.html. Accessed 28 May 2017.
5. Australian Bureau of Statistics. National health survey: first results, 2014-15 [Internet]. 2016. From: http://www.abs.gov.au/ausstats/abs@.nsf/mf/4364.0.55.001. Accessed 31 August 2017.
6. Australian Bureau of Statistics. National health survey: summary of results, Australia, 2004-05. Canberra, ACT: Australian Bureau of Statistics, 2006.
7. Australian Bureau of Statistics. 1995 national health survey: SF-36 population norms, Australia. Canberra, ACT: Australian Bureau of Statistics, 1997.
8. Statistics New Zealand. NZ social indicators, obesity [Internet]. 2017. From: http://www.stats.govt.nz/browse_for_stats/snapshots-of-nz/nz-social-indicators/Home/Health/obesity.aspx. Accessed 28 May 2017.
9. Machado LS. Cesarean section in morbidly obese parturients: practical implications and complications. N Am J Med Sci. 2012;4(1):13-18.
10. Sullivan E, Dickinson J, Vaughan G, Peek M, Ellwood D, Homer C, et al. Maternal super-obesity and perinatal outcomes in Australia: a national population-based cohort study. BMC Pregnancy Childbirth. 2015;15:322.
11. Humphrey M, Colditz P, Ellwood D, Flenady V, Whelan N. Queensland maternal and perinatal quality council report 2015 [Internet]. Queensland Health, 2015. From: https://www.health.qld.gov.au/improvement/networks/qmpqc_publications. Accessed 15 August 2017.
13. Vricella LK. Anesthesia complications during scheduled cesarean delivery for morbidly obese women. Am J Obstet Gynecol. 2010;203(3):276.e271-276.e275.
14. Eley VA, van Zundert A, Callaway L. What is the failure rate in extending labour analgesia in patients with a body mass index ≥ 40 kg/m^2 compared with patients with a body mass index < 30 kg/m^2 ? A retrospective pilot study. BMC anesthesiology. 2015;15(1):115.

15. Dennis AT, Lamb KE, Story D, Tew M, Dalziel K, Clarke P, et al. Associations between maternal size and health outcomes for women undergoing caesarean section: a multicentre prospective observational study (the MUM SIZE study). BMJ Open. 2017;7(6):1-9.
16. Ellinas EH, Eastwood DC, Patel SN, Maitra-D'Cruze AM, Ebert TJ. The effect of obesity on neuraxial technique difficulty in pregnant patients: a prospective, observational study. Anesth Analg. 2009;109(4):1225.
17. Butcher M, George RT, Ip J, Campbell JP, Yentis SM. Identification of the midline by obese and non-obese women during late pregnancy. Anaesthesia. 2014;69(12):1351-1354.
18. Perlas EA, Chaparro JL, Chin JK. Lumbar neuraxial ultrasound for spinal and epidural anesthesia: a systematic review and meta-analysis. Reg Anesth Pain Med. 2016;41(2):251-260.
19. Clinkscales CP, Greenfield ML, Vanarase M, Polley LS. An observational study of the relationship between lumbar epidural space depth and body mass index in Michigan parturients. Int J Obstet Anesth. 2007;16(4):323-327.
20. Palmer SK, Abram SE, Maitra AM, von Colditz JH. Distance from the skin to the lumbar epidural space in an obstetric population. Anesth Analg. 1983;62(10):944-946.
21. Halpenny D, O'Sullivan K, Burke JP, Torreggiani WC. Does obesity preclude lumbar puncture with a standard spinal needle? The use of computed tomography to measure the skin to lumbar subarachnoid space distance in the general hospital population. Eur Radiol. 2013;23(11):3191-3196.
22. Eappen S, Blinn A, Segal S. Incidence of epidural catheter replacement in parturients: a retrospective chart review. Int J Obstet Anesth. 1998;7(4):220-225.
23. Hamilton CL, Riley ET, Cohen SE. Changes in the position of epidural catheters associated with patient movement. Anesthesiology. 1997;86(4):778-784; discussion 729A.
24. Archer T. Super-morbidly obese patient for elective repeat cesarean section. In: Benumof L, editor. Clinical anesthesiology: lessons learned from morbidity and mortality conferences. New York: Springer New York, 2014. pp. 285-307.
25. Bang U, Helbo-Hansen H. Maternal obesity and pregnancy. In: Ovesen P, Jensen D, editors. Maternal obesity and pregnancy. Berlin, Heidelberg: Springer Berlin Heidelberg, 2012.
26. Bauhin C, Bry JTd, Bry JId. Caspari bauhini basileensis theatrvm anatomicum novis figuris oeneis illustratum et in lucem emissum opera & sumptibus theodori de brÿ p.M. Relicta viduae & filiorum ioannis theodori & ioannis israelis de brÿ. Bodleian L, editor. Francofurti at Moenum: Francofurti at Moenum : Typis Matthaei Beckeri, 1605.
27. Knox R. A system of human anatomy: on the basis of the "traite d'anatomie descriptive" of m. H. Cloquet. Edinburgh: MacLachlan and Stewart, 1830.
28. Amos B. Lessons from the history of light microscopy. Nat Cell Biol. 2000;2(8):E151-152.
29. Mayer O. Uber zwei neu entdeckte gelenke an der wirbelsaule des menschlichen korpers. Zeitschrift fuer Physiologie. 1825;2:29-35.
30. Agur A, Dalley A, Grant J. Grant's atlas of anatomy. 13th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2013.
31. Baastrup C. On the spinous processes of the lumbar vertebrae and the soft tissues between them, and on pathological changes in that region. Acta Radiol. 1933;14(1):52-55.
32. Scapinelli R, Stecco C, Pozzuoli A, Porzionato A, Macchi V, De Caro R. The lumbar interspinous ligaments in humans: anatomical study and review of the literature. Cells Tissues Organs. 2006;183(1):1-11.
33. Ellis H, Lawson A. Anatomy for anaesthetists. Chichester, West Sussex, UK: Blackwell Science Ltd., John Wiley & Sons Ltd, 2014.
34. Tandler J. Lehrbuch der systematischen anatomie. Leipzig: Vogel, 1919.
35. Kapandji I. The physiology of the joints / A.L. [sic] Kapandji ; foreword by Gérard Saillant ; 539 original drawings by the author ; translated by Louis Honoré. 6th ed. Edinburgh ; New York: Churchill Livingstone/Elsevier, 2008.
36. Fick RA. Handbuch der anatomie und mechanik der gelenke unter berücksichtigung der bewegenden muskeln. Jena: Fischer, 1904.
37. Aspden RM, Bornstein NH, Hukins DW. Collagen organisation in the interspinous ligament and its relationship to tissue function. J Anat. 1987;155:141.
38. Cousins MJ, Bridenbaugh PO, Carr DB, Horlocker, TT, editors. Cousins and Bridenbaugh's neural blockade in clinical anesthesia and management of pain. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.
39. Rissanen PM. Comparison of pathologic changes in intervertebral discs and interspinous ligaments of the lower part of the lumbar spine in the light of autopsy findings. Acta Orthop Scand. 1964;34:54-65.
40. Heylings DJ. Supraspinous and interspinous ligaments of the human lumbar spine. J Anat. 1978;125(1):127-131.
41. Bywaters EG, Evans S. The lumbar interspinous bursae and Baastrup's syndrome. An autopsy study. Rheumatol Int. 1982;2(2):87-96.
42. Netter F. Atlas of human anatomy. 5th ed. Philadelphia, PA: Saunders/Elsevier, 2011.
43. Bogduk N. Clinical and radiological anatomy of the lumbar spine. New York; Edinburgh: Churchill Livingstone, 2012.
44. Paulsen F, Waschke J. Sobotta atlas of human anatomy, vol 1: general anatomy and musculoskeletal system. 15th ed. Elsevier Health Sciences Germany, 2013.
45. Butt AM, Gill C, Demerdash A, Watanabe K, Loukas M, Rozzelle CJ, et al. A comprehensive review of the sub-axial ligaments of the vertebral column: part I anatomy and function. Childs Nerv Syst. 2015;31(7):1037-1059.
46. Standring S. Gray's anatomy the anatomical basis of clinical practice. 41st ed. [Oxford]: Elsevier Health Sciences UK, 2016.
47. Grant JCB. An atlas of anatomy. 6th ed. Baltimore: Williams and Wilkins Co., 1972.
48. Johnson GM, Zhang M. Regional differences within the human supraspinous and interspinous ligaments: a sheet plastination study. Europ Spine J. 2002;11(4):382-388.

49. Mahato NK. Anatomy of lumbar interspinous ligaments: attachment, thickness, fibre orientation and biomechanical importance. Int J Morphol. 2013;31(1):351-355.
50. Rissanen PM. The surgical anatomy and pathology of the supraspinous and interspinous ligaments of the lumbar spine with special reference to ligament ruptures. Acta Orthop Scand. 1960;31(suppl 46):3-100.
51. Yahia LH, Drouin G, Maurais G, Rivard CH. A study of the microscopic structure of the posterior ligaments of the lumbar spine. [French] Etude de la structure microscopique des ligaments posterieurs du rachis lombaire. Int Orthopaed. 1989;13(3):207-216.
52. Yahia LH, Garzon S, Strykowski H, Rivard CH. Ultrastructure of the human interspinous ligament and ligamentum flavum. A preliminary study. Spine. 1990;15(4):262.
53. Bartynski WS, Grahovac SZ, Rothfus WE. Incorrect needle position during lumbar epidural steroid administration: inaccuracy of loss of air pressure resistance and requirement of fluoroscopy and epidurography during needle insertion. Am J Neuroradiol. 2005;26(3):502-505.
54. Loubert C, Fernando R. Cesarean delivery in the obese parturient: anesthetic considerations. Womens Health. 2011;7(2):163-179.
55. Hameed F, Hunter DJ, Rainville J, Li L, Suri P. Prevalence of anatomic impediments to interlaminar lumbar epidural steroid injection. Arch Phys Med Rehabil. 2012;93(2):339-343.
56. Cowin G. Epidural trajectory MRI. Centre for Advanced Imaging: National Imaging Facility, Centre for Advanced Imaging, University of Queensland. Personal communication. 7 August 2017.
57. Corning J. Spinal anaesthesia and local medications of the cord. New York J Med. 1885;42:483-485.
58. Sicard J, Forestier J. Radiographic method for exploration of the extradural space using lipiodol. Rev Neurol. 1921;(28):1264-1266.
59. Belavy D, Ruitenberg MJ, Brijball RB. Feasibility study of real-time three-/four-dimensional ultrasound for epidural catheter insertion. Br J Anaesth. 2011;107(3):438-445.
60. Chiang HK, Zhou Q, Mandell MS, Tsou MY, Lin SP, Shung KK, et al. Eyes in the needle: novel epidural needle with embedded high-frequency ultrasound transducer--epidural access in porcine model. Anesthesiology. 2011;114(6):1320-1324.
61. Elsharkawy H, Sonny A, Chin KJ. Localization of epidural space: a review of available technologies. J Anaesthesiol Clin Pharmacol. 2017;33(1):16-27.

Abdominal wall blocks – steps to quality assurance and managing risk

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INTRODUCTION

Training in the use of "point of care" ultrasound forms a vital component of any modern critical care education program. The teaching, assessment and quality assurance issues relating to ultrasound-based techniques forms a large and growing body of literature. Critical care ultrasonography facilitates a wide range of potential applications; from trauma and rapid haemodynamic state assessment, regional anaesthesia and vascular access, basic transthoracic echocardiography, and more recently, lung, gastric and airway ultrasound. Published data suggest that point of care ultrasound can improve outcomes in regional anaesthesia[1-3], including reducing the risk of local anaesthetic systemic toxicity (LAST)[4], improve safety of vascular access[5] and guide clinical decision making[6,7]. This article will consider the issues of developing skills in the practice of ultrasound in regional anaesthesia, using ultrasound-guided abdominal wall blocks as an exemplar of a novel invasive procedure.

Education in basic ultrasound imaging skills must include aspects of probe selection, patient positioning, "knobology", image acquisition and optimisation. In addition to this knowledge, invasive techniques (particularly vascular access and regional anaesthesia) require the development of additional technical skills in needle/probe coordination. This facilitates the safe and accurate positioning of needle tips, either within (in the case of vascular structures) or adjacent to (in the case of nerves) target structures. Education programs must include theoretical and practical "hands on" components, where trainees have the opportunity to practice image acquisition skills (for example with volunteers) and then the capacity to practice invasive techniques using simulators gel models ("phantoms") or cadaveric or animal specimens[8].

The development of education programs for critical care ultrasound also requires a framework for assessment and evaluation of these skills. Experts in adult education have assisted anaesthetists to learn more about learning styles and skill acquisition in adults. One well-known set of stages were described by Dreyfus and consist of beginner, advanced novice, competent, proficient and expert levels[9]. The Accreditation Council for Graduate Medical Education (ACGME) has adapted these stages to suggest corresponding levels of required supervision when practising procedures: direct supervision, indirect supervision, conditional independence, and independence. These are analogous to the Australian and New Zealand College of Anaesthetists (ANZCA) supervision levels 1-4.

The most common statistical tool for assessing skill acquisition in novice proceduralists is cusum analysis[10]. This technique consists of observing an individual performing repeated attempts of a specific skill and rating each attempt as a "pass" or "fail". The analysis observes the trend of failures versus successes over time and generates a curve predicting the number of attempts required to attain "competence". Many authors have published studies using cusum analysis to assess competence of novice anaesthetists in performing basic invasive procedures[11,12] including peripheral nerve blocks[13], labour epidurals[14], ultrasound assessment of the lumbar spine[15] and gastric ultrasound[16,17]. It appears that 25-30 attempts are typically required to obtain competence in most procedures, although it is important to remember that this varies greatly and that training must be individualised. There is some evidence to suggest that individuals have differing visuospatial capacities and that these differences can predict novices who will perform well (or poorly) during ultrasound training tasks[18,19].

Barrington and colleagues observed novices performing sciatic nerve blocks on a cadaveric model and proposed a number of critical Quality Compromising Behaviours as criteria for assessment of competence[20]. These criteria included: 1, the ability to visualise needle while advancing; 2, ability to visualise target structures; 3, poor probe handling (unintentional or ineffective scanning); 4, operator fatigue; 5, failure to correlate sidedness of image and probe; 6, inappropriate needle insertion site; and 7, failure to recognise intramuscular or maldistribution of injectate. There is evidence to suggest that standardised assessment tools such as the ANZCA Direct Observation of Procedural Skills (DOPS) are reasonably reliable in rating novice performance in ultrasound guided regional anaesthesia[21].

QUALITY ASSURANCE

Any new skill introduction program, such as the evolution of the use of ultrasound in anaesthesia over the past two decades or so, should include establishment of a multi-level quality assurance (QA) process. At an individual level, case logbooks and audit of outcomes should be undertaken on a regular basis. The majority of ultrasound machines are capable of easily recording and storing still images or short video clips and this greatly facilitates expert review of procedures. At a department level, review of such images could form the basis of a regular department meeting. Acute pain services are also well positioned to undertake clinical audit of outcomes and complications of regional anaesthesia within departments of anaesthesia. However, QA activities at an individual or department level are unlikely to provide sufficient case numbers to accurately delineate the incidence of very rare outcomes (such as epidural abscess or haematoma). This is where national or international registers of regional anaesthesia cases are uniquely positioned[22,23]. By collecting data relating to a very large number of cases, a baseline level of safety can be assured, and additionally a denominator can be provided for risk calculations when rare events do occur. This provides invaluable data compared with publication of individual case reports.

ABDOMINAL WALL BLOCKS

Abdominal wall blocks represent an appealing starting point for the student of ultrasound guided regional anaesthesia. The past decade of anaesthesia practice has seen a move away from epidural analgesia and anaesthesia and towards more peripheral techniques including nerve blocks and catheters. This has been driven in part by increased use of low molecular weight heparin and concern regarding the risk of neuraxial haematoma, and in part a drive towards early mobilisation and enhanced recovery programs after major surgery. It is possible that the outcome of the MASTER trial, failing to demonstrate a survival benefit of epidural analgesia after major surgery, also contributed[24].

The search for alternative nerve blocks to epidurals in the setting of open abdominal surgery has led to the description of a multitude of approaches to the nerves of the abdominal wall. A “fascial pop” technique was described using short bevel needles for ilioinguinal/iliohypogastric nerve blocks, periumbilical rectus sheath blocks and transversus abdominus plane (TAP) blocks[25,26]. This has now been essentially replaced by direct ultrasound imaging of local anaesthetic spread within myofascial planes. The evolution of ultrasound has allowed the description of many different blocks across the abdominal wall including rectus sheath blocks and numerous approaches to the transversus abdominis plane (variously described as anterior, posterior, sub-costal and sub-costal oblique). More recently, even further posterior approaches have been described, including the quadratus lumborum block and the transversalis fascia plane block[27].

When considering any regional anaesthetic technique, both efficacy and safety rely on a detailed knowledge of the underlying anatomy (and sonoanatomy), both the neuroanatomy of the target nerves, and the underlying and surrounding structures at risk of inadvertent trauma. Also, the potential for local anaesthetic injectate to spread beyond the target site and to affect distant unintended nerves should be considered. In addition to this, an awareness of systemic toxicity and the potential for plasma uptake of local anaesthetic relative to the technique in question needs to be appreciated. All these issues are relevant to the practice of abdominal wall nerve blocks. Unlike many regional anaesthetic techniques, when performing abdominal wall blocks, generally no attempt is made to actually visualise individual nerves. Instead, abdominal wall blocks are “field” blocks, where large volumes of local anaesthetic are injected into tissue planes allowing distant spread to block small nerves or plexuses. Abdominal wall blocks specifically often require a long needle traversing a long subcutaneous passage. As with all regional anaesthesia techniques, it is critical that the tip of the needle can be visualised at all times.

Risks and complications

While the various abdominal wall blocks are appealing options as a low-risk alternative to neuraxial anaesthesia, it is still important to be familiar with the potential risks and complications of these blocks. These can be simply categorised as: 1, trauma to structures within the abdominal wall; 2, trauma to nearby structures (especially within the peritoneum); 3, inadvertent spread of local anaesthetic injectate to more distant sites; and 4, systemic local anaesthetic toxicity. These will each be considered in further detail.

Trauma to structures within the abdominal wall

The most obvious potential complications related to abdominal wall blocks are bruising and infection. However, there are still no reports in the literature of major abdominal wall haematoma or abscess. This is despite the fact that abdominal wall blocks are often used as an alternative to epidural analgesia in patients with coagulopathy. It is possible however, that minor (or even major) haematomas or abscesses have occurred and not been reported in the literature.

Three main arteries supply the abdominal wall: the superior and inferior epigastric arteries and the deep circumflex iliac artery. These arteries may potentially be visualised using ultrasound (particularly using colour Doppler) and avoided. The superior epigastric artery is particularly vulnerable in an upper subcostal TAP or rectus sheath block, where it emerges from the costal margin. This vessel usually has a short course running deep to the rectus muscle before penetrating into the muscle substance. In addition, the deep circumflex iliac artery turns from its lateral course on the iliacus fascia to pass into the TAP and run superiorly near the anterior superior iliac spine (ASIS). It is vulnerable to a block targeting the ilio-inguinal nerve in this area. Again, it may be possible to image this vessel with ultrasound.

Neuropraxia related to abdominal wall blocks has also not been described. This may be because the abdominal wall nerves are small, robust and mobile and therefore they are likely to slide past rather than be cut by a block needle. This may be assisted by the use of block needles which are “short bevel” in shape and relatively blunt. The clinical presentation of an isolated nerve injury in the abdominal wall is unlikely to result in significant symptoms and hence is unlikely to be reported. Transient relaxation of abdominal structures has been described when motor block is present as evident by bulging of the abdominal wall[28,29]. This effect has not been reported to cause clinical issues.

Trauma to intra-abdominal structures

As with any regional anaesthetic block, there is the risk of trauma to nearby structures. In the setting of abdominal wall blocks, especially in thin patients, this includes the risk of trauma to structures within the peritoneum. Reported cases have included trauma to the liver[30-33] and bowel wall haematomas[34]. Colonic perforation has been described following ilioinguinal block in children[35,36]. Performing nerve blocks of abdominal wall without ultrasound has been shown to frequently lead to inadvertent intra-peritoneal needle tip placement[37,38]. Ultrasound does not completely eliminate this risk as needle imaging and identification may be poor and may also be associated with difficulty precisely identifying the layers of the abdominal wall. The presence of air or surgical gas in the abdominal wall (such as following laparoscopic surgery) may increase this difficulty. There may be greater risk in the morbidly obese where imaging is more difficult, and also in paediatric patients, where the transversus muscle may only be a few millimetres in thickness. As with any regional anaesthetic technique, if identification of the anatomy is uncertain and/or precise needle tip location is undetermined, the needle should not be advanced further.

Retroperitoneal injection in the inguinal area has been reported and has been associated with retroperitoneal haematoma from deep circumflex iliac artery damage[14,15, 39, 40]. The iliaca fascia is related immediately deep to the transversus abdominis muscle in the area near the ASIS.

Spread of local anaesthetic beyond the abdominal wall

Transient femoral nerve block has been reported following abdominal wall nerve blocks including TAP block and ilio-inguinal block[41-44]. This potential must be considered in any block around the ASIS. However, it has not been reported after ultrasound guided TAP or ilio-inguinal block. Femoral block has also been described after posterior TAP injection in the area of the triangle of Petit without ultrasound guidance[19]. It has been speculated that spread of injectate may occur from deep to transversus abdominis into the iliac fossa deep to the fascia iliaca where the femoral nerve is located. Another possible route from injection in this region would be if there was direct injection into the psoas muscle as this could spread to the psoas compartment and femoral nerve. While uncommon, the potential for inadvertent femoral nerve block remains an important consideration when performing nerve blocks of the abdominal wall, especially in ambulatory or day surgery. Patients (and medical/nursing staff) are unlikely to anticipate leg weakness as a consequence of abdominal surgery, and this may increase the risk of post-operative falls.

Systemic absorption/toxicity

Abdominal wall blocks are field blocks which involve administration of large doses of local anaesthetic diluted into relatively large volumes. Efficacy relies on an adequate volume of injectate to allow spread within the anatomical plane to bathe the required nerves. There is limited published data on the relative importance of dose, volume and concentration of local anaesthetic in the injectate. Cadaveric studies have been conducted to correlate the spread of injectate within the TAP with the dermatomal anaesthesia achieved[45-47]. There is a paucity of dose finding studies in the literature however Beloeil and colleagues demonstrated that large doses of local anaesthetic were required to achieve ED50[48].

Published evidence suggests that local anaesthetic absorption from the transversus abdominis plane is intermediate, similar to other regional techniques such as the axillary plexus block, with peak levels typically achieved in approximately 30 minutes and remaining elevated for up to 90 minutes[49-52]. If the block is administered following wound closure, it is important to recognise that peak plasma concentrations of local anaesthetic are likely to occur in the recovery room when medical staff are potentially absent.

Plasma concentrations of local anaesthetic have been studied following TAP block in several settings including following gynaecological laparotomy and Caesarean section. Peak levels approach those on the threshold of low-level neurological toxicity as described by Knudsen and colleagues[53]. Several case reports have described symptomatic local anaesthetic toxicity following TAP blocks[50]. Episodes of seizures have been described, mainly involving large doses of local anaesthetic although one case of post Caesarean section seizures involved only 2.7 mg/kg ropivacaine[54-56].

There is some evidence to suggest that the addition of adrenaline (epinephrine) may reduce the systemic absorption of levobupivacaine. This has not been studied in other local anaesthetics, but would seem to offer potential, and also could serve as a marker of intravascular injection.

SPECIAL CASES

Morbid obesity

Abdominal wall blocks are significantly more difficult to perform in the setting of morbid obesity. Ultrasound guidance is difficult due to the increased depth of imaging required, and the narrow imaging window with linear ultrasound probes. Broadly curved lower frequency probes may be helpful to improve the field of imaging, but may make imaging the needle more difficult. It may be necessary to displace truncal adiposity with firm pressure from the ultrasound probe in an attempt to improve image quality. This approach however has several problems. Firstly, it may be uncomfortable to perform in an awake patient. Secondly, it is difficult to accurately image the needle through its entire passage as the needle is long (typically 100-150 mm) and may bend within the tissues. An additional problem when performing these blocks is operator fatigue. Strength and endurance is required in the arm holding the ultrasound probe. Image quality tends to deteriorate as the operator gets tired, an issue which seems prominent in trainees (who generally take longer to perform the block). Helpful strategies may include having an assistant support the abdominal wall and optimising conditions such as the operating table or bed height and having the patient close to the operator. Posterior blocks such as the quadratus lumborum or transversalis fascial plane blocks can be performed in the lateral position and may be an attractive option in obese patients.

Paediatrics

There is a significant body of evidence supporting the use of abdominal wall blocks in children[57]. However, studies also demonstrate that the deposition of the injectate in paediatric population is frequently inaccurate. Higher frequency smaller footprint probes may be required and careful attention paid to dose limits.

Pregnancy

There are many publications involving the use of TAP blocks to provide analgesia following Caesarean section. The blocks are generally performed following wound closure and therefore the patient still has many of the physiological changes of pregnancy even though they are technically no longer pregnant. There are a number of these changes which may be relevant to performing TAP blocks. Dilatation (and potentially varicosities) of the abdominal wall veins may increase the risk of abdominal wall haematoma. Plasma local anaesthetic concentrations may be increased due to the decrease in plasma binding proteins and the increase in cardiac output and tissue blood flow[50].

Coagulopathy

Truncal nerve blocks present an attractive alternative for providing analgesia in patients where neuraxial anaesthesia is contraindicated. This would include patients with coagulopathy, hepatic and renal disease and systemic sepsis. Patients with coagulopathy must be at increased risk of significant abdominal wall bleeding and haematoma. Also, patients with intra-abdominal sepsis undergoing laparotomy could theoretically be at risk of providing a locus of infection in the abdominal wall. Impaired clotting and sepsis should not be considered absolute contra-indications for abdominal wall blockade or catheters. These cases should be assessed on an individual basis.

CONCLUSION

The use of “point of care” ultrasound in critical care has expanded rapidly in recent years. Published data support the utility of ultrasound in vascular access, regional anaesthesia and haemodynamic assessment. However, data evaluating teaching methods, skill acquisition, and quality assurance are still emerging.

Adequate training, assessment and supervision is needed to facilitate safe performance of all invasive techniques, including those using ultrasound.

Quality assurance programs should be considered at individual, department and national/international levels.

Safe performance of any regional anaesthetic technique requires detailed knowledge of the relevant anatomy (and corresponding sonoanatomy), including both anatomy of target nerves and also the surrounding structures at risk of inadvertent trauma.

Abdominal wall blocks have an excellent risk profile, but have a number of potential complications. These include trauma within the abdominal wall, trauma in the peritoneal cavity, spread of local anaesthetic to more distant structures and systemic local anaesthetic toxicity.

REFERENCES

1. Lewis SR, Price A, Walker KJ, McGrattan K, Smith AF. Ultrasound guidance for upper and lower limb blocks. Cochrane Database Syst Rev. 2015;11(9):CD006459.
2. Marhofer P, Fritsch G. Safe performance of peripheral regional anaesthesia: the significance of ultrasound guidance. Anaesthesia. 2017;72(4):431-434.
3. Munirama S, McLeod G. A systematic review and meta-analysis of ultrasound versus electrical stimulation for peripheral nerve location and blockade. Anaesthesia. 2015;70(9):1084-1091.
4. Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Reg Anesth Pain Med. 2013;38(4):289-299.

5. Bodenham Chair A, Babu S, Bennett J, Binks R, Fee P, Fox B, et al. Association of Anaesthetists of Great Britain and Ireland: safe vascular access 2016. Anaesthesia. 2016;71(5):573-585.
6. Ford JW, Heiberg J, Brennan AP, Royse CF, Canty DJ, El-Ansary D, et al. A pilot assessment of 3 point-of-care strategies for diagnosis of perioperative lung pathology. Anesth Analg. 2017;124(3):734-742.
7. Heiberg J, El-Ansary D, Canty DJ, Royse AG, Royse CF. Focused echocardiography: a systematic review of diagnostic and clinical decision-making in anaesthesia and critical care. Anaesthesia. 2016;71(9): 1091-1100.
8. Corvetto MA, Pedemonte JC, Varas D, Fuentes C, Altermatt FR. Simulation-based training program with deliberate practice for ultrasound-guided jugular central venous catheter placement. Acta Anaesthesiol Scand. 2017;Jul 06.
9. Dreyfus SE. The five stage model of adult skill acquisition. Bull Science Technol Society. 2004;24(3):177-181.
10. Kestin IG. A statistical approach to measuring the competence of anaesthetic trainees at practical procedures. Br J Anaesth. 1995;75(6):805-809.
11. de Oliveira Filho GR. The construction of learning curves for basic skills in anesthetic procedures: an application for the cumulative sum method. Anesth Analg. 2002;95(2):411-416.
12. Starkie T, Drake EJ. Assessment of procedural skills training and performance in anesthesia using cumulative sum analysis (cusum). Can J Anaesth. 2013;60(12):1228-1239.
13. Nix CM, Margarido CB, Awad IT, Avila A, Cheung JJ, Dubrowski A, et al. A scoping review of the evidence for teaching ultrasound-guided regional anesthesia. Reg Anesth Pain Med. 2013;38(6):471-480.
14. Naik VN, Devito I, Halpern SH. Cusum analysis is a useful tool to assess resident proficiency at insertion of labour epidurals. Can J Anaesth. 2003;50(7):694-698.
15. Margarido CB, Arzola C, Balki M, Carvalho JC. Anesthesiologists’ learning curves for ultrasound assessment of the lumbar spine. Can J Anaesth. 2010;57(2):120-126.
16. Arzola C, Carvalho JC, Cubillos J, Ye XY, Perlas A. Anesthesiologists’ learning curves for bedside qualitative ultrasound assessment of gastric content: a cohort study. Can J Anaesth. 2013;60(8):771-779.
17. Perlas A, Van de Putte P, Van Houwe P, Chan VW. I-AIM framework for point-of-care gastric ultrasound. Br J Anaesth. 2016;116(1):7-11.
18. Duce NA, Gillett L, Descallar J, Tran MT, Siu SC, Chuan A. Visuospatial ability and novice brachial plexus sonography performance. Acta Anaesthesiol Scand. 2016;60(8):1161-1169.
19. Shafqat A, Ferguson E, Thanawala V, Bedforth NM, Hardman JG, McCahon RA. Visuospatial ability as a predictor of novice performance in ultrasound-guided regional anesthesia. Anesthesiology. 2015;123(5):1188-1897.
20. Barrington MJ, Wong DM, Slater B, Ivanusic JJ, Ovens M. Ultrasound-guided regional anesthesia: how much practice do novices require before achieving competency in ultrasound needle visualization using a cadaver model. Reg Anesth Pain Med. 2012;37(3):334-339.
21. Chuan A, Thillainathan S, Graham PL, Jolly B, Wong DM, Smith N, et al. Reliability of the direct observation of procedural skills assessment tool for ultrasound-guided regional anaesthesia. Anaesth Intensive Care. 2016;44(2):201-209.
22. Barrington MJ, Thomas RD, Tay VS. The Australian and New Zealand Registry of Regional Anaesthesia (AURORA) - results from our most recent 10,000 patients: BAPCPC1-1. Eur J Anaesthesiol. 2011;28:1.
23. Barrington MJ, Watts SA, Gledhill SR, Thomas RD, Said SA, Snyder GL, et al. Preliminary results of the Australasian Regional Anaesthesia Collaboration: a prospective audit of more than 7000 peripheral nerve and plexus blocks for neurologic and other complications. Reg Anesth Pain Med. 2009;34(6):534-541.
24. Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet. 2002;359(9314):1276-1282.
25. McDonnell JG, Curley G, Carney J, Benton A, Costello J, Maharaj CH, et al. The analgesic efficacy of transversus abdominis plane block after cesarean delivery: a randomized controlled trial. Anesth Analg. 2008;106(1):186-191.
26. McDonnell JG, O’Donnell B, Curley G, Heffernan A, Power C, Laffey JG. The analgesic efficacy of transversus abdominis plane block after abdominal surgery: a prospective randomized controlled trial. Anesth Analg. 2007;104(1):193-197.
27. Chin KJ, McDonnell JG, Carvalho B, Sharkey A, Pawa A, Gadsden J. Essentials of our current understanding: abdominal wall blocks. Reg Anesth Pain Med. 2017;42(2):133-183.
28. Bortolato A, Ori C, Freo U. Transient abdominal motor block after a transversus abdominis plane block in an elderly patient. Can J Anaesth. 2015;62(7):837-838.
29. Grady MV, Cummings KC, 3rd. The “flank bulge” sign of a successful transversus abdominis plane block. Reg Anesth Pain Med. 2008;33(4):387.
30. Lancaster P, Chadwick M. Liver trauma secondary to ultrasound-guided transversus abdominis plane block. Br J Anaesth. 2010;104(4):509-510.
31. Jankovic Z, Ahmad N, Ravishankar N, Archer F. Transversus abdominis plane block: how safe is it? Anesth Analg. 2008;107(5):1758-1759.
32. Farooq M, Carey M. A case of liver trauma with a blunt regional anesthesia needle while performing transversus abdominis plane block. Reg Anesth Pain Med. 2008;33(3):274-275.
33. O’Donnell BD, Mannion S. A case of liver trauma with a blunt regional anesthesia needle while performing transversus abdominis plane block. Reg Anesth Pain Med. 2009;34(1):75-76.
34. Frigon C, Mai R, Valois-Gomez T, Desparmet J. Bowel hematoma following an iliohypogastric-ilioinguinal nerve block. Paediatr Anaesth. 2006;16(9):993-996.
35. Amory C, Mariscal A, Guyot E, Chauvet P, Leon A, Poli-Merol ML. Is ilioinguinal/iliohypogastric nerve block always totally safe in children? Paediatr Anaesth. 2003;13(2):164-166.
36. Johr M, Sossai R. Colonic puncture during ilioinguinal nerve block in a child. Anesth Analg. 1999;88(5): 1051-1052.

37. McDermott G, Korba E, Mata U, Jaigirdar M, Narayanan N, Boylan J, et al. Should we stop doing blind transversus abdominis plane blocks? Br J Anaesth. 2012;108(3):499-502.
38. Weintraud M, Marhofer P, Bosenberg A, Kapral S, Willschke H, Felfernig M, et al. Ilioinguinal/iliohypogastric blocks in children: where do we administer the local anesthetic without direct visualization? Anesth Analg. 2008;106(1):89-93.
39. Parvaiz MA, Korwar V, McArthur D, Claxton A, Dyer J, Isgar B. Large retroperitoneal haematoma: an unexpected complication of ilioinguinal nerve block for inguinal hernia repair. Anaesthesia. 2012;67(1):80-81.
40. Vaisman J. Pelvic hematoma after an ilioinguinal nerve block for orchialgia. Anesth Analg. 2001;92(4): 1048-1049.
41. Walker G. Transversus abdominis plane block: a note of caution! Br J Anaesth. 2010;104(2):265.
42. Rosario DJ, Jacob S, Luntley J, Skinner PP, Raftery AT. Mechanism of femoral nerve palsy complicating percutaneous ilioinguinal field block. Br J Anaesth. 1997;78(3):314-316.
43. Rosario DJ, Skinner PP, Raftery AT. Transient femoral nerve palsy complicating preoperative ilioinguinal nerve blockade for inguinal herniorrhaphy. Br J Surg. 1994;81(6):897.
44. Manatakis DK, Stamos N, Agalianos C, Karvelis MA, Gkiaourakis M, Davides D. Transient femoral nerve palsy complicating “blind” transversus abdominis plane block. Case Rep Anesthesiol. 2013;2013:874215.
45. Barrington MJ, Ivanusic JJ, Rozen WM, Hebbard P. Spread of injectate after ultrasound-guided subcostal transversus abdominis plane block: a cadaveric study. Anaesthesia. 2009;64(7):745-750.
46. Jankovic ZB, du Feu FM, McConnell P. An anatomical study of the transversus abdominis plane block: location of the lumbar triangle of Petit and adjacent nerves. Anesth Analg. 2009;109(3):981-985.
47. McDonnell JG, O’Donnell BD, Farrell T, Gough N, Tuite D, Power C, et al. Transversus abdominis plane block: a cadaveric and radiological evaluation. Reg Anesth Pain Med. 2007;32(5):399-404.
48. Lahlou-Casulli M, Chaize-Avril C, Pouliquen E, Desfourneaux V, Mazoit JX, Malledant Y, et al. The median effective analgesic dose (ED50) of ropivacaine in ultrasound-guided transversus abdominis plane block for analgesia in reversal of ileostomy: A double-blind up-down dose-finding study. Eur J Anaesthesiol. 2014;32(9):640-644.
49. Griffiths JD, Barron FA, Grant S, Bjorksten AR, Hebbard P, Royse CF. Plasma ropivacaine concentrations after ultrasound-guided transversus abdominis plane block. Br J Anaesth. 2010;105(6):853-856.
50. Griffiths JD, Le NV, Grant S, Bjorksten A, Hebbard P, Royse C. Symptomatic local anaesthetic toxicity and plasma ropivacaine concentrations after transversus abdominis plane block for Caesarean section. Br J Anaesth. 2013;110(6):996-1000.
51. Kato N, Fujiwara Y, Harato M, Kurokawa S, Shibata Y, Harada J, et al. Serum concentration of lidocaine after transversus abdominis plane block. J Anesth. 2009;23(2):298-300.
52. Weiss E, Jolly C, Dumoulin JL, Meftah RB, Blanie P, Laloe PA, et al. Convulsions in 2 patients after bilateral ultrasound-guided transversus abdominis plane blocks for cesarean analgesia. Reg Anesth Pain Med. 2014;39(3):248-251.
53. Knudsen K, Beckman Suurkula M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth. 1997;78(5): 507-514.
54. Kato N, Fujiwara Y, Harato M, Kurokawa S, Shibata Y, Harada J, et al. Serum concentration of lidocaine after transversus abdominis plane block. J Anesth. 2009;23(2):298-300.
55. Landy C, Gagnon N, Boulland P, Raynaud L, Plancade D. Seizures associated with local anaesthetic intoxication. Br J Anaesth. 2012;109(3):463-464.
56. Sakai T, Manabe W, Kamitani T, Takeyama E, Nakano S. Ropivacaine-induced late-onset systemic toxicity after transversus abdominis plane block under general anesthesia: successful reversal with 20% lipid emulsion. Masui. 2010;59(12):1502-1505.
57. Long JB, Birmingham PK, De Oliveira GS, Jr., Schaldenbrand KM, Suresh S. Transversus abdominis plane block in children: a multicenter safety analysis of 1994 cases from the PRAN (Pediatric Regional Anesthesia Network) database. Anesth Analg. 2014;119(2):395-399.

Pain

Recent insights into the mechanism of opioid tolerance and withdrawal: Implications for the use of remifentanil

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INTRODUCTION

The mechanism for the development of opioid tolerance, withdrawal and hyperalgesia has never been adequately explained solely by changes in the classical opioid receptors themselves. Recent work has shown that opioids act on another set of receptors, the non-stereo-selective toll-like receptors, which reside on macrophages and, in the central nervous system, their derivatives, the microglia. Their activation by opioids and some of their metabolites is largely responsible for opioid tolerance, withdrawal and hyperalgesia. This has particular implications for the use of large doses of remifentanil, especially in opioid tolerant patients, and in patients who consume large doses of codeine.

OPIOID TOLERANCE, WITHDRAWAL AND HYPERALGESIA

Ever since their clinical use to treat pain, it has been known that the continuing use of opioids induces tolerance to their analgesic effects, and if abruptly ceased, the development of a withdrawal state, marked by a constellation of "flu like" symptoms: sweats; muscle and joint aches and pains; tremors; lacrimation; rhinorrhoea and pilo-erection ("goose flesh"). This condition may also include: agitation; anxiety and insomnia; yawning; abdominal cramps; nausea and diarrhoea. The withdrawal muscle and joint aches and pains are evidence of hyperalgesia, even allodynia, and can be severe, as almost any search on the internet of descriptions of what heroin withdrawal feels like will confirm. Opioid withdrawal hyperalgesia has even been measured after acute opioid doses in non-addicted humans[1]. The opioid withdrawal hyperalgesia can even temporarily reignite pain in an old, but recovered site of previous injury[2]. Thus pain is a prominent feature of opioid withdrawal. More recently it has been recognised that chronic doses of opioids may even exacerbate pain even while the opioids are continued, i.e. opioid induced hyperalgesia (OIH)[3], although clinical testing for this is difficult[4]. Recent discoveries as detailed below reveal a common mechanism to explain the closely related phenomena of OIH, opioid tolerance and opioid withdrawal hyperalgesia.

DIFFERENCE BETWEEN OPIOID STEREO-ISOMERS

Until recently the mechanism for opioid tolerance, hyperalgesia and opioid withdrawal has remained a phenomenon widely observed but unable to be adequately explained by changes in the expression of classically identified opioid receptors themselves. In 1960, long before classical opioid receptors were discovered, when investigating the antitussive effects of the different optical isomers of morphine, Takagi et al observed that (+) morphine is almost devoid of analgesic activity compared to (-) morphine. He also noted that a larger dose of (+) morphine given in combination with (-) morphine will antagonise the analgesic effects of (-) morphine: i.e. the (+) morphine will induce naive tolerance and antanalgesia[5]. It was also noted there was no stereo-selectiveness to the antitussive effects. These results suggested that opioid agonists do not only act at the now identified stereo-selective opioid receptors, which only respond to the (-)-opioid isomer, to cause analgesia, but also at another set of receptors responsible for the tolerance and antanalgesia/hyperalgesia. Since 2009, M Hutchinson and colleagues, by an accumulation of theoretical computerised molecular simulation ("in silico"), "in vitro" and "in vivo" experimentation have demonstrated that opioids act in a non stereo-selective manner at the toll-like receptors (TLRs) residing on microglial cells in the central nervous system (CNS)[6].

TOLL-LIKE RECEPTORS ON MICROGLIA

The TLRs, discovered in the 1990s, are an evolutionarily conserved class of "pattern recognition receptors" which reside on innate immune cells such as macrophages and dendritic cells, but also cells of adaptive immunity and non-immune cells[7]. The TLRs play a key role in innate immunity, responding to a wide variety of molecules derived from bacteria and other pathogens, or as a result of cell damage, referred to as pathogen-associated molecular patterns (PAMPs). There are about a dozen subtypes of TLR. The principle agonist for TLR4 is a lipopolysaccharide (LPS), endotoxin, from gram negative bacterial membranes, which induces an inflammatory response in macrophages. Microglial cells, which share embryological origins with macrophages, are normal residents in the CNS, and the activation of TLR4 receptors on them leads to induction of gene expression and production of many mediators of acute inflammation. These then act on neighbouring astrocytes,

disrupting the normal regulation of glutamate transporters and synthesis, and alter the expression of other mediators which impact on the functioning of neurons[8]. Hutchinson and colleagues have shown that both the (+) and (-) isomers of many opioids, and some of their metabolites, can act as agonists at TLR4, which induces the changes ultimately resulting in opioid tolerance, hyperalgesia, and if opioids are suddenly ceased, opioid withdrawal. (That endotoxin, from infection, and opioids are both acting on this same receptor may also explain much of the commonality of the opioid withdrawal state and "flu like" symptoms.) The biochemical changes associated with TLR4 activation specifically affecting the action of opioids on neurons are shown in the accompanying diagram (figure 1) from Grace et al[9]. (The article by Grace et al[9] succinctly concentrates more on the TLR4 induced effects which antagonise opioid analgesia, whereas the article by Hutchinson, et al[8] is a much more comprehensive review on the neuroimmunopharmacology of opioids, both well worth reading.) Synaptically released glutamate is removed from the region of the excitatory synapses not by enzymatic destruction but by uptake by the astrocytic glutamate transporter GLT-1. Although downregulation of this transporter is only one component of the antanalgesic effect of TLR4 activation, it is consistent with ketamine, even in low doses, occasionally being observed to be very effective in treating pain in opioid tolerant patients[10]. Ketamine pharmacology is complex, acting on many receptors, but one of its principle actions is as a non-competitive antagonist at the N-methyl-D-aspartate glutamate receptor[11]. This action would act to counterbalance the effect of increased synaptic glutamate as a result of transporter downregulation.

Figure 1. Central immune mechanisms of opioid tolerance and opioid-induced hyperalgesia

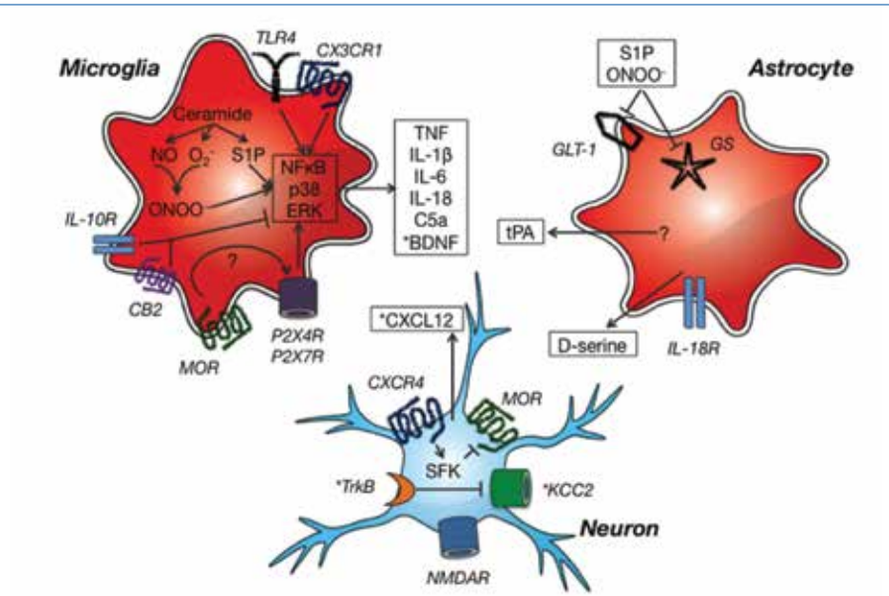

Figure.—Central immune mechanisms of opioid tolerance and opioid-induced hyperalgesia. Activation of Toll-like receptor 4 (TLR4) signaling, production of sphingosine-1 phosphate (S1P), and peroxynitrite ($ONOO^-$; formed by the interaction of superoxide [O_2^-] and nitric oxide [NO]) downstream of ceramide, as well as the purinergic receptors P2X4R and P2X7R have been shown to induce production of pro-inflammatory mediators such as tumor necrosis factor (TNF), interleukin-1β (IL-1β), IL-6, IL-18, complement factor c5a, CX3CL1 (also known as fractalkine), and tissue plasminogen activator (tpa) in microglia, astrocytes, and neurons. These immune mediators are also pro-nociceptive, and hence act as an opponent process of neuronally mediated opioid analgesia. Production is largely mediated by NFκB activation, and phosphorylation of the mitogen-activated protein kinases p38 and extracellular regulated kinase (ERK). Anti-inflammatory signaling via the cannabinoid 2 (CB2) and IL-10 (IL-10R) receptors oppose opioid tolerance by inhibiting pro-inflammatory mediator production. In addition, S1P and $ONOO^-$ dysregulate glutamate homeostasis by downregulating expression of both the glutamate transporter GLT-1 and the processing enzyme glutamine synthase (GS) in astrocytes. Microglia-derived IL-18 signals at astrocyte IL-18 receptor (IL-18R), leading to D-serine release by astrocytes, which can facilitate N-methyl-D-aspartate (NMDA) receptor activation. The chemokine receptor CXCR4 can induce heterologous desensitization of μ-opioid receptors (MOR) in neurons, mediated at least in part via activation of Src family kinases (SFK). Neuronal CXCL12 signaling at neuronal CXCR4 also contributes to opioid induced hyperalgesia. μ-opioid receptor (MOR)-signaling increases P2X4R expression, triggering brain derived neurotrophic factor (BDNF) release from microglia. Neuronal TrkB receptor activation by BDNF downregulates the principal neuronal potassium-chloride cotransporter, KCC2, which increases the intracellular Cl^- concentration in lamina I neurons. This leads to disinhibition, where Cl^- is effluxed rather than influxed through $GABA_A$ and glycine channels, resulting in opioid-induced hyperalgesia. *Indicates mechanisms specific to opioid induced hyperalgesia.

Figure from Grace P. M. et al, Headache 55:475-489, 2015, reproduced with permission.

THE PROBLEM WITH REMIFENTANIL: ITS METABOLITE REMIFENTANIL ACID

Soon after remifentanil was released for clinical use, it was noted that patients who had received it intraoperatively often had worse pain postoperatively, and required higher doses of opioid than would otherwise have been expected i.e. they had rapidly developed opioid tolerance and OIH. This has been confirmed by wide ranging systematic reviews, which show that hyperalgesia and tolerance, if it is significant, tends to be worse when larger doses of remifentanil have been given[12,13]. Remifentanil is a highly lipid soluble, potent mu agonist opioid with a very short half-life of between 3-8 minutes that is independent of renal and liver function. It is broken down by non-specific esterases throughout the body and also undergoes spontaneous degradation by hydrolysis. Its principal metabolite is remifentanil acid which is almost devoid of mu agonist activity, with only a small fraction of the potency of remifentanil at the mu opioid receptor[14,15]. Remifentanil acid is cleared by the kidneys with an elimination half-life of 80-130 minutes. A prolonged steady state infusion of remifentanil will result in a ratio 1:12 of remifentanil:remifentanil acid. Because of its very short half-life and largely mu receptor inactive metabolite, it is very easy to give large doses of remifentanil intra-operatively to achieve haemodynamic stability, and even hypotension, and yet at the end of the case have the patient spontaneously breathing with rapid emergence from anaesthesia. The phenomena of acute opioid tolerance and OIH as a result of large doses is explained by the accumulated metabolite remifentanil acid being a potent agonist at TLR4, as suggested by its binding energies at the MD2 sub-component of TLR4[16]. As it takes much longer to clear than remifentanil, the patient is left in a state akin to opioid withdrawal, clinically manifested by hyperalgesia and tolerance to mu agonist. (Over the years there have been several cases in our institution of already opioid tolerant patients receiving large doses of remifentanil intraoperatively, with minimal other longer acting mu agonist being administered, and as a result suffering extremely severe pain and/or withdrawal symptoms postoperatively for up to 48 hours, inadequately relieved even by very large doses of fentanyl and ketamine.) Our advice is thus not to use remifentanil in opioid tolerant patients, and to minimise its use in cases where there would normally be moderate to severe pain post-operatively. In treating opioid tolerant patients, besides adequate doses of fentanyl (to prevent opioid withdrawal), a low dose ketamine infusion (4 to 8 mg/hr, which minimises the risk of distressing psychotomimetic or psychedelic phenomena) is more likely to contribute to analgesia, and can be continued into the post-operative period.

Why is this not such a problem with other mu agonists, nearly all of which will induce tolerance and hyperalgesia if given over sufficient time? Morphine-3-glucuronide (M3G), one of the major metabolites of morphine, has, like remifentanil acid, almost no mu agonist activity, but is a potent agonist at TLR4, explaining its long known neuroexcitatory and antanalgesic effects[6]. But the phenomenon of immediate post dose hyperalgesia and tolerance is not as evident with morphine compared to remifentanil. This is due to the longer clearance time for the parent morphine which provides continuing mu opioid agonist activity, as well as its other major metabolite, morphine-6-glucuronide (M6G), which is a potent mu agonist but devoid of activity at TLR4. These features serve to counterbalance the M3G effect. The very large discrepancy between the half-lives of remifentanil and accumulated remifentanil acid compared to that of morphine and its metabolites M3G and M6G, would also explain why the tolerance and hyperalgesia is acutely much worse with remifentanil.

WHY CODEINE IS PROBLEMATIC

Patients who consume moderate to large doses of codeine (such as in combination analgesics paracetamol/codeine phosphate 500 mg/30 mg) have often been problematic patients to treat for pain, including in the post-operative period. This has been difficult to understand, as codeine has only about one tenth the potency of morphine at the mu opioid receptor, and much of its analgesic effect is attributed to it being metabolised to morphine by CYP2D6. The answer may be in the binding energy studies which suggest that codeine is, molecule for molecule, as potent an agonist as morphine at TLR4, thus inducing opioid tolerance and hyperalgesia out of proportion to its mu agonist effects[17]. Medication overuse headache arising from over-consumption of codeine containing medicines is a manifestation of this[9]. On theoretical grounds it would be wise to avoid remifentanil in these patients, for even though their aggregate mu opioid agonist dose may be low, the accompanying neuroinflammatory effects induced by TLR4 activation causing clinically relevant hyperalgesia and opioid tolerance are already disproportionately high, and will be further exacerbated by the use of remifentanil.

CONCLUSION

Both opioids and certain of their metabolites induce opioid tolerance and hyperalgesia through activation of TLR4 on microglia which in the case of remifentanil may be severe. The longer-lasting metabolite remifentanil acid is a particular culprit in this instance due to its potent activation of TLR4 combined with its near-total lack of mu opioid receptor agonist activity. This not infrequently results in the clinical scenario of a patient having been given large doses of remifentanil during a given procedure subsequently experiencing worse pain, and pain that is relatively opioid resistant in the post-operative period.

Suggestions have been made whereby remifentanil is avoided in patients in whom there is an expectation of moderate to severe postoperative pain; in patients who are already opioid tolerant; and most particularly in patients with substantial preoperative codeine consumption (due to the disproportionate TLR4 activation by codeine compared to its mu opioid agonist effect). Alternative non-opioid analgesia regimes may include judicious doses of fentanyl to provide analgesia to prevent withdrawal.

REFERENCES

1. Compton P, Athanasos P, Elashoff D. Withdrawal hyperalgesia after acute opioid physical dependence in nonaddicted humans: a preliminary study. J Pain. 2003;4(9):511–519.
2. Rieb LM, Norman WV, Martin RE, Berkowitz J, Wood E, McNeil R, et al. Withdrawal-associated injury site pain (WISP): a descriptive case series of an opioid cessation phenomenon. Pain. 2016;157(12):2865–2874.
3. Mao J. Opioid-induced abnormal pain sensitivity. Curr Pain Headache Rep. 2006;10(1):67–70.
4. Mao J. Clinical diagnosis of opioid-induced hyperalgesia. Reg Anesth Pain Med. 2015;40(6):663–664.
5. Takagi K, Fukuda H, Watanabe M, Sato M. Studies on antitussives. III. Yakugaku Zasshi. 1960;80(11):1506–1509.
6. Hutchinson MR, Zhang Y, Shridhar M, Evans JH, Buchanan MM, Zhao TX, et al. Evidence that opioids may have toll-like receptor 4 and MD-2 effects. Brain Behav Immun. 2010;24(1):83–95.
7. Wikipedia. Toll-like receptor [Internet]. From: https://en.wikipedia.org/ w/index.php?title=Toll-like_receptor&oldid= 796726968. Accessed 3 September 2017.
8. Hutchinson MR, Shavit Y, Grace PM, Rice KC, Maier SF, Watkins LR. Exploring the neuroimmunopharmacology of opioids: an integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. Pharmacol Rev. 2011;63(3):772–810.
9. Grace PM, Maier SF, Watkins LR. Opioid-induced central immune signaling: implications for opioid analgesia. Headache. 2015;55(4):475–489.
10. Bell RF. Low-dose subcutaneous ketamine infusion and morphine tolerance. Pain. 1999;83(1):101–103.
11. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370– 380.
12. Kim SH, Stoicea N, Soghomonyan S, Bergese SD. Intraoperative use of remifentanil and opioid induced hyperalgesia/ acute opioid tolerance: systematic review. Front Pharmacol. 2014;5:108.
13. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth. 2014;112(6):991–1004.
14. Westmoreland CL, Hoke JF, Sebel PS, Hug CC Jr, Muir KT. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. Anesthesiology. 1993;79(5):893–903.
15. Glass PSA, Gan TJ, Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanil. Anesth Analg. 1999;89(4 Suppl):S7-14.
16. Hutchinson MR, Northcutt AL, Hiranita T, Wang X, Lewis SS, Thomas J, et al. Opioid activation of toll-like receptor 4 contributes to drug reinforcement. J Neurosci. 2012;32(33):11187-11200.
17. Johnson JL, Rolan PE, Johnson ME, Bobrovskaya L, Williams DB, Johnson K, et al. Codeine-induced hyperalgesia and allodynia: investigating the role of glial activation. Transl Psychiatry. 2014;4(11):e482.

Lidocaine infusions: The golden ticket in postoperative recovery?

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INTRODUCTION

The systemic administration of lidocaine (often known by its approved British name, lignocaine) by intravenous or subcutaneous infusion is a practice that is growing in popularity. To date, studies investigating the effects of lidocaine on the perioperative course provide some evidence that intraoperative lidocaine may be a useful adjunct to general anaesthesia. They are however, as yet, uncompelling. Systemic lidocaine is administered principally for the purpose of improved perioperative analgesia. There are other outcomes, however, which potentially may be influenced by systemic lidocaine administration; namely the risk of postoperative infection, malignancy recurrence, and the incidence of chronic post-surgical pain (CPSP). The mechanisms by which systemic lidocaine can impair pain pathways, alter inflammation and immune competence, are enlightening and will be covered in this review. A summary of the evidence investigating the clinical outcomes will also feature. A number of questions still exist surrounding the practicalities of lidocaine's intravenous use and these will be explored in addition to the potential avenues of research which are required to determine whether a lidocaine infusion is simply an intervention that benefits the occasional patient, or whether it provides advantages too great to ignore.

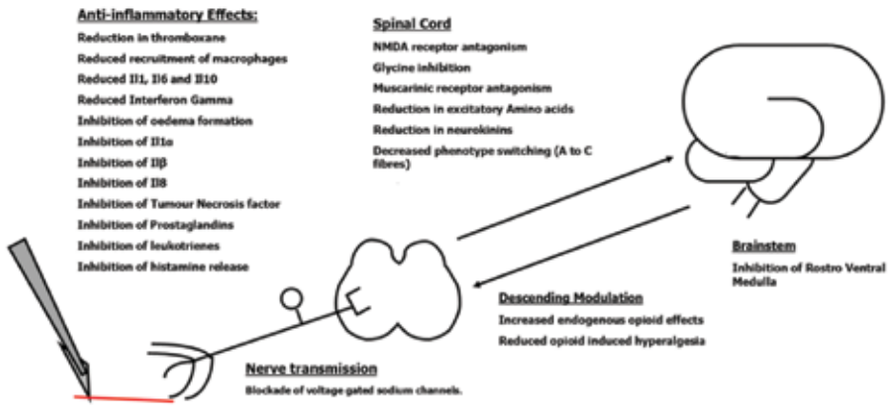
HISTORY

In the 1940s, a significant breakthrough occurred when Swedish pharmaceutical company Astra introduced a novel local anaesthetic agent. The enthusiasm for the drug, lidocaine, stemmed from the finding that it proved more effective with less undesirable effects than procaine and it lacked the toxic and addictive effects of its coca-based predecessors. It was more than 20 years later when Bartlett and Hutaserani took the novel step of introducing the drug systemically in an attempt to aid the relief of postoperative pain[1].

PHARMACOKINETICS OF LIDOCAINE

Lidocaine is a basic amide compound with a molecular weight of 234. It's pKa is 7.9, lower than other commonly used local anaesthetics, contributing to it having a greater unionised component and therefore more rapid transfer towards its intracellular site of action. On administration to the circulation, it initially is distributed to the highly vascularised tissues (including the brain and the heart where it exerts its toxic effects), before distributing to the higher capacity and less vascularised tissues shortly after. Its steady state volume of distribution is about 1L/kg and about 64 per cent is protein bound, largely to the high affinity, alpha-1 acid glycoprotein molecules. About 90 per cent is metabolised in the liver via the cytochrome P450 system, by oxidation to monoethylglycine xylidide and much of this is hydrolysed further to glycine xylidide. Both of these by-products are active and potentially contribute to toxicity, especially in those who have severely limited renal function and therefore an inability to clear them. The clearance of lidocaine in healthy adults is about 0.85 L/kg/hour and the terminal half-life is 1.5 to 2 hours although this is significantly shorter and therefore context-specific before the drug has fully redistributed[2-4]

Figure 1. Proposed mechanisms of action of systemic lidocaine



MECHANISMS OF ACTION: SODIUM CHANNELS AND BEYOND

Lidocaine has multiple systemic effects, most of which appear to be due to actions at specific receptor subtypes. Its analgesic effects can be explained by its effect on the following receptors and pathways[5,6] and are categorised into site of action in figure 1.

1. Voltage-gated sodium channels
2. Voltage-gated potassium channels
3. Voltage-gated calcium channels
4. NMDA receptor
5. Muscarinic receptors (M1 and M2)
6. G-protein coupled receptors
7. Reduced neurokinin activity
8. Reduced glycine activity
9. Reduced thromboxane

It also has systemic effects which appear to be independent of receptor specificity or which may be the manifestations of the cumulative effect of lidocaine at multiple receptors.

These are:

1. Anti-inflammatory effects
2. Antibacterial effects
3. Cytotoxic/anticancer effects
4. Antiarrhythmic effects (as a Ib agent)

Sodium channel blockade

The traditional explanation for lidocaine's analgesic effect is related to its ability to block voltage gated sodium channels, and hence, to interrupt action potential transmission in nociceptive neurones. These units structurally comprise a single alpha subunit forming an ion pore and varying auxiliary beta subunits. Local anaesthetics dose-dependently decrease peak sodium current by selectively binding intracellularly to and stabilising these alpha subunits in their inactivated state (inactivated block). They can also bind within the ion channel pore to prevent ion flux (open state block). Both of these actions rely on the channel being activated and therefore, with repeated depolarisation, there is an incremental decrease in Na+ current. This is termed a use-dependent or phasic inhibition[7]. Given that this is a dose dependent effect, and with intravenous administration the concentrations at the nociceptive neuronal membranes are likely to be extremely low in comparison, this theory cannot entirely explain systemic lidocaine's promising clinical effects. It also fails to explain the findings of a review by Barreveld et al, which concluded that lidocaine is a useful preventative analgesic agent. Ten of the 13 clinical trials studied demonstrated the effect of lidocaine lasting longer than eight and a half hours (which is five-and-a-half times the half-life of intravenous lidocaine)[8].

The voltage gated sodium channel has numerous subtypes which differ in the structure of their homologous alpha subunit. Of the subtypes NaV1.7, NaV1.8 and NaV1.9 are thought to be expressed exclusively in peripheral

neurons and play an essential part in nociceptive transmission[9]. Individuals with an overexpression of NaV1.7 are known to have a decreased sensitivity to local anaesthetics[10] and a strong predisposition to certain pain syndromes such as erythemalgia and paroxysmal extreme pain disorder[11]. In contrast, loss of function mutations of NaV1.7 (also referred to as SCN9A channelopathy) are reported in humans with an inability to experience pain[12]. Of particular interest, a recent study in both humans and mice with such loss of function mutations, showed that the administration of naloxone led to profound loss of congenital analgesia in these subjects. This suggests that the absence of NaV1.7 function led to alterations in gene expression resulting in endogenous opioids contributing to the congenital analgesia. This is supported by the findings that specific NaV1.7 channel blockers do not replicate the analgesic phenotype of those with loss of function mutations[13]. It also potentially supports the clinical data suggesting that lidocaine infusions may result in a significant opioid sparing effect. There is speculation among pain researchers that specific NaV1.7 channel blockers in combination with opioids, dosed well below the current perceived therapeutic window, could potentially lead to side effect free analgesia[13,14].

Other channels

Other voltage gated ion channels (namely calcium and potassium) have been implicated in contributing to lidocaine's efficacy as a systemic analgesic agent, although early in vitro studies suggest that this is likely to be at concentrations significantly greater than is seen safely in humans[6].

NMDA receptors

Further explanation for systemic lidocaine's anti-hyperalgesia, preventative analgesic and opioid-sparing effects may come from its ability to influence N-methyl-D-aspartate (NMDA) receptors in a manner similar to ketamine. Early studies in Xenopus oocytes whereby human NMDA receptors were expressed and then stimulated with glutamate and glycine showed that lidocaine inhibited their function in a dose dependent manner. The fact that lidocaine dosages to achieve blockade were relatively high does question its contribution to lidocaine's systemic clinical effect[15].

Immunomodulation

A number of studies carried out in humans have strongly suggested that a key contributor to lidocaine's systemic analgesia and its positive effects on bowel motility are secondary to its immunomodulatory effects. In 2007 one study demonstrated significantly lower levels of inflammatory mediators Il-6 and Il-8 in abdominal surgical patients receiving lidocaine infusions intraoperatively. Another study published data to support this further in 2008, this time finding a decrease by about 30 per cent in cytokines Il-1ra and Il-8 following similar surgery[16]. More recently two further studies show a decrease in Il-1, Il-6, Il-10, IFN gamma, TNF alpha, leukocyte count and CRP in those within the lidocaine arms of the trials[17-19]. Berger et al studied the effect of neutrophil recruitment in vivo and showed a marked decrease in chemokine induced neutrophil arrest and transmigration compared to a control group[19]. An overproduction of these mediators is thought to be responsible for the development of a number of perioperative disease states including post-operative pain which may, in part, explain some of lidocaine's promise as a systemic analgesic. Theories concerning how lidocaine limits this immune response are numerous and studies have implicated the inhibition of nuclear factor Kappa B as a likely contributor[20,21], with inhibition of inducible nitric oxide synthase[22] and direct effects of voltage gated sodium channels on macrophages also implicated[23]. There is also a possibility it results from its ability to target G-protein coupled receptors (GPCRs) on sensory neurons which are activated by the variety of inflammatory mediators produced by tissue injury. The muscarinic receptors m1 and m3, platelet activating factor receptors and thromboxane A2 receptors are all examples which have been shown to be downregulated by the presence of lidocaine[6].

Anti-inflammatory effects on pain are clearly beneficial, however, it could be argued they would be detrimental in circumstances where inflammation is vital to fight disease, namely infection, wound healing and cancer recurrence. A recent study into wound healing in mice suggested that, despite lidocaine decreasing local inflammatory factors, they did not impair the rate of healing[24]. Regarding wound infection, a detailed analysis recently provided evidence that local anaesthetics are in fact antibacterial with the mechanism of action being attributed to a disruption of microbial cell membrane[25].

Potential targets in preventing chronic post-surgical pain

A review of lidocaine infusions' use in treating chronic pain is beyond the scope of this article, however the prevention of chronic post-surgical pain (CPSP) is of undoubted relevance to anaesthetists. The mechanisms of lidocaine's potential effects are not clear nor are the mechanisms which lead to a patient developing CPSP. What is clear is that long term neurobiological changes are occurring within hours of injury[26] and that damage to nerves trespassing the surgical field is implicated in most cases[27]. Peripherally, the changes occurring at molecular level include various substances that sensitize the nociceptor including downregulation of tetrodoxin resistant sodium channels (Nav 1.8 and 1.9 – both targets of lidocaine)[28]. The anti-inflammatory effects of lidocaine have potential to exert an influence here as neuroinflammation is thought to be responsible for A(beta) fibres undergoing a phenotypic switch such that they resemble C-fibres in their function[26]. When an axon is cut, the distal end degenerates and is engulfed by inflammatory cells. This leads to activation of immune-like glial cells (microglia and astrocytes) which likely contribute to pain hypersensitivity and, potentially, neuroma formation. It is known, albeit in a rat model, that a low dose of lidocaine leads to a silencing of ectopic neuroma discharge[29] and given its effect on reducing inflammatory cell recruitment at the time of injury[19], lidocaine has potential to decrease their formation.

Systemic lidocaine also has potential to limit central sensitisation which otherwise would result in enhanced excitability at the synapse, expansion of the receptive fields and development of hyperalgesia and allodynia. NMDA receptors, upon which lidocaine has some effects[15], are implicated and upregulation of specific sodium channels in the dorsal horn are other potential targets where lidocaine may confer benefit. It is known, using patch clamp analysis, that lidocaine significantly reduces dorsal horn neuronal discharge which helps explain its acute and chronic analgesic effects[30].

Descending pain modulatory pathways are thought to be important in the development of chronic pain. It is therefore of interest that, in rats, hyperalgesia was abolished by intra rostro ventral medullary injection of lidocaine in one study[31].

Other theoretical mechanisms for lidocaine reducing CPSP are linked to its reduction in acute pain (linked to the development of CPSP)[32] or a reduction in opioid use which may limit the opioid's potential for triggering pro-nociceptive pathways[33].

CLINICAL USES AND EVIDENCE BASE FOR INTRAVENOUS USE

There have been several meta-analyses performed since lidocaine's first intravenous use was documented, each describing a heterogeneous group of trials.

Two of the earlier meta-analyses examined all of the data obtained regardless of surgical speciality[34,35] and one looked specifically at abdominal surgery shortly afterwards[36]. Vignault et al included 1754 patients in their analysis of which 573 were undergoing cardiac surgery and receiving highly variable doses, often with the aim of assessing cardiac stability rather than pain control. They found that an intravenous lidocaine infusion, at six hours, reduced pain at rest (weighted mean difference [WMD] on a 100 mm scale was -8.7 mm, (95 per cent confidence intervals [CI] -16.19 to -1.21) during cough -11.19 mm (95 per cent CI -17.73 to -4.65), and during movement -8.44 mm (95 per cent CI -17.31 to -1.80). They also found a decrease in overall opioid requirements (morphine) by 8.44 mg (95 per cent CI -11.32 mg to -5.56 mg). McCarthy et al, who published their meta-analysis the same year, included 764 patients, only 22 of which had not featured in the earlier analysis by Vignault. Rather than focus on the overall group, they divided the patients into specific surgery types and analysed them separately. Of the seven studies that looked at pain scores post abdominal surgery, five showed a significant reduction in pain scores. A meta-analysis of the pain scores at 24 hours were significantly lower in the lidocaine group (WMD -5.93 [95 per cent CI -9.63, -2.23]).

Sun et al more specifically examined abdominal surgical procedures in 2012 and reported on studies including 1108 patients. Of those subjects that had not been included in the above analyses, all were either looking at IV lidocaine boluses or exclusively post-operative lidocaine infusions. Their analyses demonstrated a reduction in opioid (morphine) consumption at 48 hours of -7.08 mg (95 per cent CI: -10.40 to -3.68), with a reduction in pain intensity at rest after six hours of -10.56 mm (95 per cent CI: -16.89 to -4.23)[36].

In 2015, an up-to-date Cochrane review was published which included 45 trials including 2802 surgical patients[37]. This was followed in 2016 by a trial sequential analysis using the same 45 trials[38] as the authors examined specific outcomes, including postoperative pain and opioid requirement, following various specific surgery types. These included 17 new trials that had not featured in the above meta-analyses. Overall, the analyses showed a statistically significant overall reduction in pain scores at 1-4 hours, (mean difference [MD] -0.84 centimetres, 95 per cent CI -1.1 to -0.59), and at 24 hours (MD -0.34 cm, 95 per cent CI -0.57 to -0.11) but not at 48 hours (MD -0.22 cm, 95 per cent CI -0.47 to 0.03). Combined analysis of opioid consumption (Intravenous morphine equivalents) showed a significant reduction in the lidocaine group in Post Anaesthesia Care Unit (PACU) (MD -4.17 mg, 95 per cent CI -6.40 to -1.94) and during the whole postoperative period (MD -5.36 mg, 95 per cent CI -7.12 to -3.59).

While there is difficulty in interpreting the clear clinical benefit of reducing morphine equivalent consumption by 5-10mg during a hospital admission, the findings related to length of hospital stay reduction do potentially show more significant clinical and economic benefits of intraoperative lidocaine infusions. When analysing the 21 studies (n=1424) addressing length of stay in Kranke et al's review, a reduction of 0.31 days (95 per cent CI -0.56 to -0.07) was noted (about eight hours). Given the cost of a hospital admission and with many hospitals operating beyond capacity, this finding is likely to be significant to health economists.

One clear observation when assessing these reviews is that the number of patients in each individual trial are low. In the most recent reviews, the trial (excluding cardiac procedures) with the greatest number of patients enrolled contained 57 patients in each group and the average number of patients across the trials was 31 patients in each. Eliminating bias in small single centred trials is notoriously difficult and results of well structured, large randomised control trials have been shown to differ significantly when compared to the meta-analyses that have preceded them[39].

SPECIFIC CLINICAL SITUATIONS

Open abdominal surgery

Of the six studies included in this group in the recent metanalysis[37], all demonstrated a mean difference in pain score, at 1-4 hours, of -5 mm or more although in three[40-42] this did not reach statistical significance. This equated to an overall difference of 7.2 mm (CI 95 per cent -0.96 to -0.47). There were no statistical differences in pain scores at intermediate (24 hours) and late time points (48 hours). It should be noted that all patients were given free access to patient controlled analgesia and therefore with the late time points, opioid sparing data is perhaps more telling. Overall opioid consumption within this subgroup was decreased by 3.26 mg (CI 95 per cent -4.80 to -1.71) of morphine equivalents (MEQ). This is a statistically significant result but one of questionable clinical significance. Of the three studies (n=140) that looked at length of hospital stay in this group[42-44], all found a reduction. When combined, the mean difference was -0.43 days (CI 95 per cent -1.00 to 0.14) which was not statistically significant although with greater power these studies may have demonstrated a difference of economical relevance.

Of particular interest to surgeons is the theory that lidocaine infusions may improve gastrointestinal recovery and lead to a decrease in rates of ileus. Kranke et al used ileus as an important endpoint in their meta-analysis and found weak evidence to support the use of lidocaine[37]. These amounted to reductions in time to first flatus (MD -5.49 hours, 95 per cent CI -7.97 to -3.00), time to first bowel sounds (MD -6.12 hours, 95 per cent CI 7.36 to 4.89) and a decrease in diagnosed paralytic ileus (risk ratio 0.38, 95 per cent CI: 0.15 to 0.99).

Laparoscopic abdominal surgery

Nine studies have reported on pain at one to four hours following laparoscopic abdominal surgery as an endpoint[45-53]. Of these, seven showed a marked difference in mean pain scores and two showed no demonstrable differences. Despite the dichotomy between the two groups of trials, there was an overall significant reduction in mean pain scores of -1.14 cm (95 per cent CI: -1.51 to -0.78). Opioid consumption intraoperatively was decreased by 4.05 mg (95 per cent CI -8.01 to -0.09) MEQ and by a further 4.87 mg (95 per cent CI: -8.17 to -1.58) MEQ in the Post Anaesthetic Care Unit (PACU). Overall opioid consumption was reduced by 7.40 mg (95 per cent CI: -11.41 to -3.38). Mean length of stay was reduced by 0.14 days but again this was not of statistical significance. Given the shorter length of stay expected in those undergoing laparoscopic cholecystectomy this is perhaps not surprising although greater numbers may yield more interesting results. Indeed, the differences are so small that they could arguably be the result of measurement error, bias or a simple Type I error.

Prostate surgery

Two studies have examined eligible outcomes in patients undergoing open prostate surgery with promising effects identified. In the first (n=38), total pain index was reduced by a third in the lidocaine group and postoperative stay was reduced by 1.10 days (95 per cent CI: -2.11 and -0.09)[54]. In the second, more recent study (n=76), morphine consumption in the first 24 hours was decreased by a mean of 13.9 mg (95 per cent CI 2.2 to 25.7) and again a marked shortening of postoperative stay was demonstrated (-1.30 days, 95 per cent CI: 0.3 to 2.4)[55]. Two studies included patients undergoing laparoscopic urological surgery and both found little improvements with intravenous lidocaine infusion[48,52].

Orthopaedics and spinal surgery

The use of lidocaine infusions in the setting of joint surgery has been investigated in only one study, and the authors did not identify any significant differences in pain control within their cohort of 60 total hip joint replacement patients[56].

In 2013, a study investigated lidocaine infusions during 116 patients' complex spine procedures. The trial found that lidocaine infusions significantly improved pain scores from 5.5 to 4.4 on an 11-point Likert scale. Patients receiving lidocaine had significantly greater SF-12 physical composite scores than placebo at 1 (38 [31–47] versus 33 [27–42]; P = 0.002) and three months (39 [31–49] versus 34 [28–44]; P = 0.04) postoperatively[57]. This perceived gain may highlight the potential for long term benefits from lidocaine infusions. Another study in 2013 also demonstrated a positive effect in spinal surgery. Their study of 55 patients undergoing lumbar disk operations found significantly reduced reported pain over the first 24 hours and reduced PCA bolus requests in the lidocaine group (18.2, 95 per cent CI: 8.32 to 28.09)[58]. However, in April 2017, a further trial contradicted these findings when they published a study in 70 patients undergoing posterior spinal arthrodesis where no effect on pain nor function of perioperative lidocaine with a regime lasting six hours after surgery was demonstrated[59].

As part of an opioid-free regime

There are a number of potential benefits to carrying out general anaesthesia without opioids. It has been theorised that an opioid-free anaesthetic may result in benefits in surgery for the obese (both bariatric and non-bariatric surgery), cancer surgery, surgery for those with sleep disordered breathing and surgery for those with a history of severe postoperative nausea and vomiting (particularly when opioids have been demonstrated as the likely culprit). Of the studies that have explored the benefits of opioid free anaesthesia in obese patients, both have achieved it with a regime that involves a lidocaine infusion[60,61]. Neither of these studies were designed to show a benefit in clinical endpoints but they did both show significant opioid-sparing effects.

THE PRACTICALITIES OF LIDOCAINE INFUSIONS FOR PERIOPERATIVE ANALGESIA

Dose

Of the trials available to date, the great majority and all of those that were analysed in the above meta-analyses were conducted with a bolus dose of 1-3 mg/kg and an infusion between 1 mg/kg/h and 4 mg/kg/h intraoperatively (40 of the 45 studies analysed were between 1.5 mg/kg/h and 2.5 mg/kg/h). Kranke et al divided the studies into those randomised control trials where the patients were given a lidocaine infusion rate of less than 2mg/kilogram/hour (low dose) and those greater than or equal to 2 mg/kilogram/hour and compared them both, independently, with controls. The high dose groups' mean score at early (one to four hours) and intermediate (24 hours) time points were both statistically significantly reduced but the low dose group were statistically significant in neither[37]. The most common regime, that of a 1.5 mg/kilogram bolus and a 2 mg/kg/h infusion, was investigated by Kaba et al with regards to its safety by measuring plasma levels as various intervals throughout the perioperative period during laparoscopic colectomies. Of their 15 patients, the highest concentration reached was 4.6 mcg/mL which was recorded after a 24-hour infusion of 1.33 mg/kg/h following the above intraoperative dosing strategy[45]. Despite the uncertainty that exists due to the paucity of human trials in local anaesthetic toxicity, it is thought the mild negative effects of lidocaine are likely to occur at plasma concentrations greater than 5 mcg/mL with seizures only likely once it is above 10 mcg/mL and significantly higher concentrations are required to cause life threatening cardiovascular collapse[7]. None of the studies in any of the meta-analyses outlined above identified any issues with local anaesthetic toxicity.

Timing

In 2016, Kahn et al performed a comparative meta-analysis to establish an appropriate end time for an intraoperative intravenous lidocaine infusion in bowel surgery. Three studies (n=160) were identified that used an intraoperative infusion only, and four (n=202) used both an intraoperative and a postoperative continued infusion. The analysis did not show a statistically significant difference in pain scores between the two. They failed to comment on opioid dosing during this period and as the individual trials had access to on demand opioid medication, the failure to find a decreased pain score carries questionable significance[62]. This is an area that merits further research input given the challenges, both practically and in terms of safety, that continuing a 24-hour infusion is likely to create relative to just an intraoperative infusion.

In combination with regional anaesthesia

The majority of the small studies to date either did not include or did not mention regional anaesthesia techniques in their study. If a clinician is performing regional techniques at the outset of surgery and a lidocaine infusion is planned, a clinician is right to be concerned about the potential for local anaesthetic toxicity. We know from early studies in monkeys[63] that the toxicity of two amide local analgesics are additive not synergistic. We also know from Kaba's study that the maximum level in patients is likely to be about 4 mcg/mL at the point at which the regional technique local anaesthetic has produced its peak[45]. From this, a cautious approach may be to reduce the regional dose by 40 per cent to be confident toxicity was not likely to occur intraoperatively (at a level similar to 10 micrograms/millilitre of lidocaine). If a regional technique, such as a rectus sheath block, was to be performed at the end of the case, it is likely to reach its peak concentration at about 45 minutes post injection[64]. Given that lidocaine has a terminal half-life of about 90 minutes[7] and if an infusion is stopped at the time of the injection, there is little concern that local anaesthetic toxicity is likely to occur if maximum doses of local anaesthetic are adhered to. A dose reduction in the local anaesthetic agent used for the block would be sensible if an ongoing infusion was planned although by how much is yet to be defined, especially given that a patient may experience negative psychological effects at lower doses which may not present an issue intraoperatively.

A study by Brydone et al examined 28 patients undergoing total knee arthroplasty to all of whom 400 mg (200 mL of 0.2 per cent) Ropivacaine followed by 20 mg per hour for 24 hours thereafter, was administered. For some this equated to a dose of greater than 6 mg/kg in the bolus alone. No patients exceeded the toxic threshold for free plasma ropivacaine in this study and no mild local anaesthetic toxicity was noted[65]. It is unlikely that the addition of a lidocaine infusion will contribute to serious toxicity however there is very little evidence available to confirm or indeed refute this assertion.

The combination of lidocaine administered solely intraoperatively to reduce hyperalgesia and inflammation, followed by regional techniques at the incision sites (or nebulised via the ports in laparoscopic surgery) seems one possible pragmatic solution albeit admittedly unproven. A lidocaine infusion or regional anaesthesia catheter infusion could then be commenced in recovery after an hour (at which point the concentration of the initial regional bolus will have already peaked) and the patient should be closely monitored for at least another hour in recovery before moving to a ward. The strategy of lidocaine infusions combined with regional catheter infusions, both running on the ward, would need significant dose reduction versus conventional doses before safety could be assumed.

Special patient groups

There are a number of both strong and relative contraindications that exist to lidocaine infusions. The half-life of lidocaine in those with liver failure averages 343 minutes and in those with heart failure it is extended to 136 minutes. Lidocaine infusions should be avoided in those with end stage renal failure, symptomatic heart failure or anybody with a reduced level of consciousness. Anyone who may have vulnerability in their electrophysiology should have the potential for complications considered, including those who have suffered a recent myocardial infarction. Although there is uncertainty surrounding vulnerability of epileptic patients to central nervous system adverse effects of local anaesthetics, it also seems logical to consider its use in these patients. It is thought to be probably porphyrinogenic and should only be used on patients with acute porphyria where there are strong or urgent indications[66].

Monitoring

If the patient is to receive an intraoperative infusion, inevitably by modern standards, monitoring will include an ECG and regular blood pressure measurements until they are to leave PACU. The chance of significant arrhythmias going unnoticed in this period is therefore minimised. As the infusion is ceased at the end of surgery, the plasma lidocaine levels will drop and subsequent complications on the ward are highly unlikely.

In the event that lidocaine is to be continued on the ward, the question is often raised whether ongoing cardiovascular monitoring is required. Given the large window that exists between the initial symptoms of local anaesthetic toxicity and its potential harmful effects, sudden onset of seizures or cardiovascular collapse are unlikely to occur especially without preceding signs or symptoms when a steady state infusion is used. The infusions should therefore be reserved for those without cognitive deficit or communication difficulties and nursing staff should be aware of early features of toxicity, and formal protocols should be in place to advise them on a course of action should each occur. If we were to monitor every patient in a critical care setting with ongoing ECG monitoring, we risk wasting valuable resources on something not shown to represent a significant problem.

Of the recent studies using prolonged infusions (≥24 hours), two measured levels and found a peak was reached slowly at 24 hours[45,55]. The maximum value in both was 4.96 micrograms/millilitre (The patient was asymptomatic). Of the four studies that examined postoperative infusions, only one included 24-hour ECG monitoring (and no changes were noted)[45,50,52,55]. The rest took place on the ward with nurses monitoring clinical signs only. No symptoms nor signs of local anaesthetic toxicity were noted. These studies included 120 patients in the lidocaine groups.

In a study of 49 patients with Complex Regional Pain Syndrome, each were given infusions of 1 mg/minute of lidocaine which was titrated upwards to achieve a plasma level of 5 mcg/mL on daily sampling, for five days. Eight had mild side effects, one had an unspecified atrial arrhythmia all of which occurred after 24 hours and at rates significantly greater than 120 mg/hour of lidocaine[67].

Eipe et al have published a detailed review of this topic, where they detail their experience in the Ottawa hospital. They provide an example of their policies with on-ward infusions and report excellent safety profile with use of the drug in the ward environment. An audit of 169 patients receiving 0.5 to 2 mg/kg/min showed only six patients had minor side effects (In four the infusion was continued at a lower dose), all of which were easily detected by the ward nurses.

Given that levels above 5 mcg/mL is thought to be the point at which mild symptoms become apparent, and no patients in the perioperative period have achieved these levels when measured, there is little to suggest ongoing monitoring is required as long as patients are well selected, nurses are educated in when to call for help and infusion systems are robust and tamper-proof. In fact, the window of safety for lidocaine appears to be significantly wider than that of opioid based patient controlled analgesia, a common postoperative ward based treatment regime.

THE BIG QUESTIONS IN ANAESTHESIA – CANCER AND CHRONIC PAIN PREVENTION

Cancer

The influence that the anaesthetist can have on cancer recurrence following surgery is a current topic of much discussion, particularly the way in which different anaesthetic agents interact with the cellular immune system and influence long-term outcome. In a human tongue model, lidocaine has been demonstrated to have a direct inhibitory effect on the EGF receptor resulting in tumour cell proliferation inhibition at clinical concentrations[68]. It is also apparent that opioids suppress postoperative natural killer cell cytotoxicity, a process essential for defences against malignant cells. This has been demonstrated in a dose dependent fashion therefore if lidocaine infusions were to limit opioid use, this could further their anti-cancer effects[69]. The fact that studies have demonstrated improved function in these defences with lidocaine administration, shows promise[70,71]. It is also of great interest that voltage gated sodium channel blockade of cancer cell membranes have been shown to limit metastatic processes in vitro[69].

There is growing evidence, albeit far from compelling, to support regional anaesthesia in cancer surgery. Whether this relates to the nerve block itself or the result of local anaesthetic entering the systemic circulation is yet to be seen. Studies investigating the recurrence of cancer in those receiving intravenous intraoperative lidocaine would require significant recruitment but could potentially reveal a significant mortality advantage.

Chronic post-surgical pain prevention

Four recent studies have investigated the effects of lidocaine infusions in breast surgery and uniquely all included an analysis of CPSP. The first group to test this, Grigoras et al (n=36), at three months, found two (11.8 per cent) patients had persistent postoperative pain in the lidocaine group, versus nine (47.4 per cent) in the control group (p=0.031). This study looked at secondary hyperalgesia by measuring the area of hyperalgesia and dividing it by the length of the incision. At three months, they found hyperalgesia to be significantly less in the lidocaine group compared with the control group (0.2+/-0.8 versus 3.2+/- 4.5 cm, p=0.002)[72]. Terkawi et al attempted to answer the same question in 2015 and again found no statistical differences in the acute setting. When the same group performed telephone follow ups on these patients after six postoperative months, of the 61 (out of 71 original patients) that responded, 8/27 (30 per cent) in the placebo group and 4/34 (12 per cent) in the lidocaine group had developed persistent post-surgical pain (p=0.013)[73,74]. In 2017, a third small study was performed which resulted in similar findings, reducing the risk of chronic pain by 50 per cent in a similar subset (n=42 in the lidocaine arm)[75]. Recently, the importance of these findings has been questioned by a group who studied not just chronic pain as a simple dichotomous endpoint but also the presence of chronic pain that is significant according to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) criteria. The patients who answered yes to having chronic pain at six months were similar in frequency to those other trials outlined above, however those who were deemed to have significant pain, according to the IMMPACT criteria, had a far lower incidence[76]. The study did not identify a risk reduction in those 121 patients treated intraoperatively with lidocaine infusions who were successfully followed up when these criteria were considered.

One recent study in robotic thyroid surgery compared lidocaine and placebo infusions. Their conclusion was that CPSP was more prevalent in the control group (16/43) versus the lidocaine group (6/41, p=0.025)[77].

Perioperative ketamine as a strategy to reduce CPSP has been studied extensively, particularly in small randomised control trials. The ANZCA Clinical Trials Network has recently set out a plan to investigate the presence and extent of this preventative analgesia in the ROCKET trial which has received an award of $A4.8 million from the NHMRC. Interestingly, when ketamine and lidocaine were studied separately within the same trial in open nephrectomy patients, it was lidocaine and not ketamine that was found to have the most significant effect on the prevention of CPSP[78].

These are small studies demonstrating promise in the area of chronic pain development post surgery. If this could be replicated in a bigger multicentre trial, it could have a significant impact on a large number of individuals in whom persistent post-surgical pain is a major issue and could go some way to showing the potential of lidocaine infusions as part of the “holy grail” of CPSP[79] prevention.

CONCLUSION

Perioperative intravenous lidocaine administration is a field that has been extensively explored in a number of small randomised control trials and subsequent meta-analyses. Its anti-inflammatory, anti-hyperalgesic and analgesic properties result in improved perioperative outcomes albeit with great heterogeneity in effect size. More small trials and meta-analyses in this area are unlikely to help us form clear conclusions. A large, multi-centred randomised control trial is the only sensible next step that will help us decide whether lidocaine intravenously is an exercise in futlilty or a golden ticket in an area in which opioids are currently proving imperfect.

REFERENCES

1. Bartlett EE, Hutserani O. Xylocaine for the relief of postoperative pain. Anesth Analg. 1961;40:296–304.
2. McLure HA, Rubin AP. Review of local anaesthetic agents. Minerva Anestesiol. 2005;71(3):59–74.
3. de Oliveira CM, Issy AM, Sakata RK. Intraoperative intravenous lidocaine. Rev Bras Anestesiol. 2010;60(3):325–333.
4. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. BJA Education. 2016;16(9):292–298.
5. Weinberg L PB, Tan C, Nikfarjam M. Pharmacokinetics and pharmacodynamics of lignocaine. World J Anesthesiol. 2015;4(2):17–29.
6. van der Wal SE, van den Heuvel SA, Radema SA, van Berkum BF, Vaneker M, Steegers MA, et al. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. Eur J Pain. 2016;20(5):655–674.
7. Hilal-Dandan R, Brunton LL, Goodman LS. Goodman and Gilman’s manual of pharmacology and therapeutics. New York: Mcgraw-Hill, 2014.
8. Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. Anesth Analg. 2013;116(5):1141–1161.
9. Akopian AN, Sivilotti L, Wood JN. A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. Nature.1996;379(6562):257–262.
10. Sheets PL, Jarecki BW, Cummins TR. Lidocaine reduces the transition to slow inactivation in Na(v)1.7 voltage-gated sodium channels. Br J Pharmacol. 2011;164(2b):719–730.
11. Jarecki BW, Sheets PL, Jackson JO 2nd, Cummins TR. Paroxysmal extreme pain disorder mutations within the D3/S4-S5 linker of Nav1.7 cause moderate destabilization of fast inactivation. J Physiol. 2008;586(17):4137–4153.

12. Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, et al. An SCN9A channelopathy causes congenital inability to experience pain. Nature. 2006;444(7121):894–898.
13. Minett MS, Pereira V, Sikandar S, Matsuyama A, Lolignier S, Kanellopoulos AH, et al. Endogenous opioids contribute to insensitivity to pain in humans and mice lacking sodium channel Nav1.7. Nature Comm. 2015;6:8967.
14. Emery EC, Luiz AP, Wood JN. Nav1.7 and other voltage-gated sodium channels as drug targets for pain relief. Expert Opin Ther Targets. 2016;20(8):975–983.
15. Hahnenkamp K, Durieux ME, Hahnenkamp A, Schauerte SK, Hoenemann CW, Vegh V, et al. Local anaesthetics inhibit signalling of human NMDA receptors recombinantly expressed in Xenopus laevis oocytes: role of protein kinase C. Br J Anaesth. 2006;96(1):77–87.
16. Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H. The effect of perioperative intravenous lidocaine on postoperative pain and immune function. Anesth Analg. 2009;109(5):1464–1469.
17. Sridhar P, Sistla SC, Ali SM, Karthikeyan VS, Badhe AS, Ananthanarayanan PH. Effect of intravenous lignocaine on perioperative stress response and post-surgical ileus in elective open abdominal surgeries: a double-blind randomized controlled trial. ANZ J Surg. 2015;85(6):425–429.
18. Ortiz MP, Godoy MC, Schlosser RS, Ortiz RP, Godoy JP, Santiago ES, et al. Effect of endovenous lidocaine on analgesia and serum cytokines: double-blinded and randomized trial. J Clin Anesth. 2016;35:70–77.
19. Berger C, Rossaint J, Van Aken H, Westphal M, Hahnenkamp K, Zarbock A. Lidocaine reduces neutrophil recruitment by abolishing chemokine-induced arrest and transendothelial migration in septic patients. J Immunol. 2014;192(1):367–376.
20. Lang A, Ben Horin S, Picard O, Fudim E, Amariglio N, Chowers Y. Lidocaine inhibits epithelial chemokine secretion via inhibition of nuclear factor kappa B activation. Immunobiology. 2010;215(4):304–313.
21. Lahat A, Ben-Horin S, Lang A, Fudim E, Picard O, Chowers Y. Lidocaine down-regulates nuclear factor-kappaB signalling and inhibits cytokine production and T cell proliferation. Clin Exp Immunol. 2008;152(2):320–327.
22. Gorczynski MJ, Huang J, King SB. Regio- and stereospecific syntheses and nitric oxide donor properties of (E)-9- and (E)-10-nitrooctadec-9-enoic acids. Org Lett. 2006;8(11):2305–2308.
23. Lee PY, Tsai PS, Huang YH, Huang CJ. Inhibition of toll-like receptor-4, nuclear factor-kappaB and mitogen-activated protein kinase by lignocaine may involve voltage-sensitive sodium channels. Clin Exp Pharmacol Physiol. 2008;35(9):1052–1058.
24. Waite A, Gilliver SC, Masterson GR, Hardman MJ, Ashcroft GS. Clinically relevant doses of lidocaine and bupivacaine do not impair cutaneous wound healing in mice. Br J Anaesth. 2010;104(6):768–773.
25. Wubbels GG, Brown TR, Babcock TA, Johnson KM. The element effect and nucleophilicity in nucleophilic aromatic photosubstitution (SN2Ar*): local atom effects as mechanistic probes of very fast reactions. J Org Chem. 2008;73(5):1925–1934.
26. Shipton E. Post-surgical neuropathic pain. ANZ J Surg. 2008;78(7):548–555.
27. Aasvang EK, Møhl B, Bay-Nielsen M, Kehlet H. Pain related sexual dysfunction after inguinal herniorrhaphy. Pain. 2006;122(3):258–263.
28. Cummins TR, Waxman SG. Downregulation of tetrodotoxin-resistant sodium currents and upregulation of a rapidly repriming tetrodotoxin-sensitive sodium current in small spinal sensory neurons after nerve injury. J Neurosci. 1997;17(10):3503–3514.
29. Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. Pain. 1992;48(2):261–268.
30. Kurabe M, Furue H, Kohno T. Intravenous administration of lidocaine directly acts on spinal dorsal horn and produces analgesic effect: an *in vivo* patch-clamp analysis. Sci Rep. 2016;6:26253.
31. Porreca F, Ossipov MH, Gebhart GF. Chronic pain and medullary descending facilitation. Trends Neurosci. 2002;25(6):319–325.
32. Shipton EA. The transition from acute to chronic post surgical pain. Anaesth Intensive Care. 2011;39(5):824–836.
33. Heinl C, Drdla-Schutting R, Xanthos DN, Sandkuhler J. Distinct mechanisms underlying pronociceptive effects of opioids. Journal Neurosci. 2011;31(46):16748–16756.
34. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs. 2010;70(9):1149–1163.
35. Vigneault L, Turgeon AF, Côté D, Lauzier F, Zarychanski R, Moore L, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anaesth. 2011;58(1):22–37.
36. Sun Y, Li T, Wang N, Yun Y, Gan TJ. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. Dis Colon Rectum. 2012;55(11):1183–1194.
37. Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev. 2015(7):CD009642.
38. Weibel S, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. Br J Anaesth. 2016;116(6):770–783.
39. Sivakumar H, Peyton PJ. Poor agreement in significant findings between meta-analyses and subsequent large randomized trials in perioperative medicine. Br J Anaesth. 2016;117(4):431–441.
40. Bryson GL, Charapov I, Krolczyk G, Taljaard M, Reid D. Intravenous lidocaine does not reduce length of hospital stay following abdominal hysterectomy. Can J Anaesth. 2010;57(8):759–766.
41. Grady P, Clark N, Lenahan J, Oudekerk C, Hawkins R, Nezat G, et al. Effect of intraoperative intravenous lidocaine on postoperative pain and return of bowel function after laparoscopic abdominal gynecologic procedures. AANA J. 2012;80(4):282–288.
42. Herroeder S, Pecher S, Schonherr ME, Kaulitz G, Hahnenkamp K, Friess H, et al. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. Ann Surg. 2007;246(2):192–200.

43. Koppert W, Weigand M, Neumann F, Sittl R, Schuettler J, Schmelz M, et al. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. Anesth Analg. 2004;98(4):1050–1055.
44. Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, et al. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. Br J Anaesth. 2006;97(5):640–646.
45. Kaba A, Laurent SR, Detroz BJ, Sessler DI, Durieux ME, Lamy ML, et al. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. Anesthesiology. 2007;106(1):11–18; discussion 5–6.
46. Kim JE, Choi JB, Koo BN, Jeong HW, Lee BH, Kim SY. Efficacy of intravenous lidocaine during endoscopic submucosal dissection for gastric neoplasm: a randomized, double-blind, controlled study. Medicine. 2016;95(18):e3593.
47. Kim TH, Kang H, Choi YS, Park JM, Chi KC, Shin HY, et al. Pre- and intraoperative lidocaine injection for preemptive analgesics in laparoscopic gastrectomy: a prospective, randomized, double-blind, placebo-controlled study. J Laparoendosc Adv Surg Tech A. 2013;23(8):663–668.
48. Lauwick S, Kim DJ, Mistraletti G, Carli F. Functional walking capacity as an outcome measure of laparoscopic prostatectomy: the effect of lidocaine infusion. BrJ Anaesth. 2009;103(2):213–219.
49. Saadawy IM, Kaki AM, Abd El Latif AA, Abd-Elmaksoud AM, Tolba OM. Lidocaine vs. magnesium: effect on analgesia after a laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2010;54(5):549–556.
50. Tikuišis R, Miliauskas P, Samalavičius NE, Žurauskas A, Samalavičius R, Zabulis V. Intravenous lidocaine for post-operative pain relief after hand-assisted laparoscopic colon surgery: a randomized, placebo-controlled clinical trial. Tech Coloproctol. 2014;18(4):373–380.
51. Wu CT, Borel CO, Lee MS, Yu JC, Liou HS, Yi HD, et al. The interaction effect of perioperative cotreatment with dextromethorphan and intravenous lidocaine on pain relief and recovery of bowel function after laparoscopic cholecystectomy. Anesth Analg. 2005;100(2):448–453.
52. Wuethrich PY, Romero J, Burkhard FC, Curatolo M. No benefit from perioperative intravenous lidocaine in laparoscopic renal surgery: a randomised, placebo-controlled study. Eur J Anaesthesiol. 2012;29(11):537–543.
53. Su N, Liu Y, Yang X, Shi Z, Huang Y. Efficacy and safety of mepivacaine compared with lidocaine in local anaesthesia in dentistry: a meta-analysis of randomised controlled trials. Int Dent J. 2014;64(2):96–107.
54. Groudine SB, Fisher HA, Kaufman RP Jr, Patel MK, Wilkins LJ, Mehta SA, et al. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. Anesth Analg. 1998;86(2):235–239.
55. Weinberg L, Rachbuch C, Ting S, Howard W, Yeomans M, Gordon I, et al. A randomised controlled trial of peri-operative lidocaine infusions for open radical prostatectomy. Anaesthesia. 2016;71(4):405–410.
56. Martin F, Cherif K, Gentili ME, Enel D, Abe E, Alvarez JC, et al. Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. Anesthesiology. 2008;109(1):118–123.
57. Farag E, Ghobrial M, Sessler DI, Dalton JE, Liu J, Lee JH, et al. Effect of perioperative intravenous lidocaine administration on pain, opioid consumption, and quality of life after complex spine surgery. Anesthesiology. 2013;119(4):932–940.
58. Kim KT, Cho DC, Sung JK, Kim YB, Kang H, Song KS, et al. Intraoperative systemic infusion of lidocaine reduces postoperative pain after lumbar surgery: a double-blinded, randomized, placebo-controlled clinical trial. Spine J. 2014;14(8):1559–1566.
59. Dewinter G, Moens P, Fieuws S, Vanaudenaerde B, Van de Velde M, Rex S. Systemic lidocaine fails to improve postoperative morphine consumption, postoperative recovery and quality of life in patients undergoing posterior spinal arthrodesis: a double-blind, randomized, placebo-controlled trial. Br J Anaesth. 2017;118(4):576–585.
60. Halls ML, Yeatman HR, Nowell CJ, Thompson GL, Gondin AB, Civciristov S, et al. Plasma membrane localization of the μ-opioid receptor controls spatiotemporal signaling. Sci Signal. 2016;9(414):ra16.
61. Bakan M, Umutoglu T, Topuz U, Uysal H, Bayram M, Kadioglu H, et al. Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. Braz J Anesthesiol. 2015;65(3):191–199.
62. Amatya B, Elmalik A, Lowe M, Khan F. Evaluation of the structured bowel management program in inpatient rehabilitation: a prospective study. Disabil Rehabil. 2016;38(6):544–551.
63. Wear JB Jr, Crummy AB, Munson BO. A new approach to the treatment of priapism. J Urol. 1977;117(2):252–254.
64. Wada M, Kitayama M, Hashimoto H, Kudo T, Kudo M, Takada N, et al. Brief reports: plasma ropivacaine concentrations after ultrasound-guided rectus sheath block in patients undergoing lower abdominal surgery. Anesth Analg. 2012;114(1):230–232.
65. Brydone AS, Souvatzoglou R, Abbas M, Watson DG, McDonald DA, Gill AM. Ropivacaine plasma levels following high-dose local infiltration analgesia for total knee arthroplasty. Anaesthesia. 2015;70(7):784–790.
66. Medsafe. New Zealand Data Sheet - Lidocaine-Claris 2017. From: http://www.medsafe.govt.nz/profs/Datasheet/l/lidocaineclarisinj.pdf. Accessed 2 October 2017.
67. Schwartzman RJ, Patel M, Grothusen JR, Alexander GM. Efficacy of five-day continuous lidocaine infusion for the treatment of refractory complex regional pain syndrome. Pain Med. 2009;10(2):401–412.
68. Sakaguchi M, Kuroda Y, Hirose M. The antiproliferative effect of lidocaine on human tongue cancer cells with inhibition of the activity of epidermal growth factor receptor. Anesth Analg. 2006;102(4):1103–1107.
69. Park JJ, Lang CC, Manson L, Brackenbury ET. Aortic valve replacement in a Jehovah's Witness: a case of multi-disciplinary clinical management for bloodless surgery. BMJ Case Rep. 2012;2012:bcr1220115403.
70. Wang HL, Liu YY, Yan HD, Wang XS, Huang R, Lei WF. Intraoperative systemic lidocaine inhibits the expression of HMGB1 in patients undergoing radical hysterectomy. Int J Clin Exp Med. 2014;7(10):3398–3403.
71. Ramirez MF, Tran P, Cata JP. The effect of clinically therapeutic plasma concentrations of lidocaine on natural killer cell cytotoxicity. Reg Anesth Pain Med. 2015;40(1):43–48.

72. Grigoras A, Lee P, Sattar F, Shorten G. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. Clin J Pain. 2012;28(7):567–572.
73. Terkawi AS, Durieux ME, Gottschalk A, Brenin D, Tiouririne M. Effect of intravenous lidocaine on postoperative recovery of patients undergoing mastectomy: a double-blind, placebo-controlled randomized trial. Reg Anesth Pain Med. 2014;39(6):472–477.
74. Terkawi AS, Sharma S, Durieux ME, Thammishetti S, Brenin D, Tiouririne M. Perioperative lidocaine infusion reduces the incidence of post-mastectomy chronic pain: a double-blind, placebo-controlled randomized trial. Pain Physician. 2015;18(2):E139–E146.
75. Kim MH, Lee KY, Park S, Kim SI, Park HS, Yoo YC. Effects of systemic lidocaine versus magnesium administration on postoperative functional recovery and chronic pain in patients undergoing breast cancer surgery: a prospective, randomized, double-blind, comparative clinical trial. PloS One. 2017;12(3):e0173026.
76. Kendall MC, McCarthy RJ, Panaro S, Goodwin E, Bialek JM, Nader A, et al. The effect of intraoperative systemic lidocaine on postoperative persistent pain using IMMPACT criteria assessment following breast cancer surgery: a randomized, double-blind placebo controlled trial. Pain Pract. 2017: [Epub ahead of print].
77. Choi KW, Nam KH, Lee JR, Chung WY, Kang SW, Joe YE, et al. The effects of intravenous lidocaine infusions on the quality of recovery and chronic pain after robotic thyroidectomy: a randomized, double-blinded, controlled study. World J Surg. 2017;41(5):1305–1312.
78. Jendoubi A, Naceur IB, Bouzouita A, Trifa M, Ghedira S, Chebil M, et al. A comparison between intravenous lidocaine and ketamine on acute and chronic pain after open nephrectomy: a prospective, double-blind, randomized, placebo-controlled study. Saudi J Anaesth. 2017;11(2):177–184.
79. Cohen SP, Raja SN. Prevention of chronic postsurgical pain: the ongoing search for the holy grail of anesthesiology. Anesthesiology. 2013;118(2):241–243.

Caution with ketamine

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INTRODUCTION

Ketamine, traditionally used as a single anaesthetic agent in battlefield and disaster situations, has recently seen increasing interest and use in other fields. These include in pain management: to reduce opioid use and tolerance; to improve post operative analgesia; to reduce neuropathic pain symptoms acutely and possibly chronically, and in palliative cancer pain management[1]. It is also being trialled in psychiatry to reduce suicidal ideation in depression and in post traumatic stress disorder[1,2]. There has also been a large increase in its traditional use for procedural analgesia and sedation by emergency physicians and first aid personnel[3].

A body of literature comprised of both studies and meta-analyses has provided mixed results on the efficacy of the drug to achieve these goals[4-7], and there are as yet no clear guides on what doses and durations of administration are optimal, and whether any treatment effects are sustained. What is often not appreciated, or is underplayed, is that ketamine, given with the best of intentions to benefit the patient, may cause in some a significant dysphoric experience, and for a few, the most terrifying and frightening experience of their life, often with an impending sense of death. That ketamine has the potential to cause dysphoria, variously referred to as psychotomimetic, psychodysleptic or psychedelic phenomena, which may be similar to symptoms of schizophrenia, as well as hallucinations and mood changes, has been well known since the original studies of the drug, known early as CI-581[8]. The severity of these disturbing neuropsychiatric phenomena are unlikely to be recognised at the time of administration as there are no physical outward indicators, nor, when higher doses are given, are the patients able to express these at the time: the effect of the drug appears to be all that the physician desires in that the patient lies still and does not complain, keeps breathing and maintains a stable (possibly elevated) blood pressure. It is only by interviewing the patients later that they can describe and express with vivid clarity the disturbing and sometimes terrifying experience that the drug induces which they are unable to articulate at the time. These effects can be so severe that some patients described never wanting to have the drug again.

The main purpose of this article is to draw attention to two aspects of ketamine pharmacology: 1) it can exert analgesic efficacy at very low doses; 2) the potential for dysphoria. Although the latter are usually most severe with intravenous (IV) bolus administration, they may also occur at low plasma levels of the drug in some patients, as close scrutiny of studies which include assessing these effects reveal. A second note of caution relates to its potential for abuse in patients with drug dependency.

KETAMINE: A DISSOCIATIVE ANAESTHETIC WITH ABUSE POTENTIAL

The pharmacology of ketamine is complex[9]. Ketamine is related to phencyclidine (trade name Sernyl), its precursor, which was eventually withdrawn as an anaesthetic drug due to the severity of its psychotomimetic effects. The efficacy of ketamine to induce similar effects should not be discounted: it has become a major drug of abuse for those seeking its mind and mood altering effects. In an excellent review undertaken by the Advisory Council on the Misuse of Drugs (UK), besides the pharmacology and potential toxicity of the drug, the acute psychological effects are described: "At low doses, ketamine induces distortion of time and space, hallucinations and mild dissociative effects. At large doses, ketamine induces more severe dissociation commonly referred to as a 'K-hole', wherein the user experiences intense detachment to the point that their perceptions appear completely divorced from their previous reality. This is a desired effect for some users, but for others it can be an unpleasant and frightening experience[10]." It is instructive to read a description of the first clinical studies of ketamine by Corssen and Domino, for it is here they first termed it a "dissociative anaesthetic"[8]. They noted that:

> "phencyclidine related drugs do not produce true sensory blockade." …."These and previous studies recording visual and somesthetic evoked potentials appear to indicate that sensory input may reach cortical receiving areas but fail to be perceived in some of the association areas because these are depressed. This interference in proper association of afferent impulses results in 'dissociation'. It is therefore suggested that the state induced by CI-581 be called 'dissociative anesthesia'."

Much of the discussion in Corssen and Domino's article[8] relates to the difference, compared to conventional anaesthetic drugs, in the anaesthetic state induced by ketamine, "a state resembling catalepsy", and of the psychotomimetic reactions, described by them as emergence delirium and awakening phase hallucinations:

> "Some of the adult patients had vivid dreams or frank hallucinations during the awakening phase. Some described the dreams as amusing and pleasant, others considered them frightening. As a rule, such dreaming episodes lasted from 5 to 15 minutes, after which the patient promptly returned to reality and became clear and coordinated. The dreams frequently involved outer space. Two patients, both middle-aged, showed signs of schizoid behavior during awakening. Both experienced travelling in outer space and thought that they had died and were flying to hell."

DISTURBING DESCRIPTIONS OF KETAMINE INDUCED DYSPHORIA

But is it possible that this "dreaming" occurs not just during emergence? It is known that the electroencephalographic effects of ketamine are very different from conventional anaesthetics, and that the bispectral index, used to indicate depth of anaesthesia induced by volatile agents and propofol, may not decrease, but increase, under the influence of ketamine[11]. This may indicate ongoing cortical activity, as evidenced by the following description of the dysphoria from ketamine as experienced by a patient. This account was recorded in the context of the patient being offered a low dose ketamine infusion for post operative analgesia three days after his injury. The patient, a healthy 26 year old male who sustained a fractured femur following a fall from a motorbike, without other injuries or loss of consciousness, distinctly remembered two dysphoric episodes at the time of his retrieval. He was given 10 mg morphine IV followed by two separate 50 mg IV bolus doses of ketamine four minutes apart to enable straightening of his leg prior to transport to hospital.

> "As I was given the ketamine I slowly lost my grip with reality with no way to communicate with the paramedics. I was just along for the ride and petrified. I was completely paralysed but could hear everything happening around me but being unable to communicate led me to believe I was dead. Absolutely horrible feeling. I felt like my conscience was just on a loop and I was stuck in a bad trip just waiting for everything to be over and go black. Several times I felt like I was being folded into a small cube to just disappear and then a big white flash and back to the start. The ketamine experience was much worse in itself than any pain I felt at any point and (I) highly suggest that doses like that are not given as no one should have to feel that sense of helplessness and pure terror ever in their life!!!"

He remembered being able to hear, and felt unable to move, but did not feel pain from his leg manipulations. It is clear that he was far from comfortable. Not all patients suffer such severe dysphoria. Some have no memory of any dreams or hallucinations; some may even find it pleasant; others are unable to give a description as it is so alien to any ordinary conscious experience. Many staff think that by telling the patient that everything is alright will allay their anxiety[3], but this is misconceived. The following is a description of the effect of a 50 mg IV bolus dose of ketamine given in the emergency department to facilitate the reduction of a dislocated shoulder. The patient, a 60 year old female, had also sustained a fractured pelvis in a cycling accident but no head injury, and had been given a penthrox® (methoxyflurane) inhaler and a total of 270 micrograms IV fentanyl by ambulance staff prior to hospitalisation.

> "The experience was alarming in the sense that I was able to converse with and see the staff treating me and yet I'd been transferred to another dimension.. the fourth dimension, straight out of the movie Interstellar. The room was psychedelic, the staff had auras and I was convinced my brain had been permanently changed by a drug. Being reassured by the staff that it was a normal response and would wear off, failed to stop my anxiety. I was convinced that those treating me were not yet aware of their mistake. I actively contemplated whether I could work and drive with the special effects, how difficult would it be to hide the brain dysfunction and how many appointments with neurologists would it take to be diagnosed. My experience reflected that of fellow patients in the rehabilitation hospital with the consensus being to avoid the Special K world whenever possible."

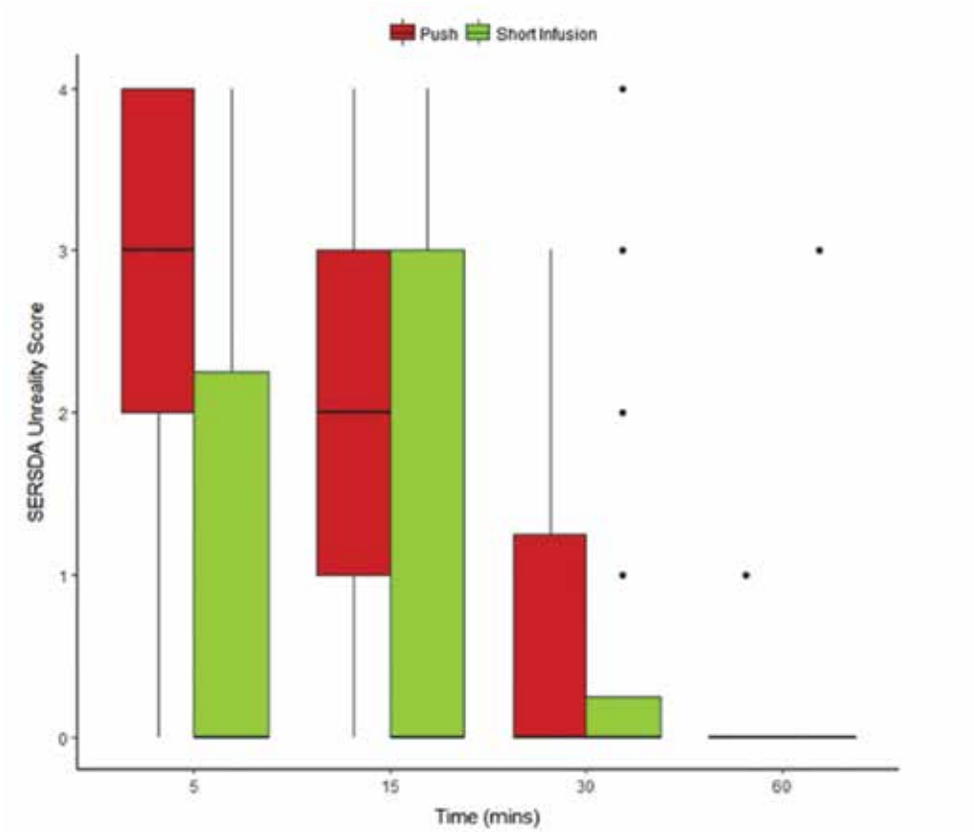
(Special K is a slang term for ketamine. The reduction was unsuccessful, as ketamine increases muscle tone, described in the initial studies[8]).

LOW DOSE KETAMINE

Emergency physicians often administer sub-anaesthetic or "low dose" IV bolus doses of ketamine in the range of approximately 0.1-0.3 mg/kg, instead of 1.0-2.0 mg/kg traditionally used for anaesthesia. They report its effectiveness as an analgesic, its opioid sparing effect and its physical safety[3]. But such retrospective reports are unlikely to detect the real incidence and severity of the dysphoric effects, unless they were specifically assessed and recorded at the time. Ahern et al[3] reported a 3.5 per cent incidence of dysphoric reactions, and deemed most of them mild and transient, whereas a prospective placebo controlled study by Galinski et al recorded a much higher incidence[12]. In this trial the ketamine group received 0.2 mg/kg IV bolus, the other placebo, both given IV 3 mg morphine five minutely as required. They reported reduced morphine requirements in the ketamine group, but no significant difference in the pain relief and net patient satisfaction between the groups. There was a much higher incidence of adverse neurophysiological effects in the ketamine group, including dysphoria, six out of 33, and hallucinations, four out of 33, with only one out of 32 in the placebo group reporting dysphoria.

More comprehensive recent studies by emergency staff have compared low dose ketamine infusions to IV bolus and have measured not only the incidence but also the severity of the dysphoric effects using the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA), based on work done by Eide et al[13]. This gives a zero to four rating for nine symptoms: fatigue, dizziness, headache, unreality, hearing, vision, mood change, discomfort and hallucination. Motov et al's prospective, randomised, double-dummy study comparing the same dose, 0.3 mg/kg, by IV push over 5 minutes to IV infusion over 15 minutes showed that the analgesic efficacy over 15 minutes was comparable, but the infusion group had a far lower rate of feelings of unreality, 54 per cent versus 92 per cent for the push group[14]. There was also a marked difference in the severity of the feeling of unreality at 5 minutes: 46 per cent with the most severe rating of 4 in the IV push group versus 17 per cent in the infusion group. Although there was no statistical difference in the median score for unreality at 15 minutes, their box and whisker plot reproduced in figure 1 shows that some patients in both groups still scored it as severe.

Figure 1. Severity of feeling of unreality (according to SERSDA severity score). Reproduced with permission from Motov S et al, American Journal of Emergency Medicine 35(8):1095–1100, 2017. Copyright © 2017 Elsevier Inc



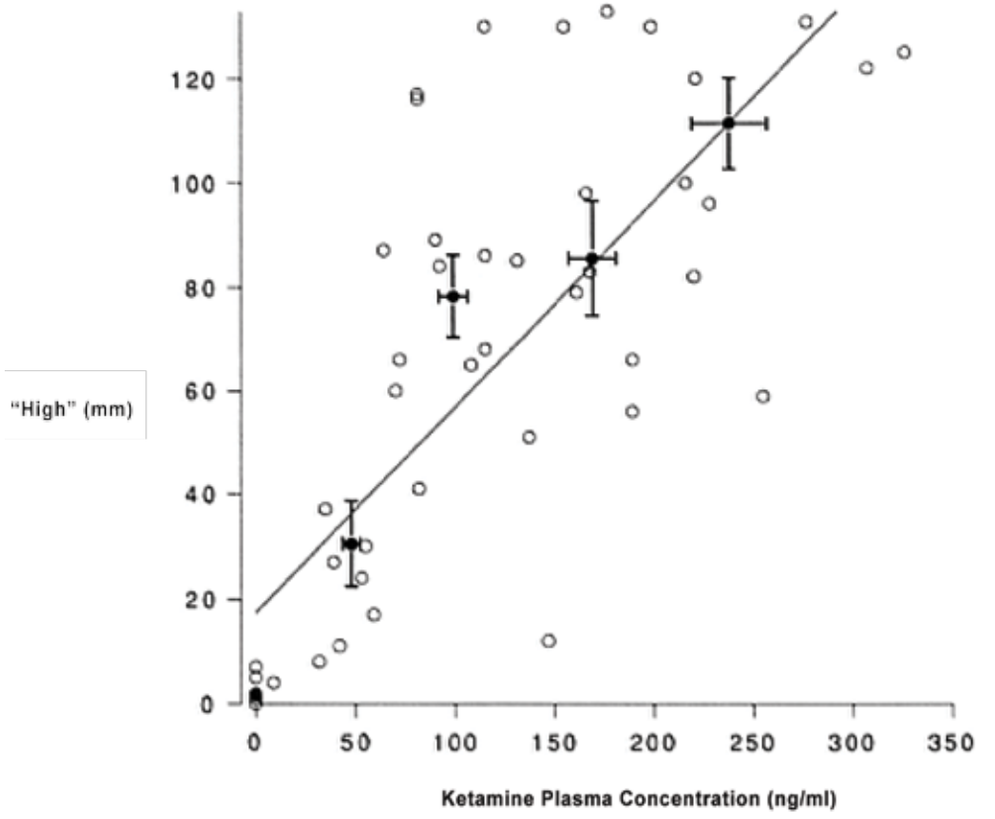
[1] Median SERSDA severity score for feelings of unreality declined to 0 by 60 minutes; results for subsequent time points not shown.

EFFECTS OF KETAMINE: RELATION TO DOSE

The anaesthesia induced by bolus IV ketamine in the range of 1.0-2.0 mg/kg is of rapid onset but only lasts from five to eight minutes, with the longer times for the elderly and very young[8]. This is readily explained by ketamine's high lipid solubility, rapid brain penetration and rapid redistribution, as revealed in pharmacokinetic studies by Clements and Nimmo[15] and Domino et al[16]. In early studies of patients given larger doses of ketamine, conscious responses returned when plasma concentrations were in the range 700-1120 ng/ml after an initial 2.2 mg/kg IV bolus[16,17], and when plasma levels were below 640 ng/ml after an IV infusion was ceased[18]. The analgesic effects of smaller doses of 0.125 mg/kg and 0.25 mg/kg in volunteers were almost immediate, but lasted less than 5 and 10 minutes respectively: Clements and Nimmo estimated that the analgesic effects of ketamine were present when the plasma concentrations were as low as 100 ng/ml[15]. There is evidence that ketamine in "very low" doses, given by infusion at the rate of 1 mg/kg/24 h, can still provide significant analgesic effects, especially in opioid tolerant patients[19]. Weinbroum has shown that in many patients a single IV dose of 0.25 mg/kg ketamine combined with 0.015 mg/kg morphine in the post-anaesthesia care unit had an almost immediate onset and long lasting effect that exceeded two hours, in the context of patients who still had severe pain despite more than 0.1 mg/kg morphine in the preceding 30 minutes after surgery[20]. These observations suggest that extremely low plasma levels of ketamine, especially in opioid tolerant patients or those with opioid resistant pain, have the potential to be efficacious. Whether Weinbroum would have observed similar results with lower doses remains to be studied. Bell et al have conducted a systematic review of perioperative ketamine, given by various routes and at various times, to assess its effectiveness and adverse effects in the treatment of post-operative pain[6]. They concluded that in 27 of 37 trials it was beneficial, in 10 it was not. Overall adverse effects were either mild or absent: in 21 of 27 trials there were no reports of dysphoric effects, bad dreams or hallucinations, but in four trials there were reports of such effects. In the trial by Burstal et al using patient controlled analgesia (PCA) post abdominal hysterectomy, the control group had 1 mg bolus morphine and the ketamine group received 1 mg morphine plus 2 mg ketamine PCA bolus: 10 patients of 37 in the ketamine group withdrew prematurely from the trial due to adverse side effects, four of these stating dysphoria as the cause, compared to 1 of 33 withdrawing in the control group due to nausea. They did not report any significant difference in pain scores, morphine consumption, nausea scores or even patient satisfaction[21]. Bell et al attempted to estimate from the trials if ketamine exerted a dose related effect, and concluded: "Interestingly there seemed to be no increased morphine sparing effect on increasing the ketamine dose above an estimated dose of 30 mg/24 hours"[6]. Thus although the use of ketamine is not always efficacious, there may be little advantage in using higher doses for effect: 30 mg/24 hours for an average adult would place the dose in the "very low" dose range used in cases reported by Bell[19]. Other controlled studies have shown beneficial effects of ketamine for post operative pain relief when given by infusion for 24 hours at the low rate of 2 microgram/kg/h, albeit preceded by a bolus dose either after induction of anaesthesia, 0.2 mg/kg[22], or immediately post-operatively, 0.5 mg/kg[23].

The relationship between low doses of ketamine and its psychic effects has been studied by Bowdle et al[24] in 10 young healthy male volunteers using a target controlled infusion to achieve steady target blood levels. They used pharmacokinetic parameters derived from 2.2 mg/kg IV bolus doses in eight male volunteers[16]. Target levels of 0, 50, 100, 150 and 200 ng/ml were maintained for 30 minutes each, and subjects asked to give a visual analogue scale (VAS) rating to each of 13 descriptors of the mental experience 20 minutes into each level period. The conclusion was that even in these very low doses ketamine produces psychedelic effects strongly correlated with doses above 50 ng/ml for all 13 descriptors, with the average VAS score at the target 200 ng/ml being highest for the "HIGH"(111), "SURROUNDINGS"(87), "TIME"(84) and "UNREALITY"(79) descriptors. Close examination of their correlation of the "HIGH" attribute with measured drug levels, shows in figure 2, that despite the high correlation with the average of the target levels, that any actual measured levels above 100 ng/ml are capable in some subjects of eliciting very high scores on the "HIGH" attribute. Given the opportunity to describe the experience after the study, subjects included the following responses: "floating, very carefree feelings throughout entire body"; "felt so different. Wasn't able to describe the way I was feeling"; "floating in space"; "almost complete annihilation of physical self, shrunken"; "dizzy, shaky, lightheaded"; "The experience seems to be a mystical experience, an incomprehensible comprehension of the universe. There seemed to be no past, present or future, no time, just existence. Life and death at the same time."

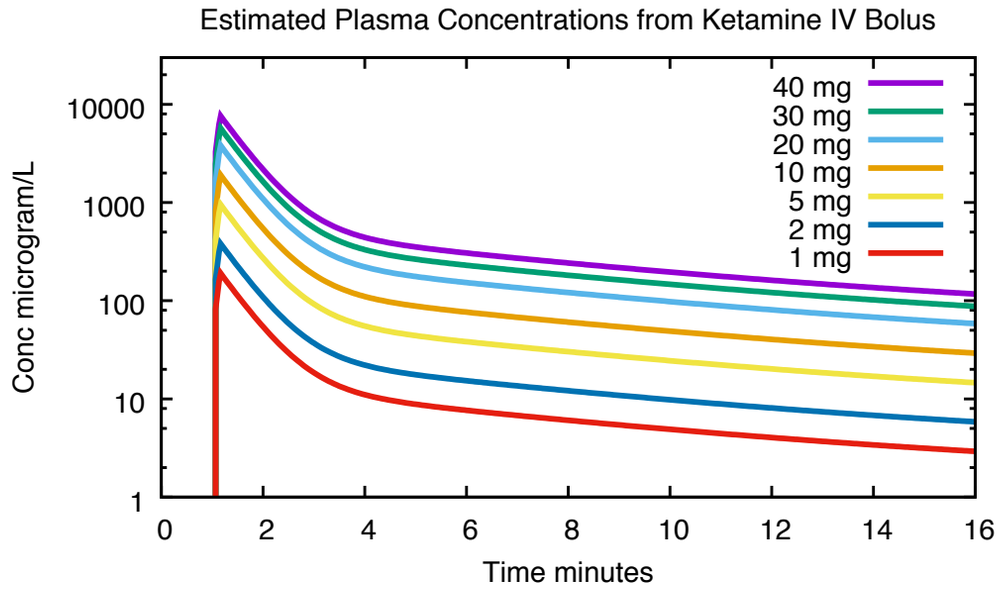
Figure 2. Visual analogue scores for scale item HIGH ("I felt high") are plotted versus ketamine plasma concentrations. Each open circle represents one pair of data points. Mean values (± SEM) are shown for each target concentration step (closed circles). Targets were 0, 50, 100, 150, and 200 ng/ml. The fit of the data by linear regression is indicated by the line. Reproduced with permission from Bowdle T A et al, Anesthesiology 88(1):82–88, 1998. Copyright © 1998, Wolters Kluwer



Note: microgm/L = ng/ml

As an indication of what low doses are required for these very low, but still mind-altering blood levels, 10 mg of ketamine infused IV steadily over 30 minutes reaches a mean peak plasma level close to 125 ng/ml[25]. Predicted plasma levels calculated using the pharmacokinetic parameters of Domino et al[16] show in figure 3 that even very low IV bolus doses such as 5 mg are likely to transiently reach much higher peak plasma levels than those used in the study by Bowdle et al, and have the potential to cause immediate dysphoria.

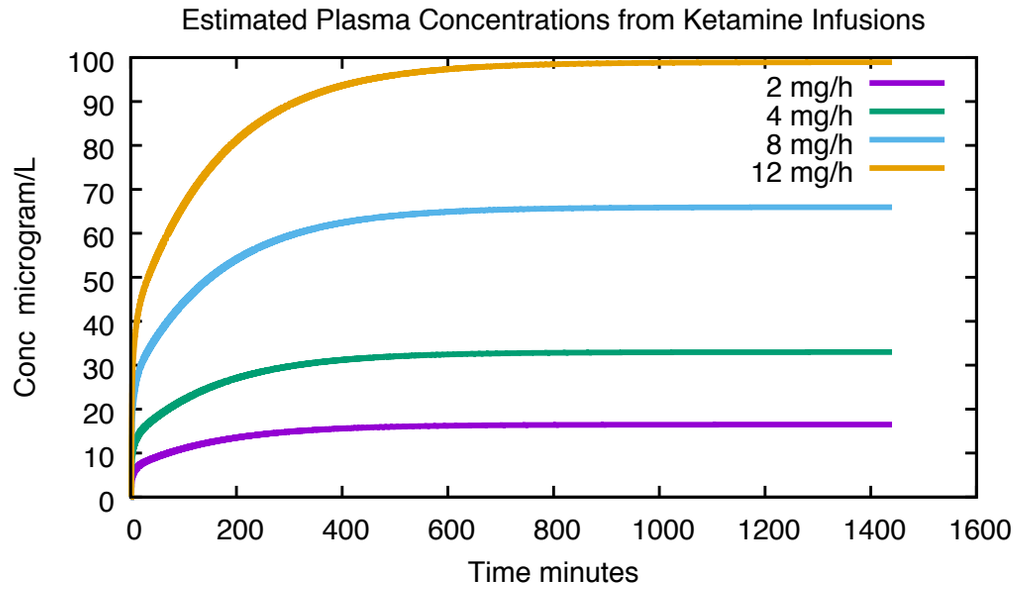
Figure 3. Calculated plasma concentrations of ketamine following an IV bolus of doses ranging from 1 to 40 mg, using the pharmacokinetic parameters derived by Domino et al[16]



Contemporaneously with Bells 1999 description[19], the Acute Pain Service at the Royal Adelaide Hospital has used low dose continuous IV infusions of ketamine at a rate of 2, 4 and 8 mg/h to facilitate analgesia, usually in combination with opioids delivered by PCA, predominantly in opioid tolerant patients, and after limb amputation, but also in opioid naive patients whose pain has been difficult to control, often with considerable beneficial effect. As for side effects, vivid, usually non-distressing dreams when the eyes are closed are commonly the first manifestation of psychotomimetic effects which are usually only evident in a small percentage patients receiving 8 mg/hr, but occasionally at lower doses, especially in the elderly where only 2 and 4 mg/hr are prescribed. At 12 mg/h they are more common. Figure 4 shows the calculated blood levels of ketamine from constant IV infusions of 2, 4, 8 and 12 mg/h using the three compartment pharmacokinetic parameters derived by Domino et al[16]. Doses higher than 12 mg/h are much more likely to induce undesirable dysphoric effects in many, but not all, patients. Having experienced these effects many patients are reluctant to have the drug again, even at lower doses where some benefit may have been derived. As an indicator of the potency of the drug, at the target level of 200 ng/ml in the study by Bowdle et al, all patients experienced lateral gaze nystagmus[24]. After prolonged infusions, the effect of the major metabolite of ketamine, norketamine, which is pharmacologically active as an NMDA glutamate receptor antagonist, needs to be taken into account, and the infusion rate may need to be reduced. Norketamine reaches a stable blood level approximately one third that of ketamine and there is some suggestion that it may contribute significantly to the relief of pain, especially neuropathic pain[26,27].

From figure 4 it is seen that the predicted steady state plasma level of ketamine from an 8 mg/h infusion is about 65 ng/ml. This is close to the same level achieved by a recent novel sublingual wafer formulation of 25 mg ketamine, with a bioavailability of 29 per cent, developed by Rolan et al[25]. Unfortunately this is not yet available for clinical use, as it could offer a very useful adjunct for the control of brief procedural or incidental pain with minimal risk of dysphoria. Eide et al measured levels of ketamine after prolonged subcutaneous infusions (which after several days cause painful induration at the infusion site): 0.1 mg/kg/h gave a median of 0.6 micromol/L or 142 ng/ml[13], higher than the predicted levels using the parameters of Domino et al.

Figure 4. Calculated plasma concentrations of ketamine during constant IV infusions of ketamine at 2, 4, 8 and 12 mg/h, using the pharmacokinetic parameters derived by Domino et al[16]



CONCLUSION

Ketamine is a useful drug as an adjunct for pain control, especially in opioid tolerant patients or in those whose pain is poorly responsive to opioids. Unfortunately it also has the potential to cause acute and potentially severe dysphoria which is often unable to be clearly expressed or articulated by patients at the time they are experienced. This adverse effect is generally dose related, and is usually most severe when larger doses of ketamine are administered (to unanaesthetised patients) by IV bolus. But it may also occur with very small bolus doses, and although less often, with low dose intravenous infusions. Fortunately, the analgesic effects are manifest at very low blood concentrations. Avoiding bolus doses and starting infusions at very low rates such as 2 or 4 mg/h, before gradually increasing them to 4 or 8 mg/h if there are no adverse effects may help to achieve the desired analgesic outcomes, while minimising the risk of the adverse dysphoric effects. Not all patients respond to ketamine, and increasing the infusions to higher doses where predicted plasma levels exceed 100 ng/ml may provide little extra clinical benefit with a greater risk of patients subsequently refusing to continue to have any of the drug due to dysphoria. Providing ketamine to patients to self administer would require caution due to its abuse potential.

REFERENCES

1. Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. Acta Pharmacol Sin. 2016;37(7):865–872.
2. Hasselmann HWW. Ketamine as antidepressant? Current state and future perspectives. Curr Neuropharmacol. 2014;12(1):57–70.
3. Ahern TL, Herring AA, Anderson ES, Madia VA, Fahimi J, Frazee BW. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. Am J Emerg Med. 2015;33(2):197–201.
4. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 1999;82(2):111–125.
5. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg. 2004;99(2):482-495.
6. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1);CD004603.
7. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Med. 2015;16(2):383–403.
8. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg. 1966;45(1):29–40.
9. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370–380.

10. Advisory Council on the Misuse of Drugs. ACMD ketamine: a review of use and harm [Internet]. London: the Government of the United Kingdom, 2013. Available from: https://www.gov.uk/ government/publications/ketamine-report. Accessed 17 October 2017.
11. Hans P, Dewandre PY, Brichant JF, Bonhomme V. Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia. Br J Anaesth. 2005;94(3):336–340.
12. Galinski M, Dolveck F, Combes X, Limoges V, Smail N, Pommier V, et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. Am J Emerg Med. 2007;25(4):385–390.
13. Eide K, Stubhaug A, Oye I, Breivik H. Continuous subcutaneous administration of the N-methyl-D-aspartic acid (NMDA) receptor antagonist ketamine in the treatment of post-herpetic neuralgia. Pain. 1995;61(2):221–228.
14. Motov S, Mai M, Pushkar I, Likourezos A, Drapkin J, Yasavolian M, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. Am J Emerg Med. 2017;35(8):1095–1100.
15. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. Br J Anaesth. 1981;53(1):27–30.
16. Domino EF, Domino SE, Smith RE, Domino LE, Goulet JR, Domino KE, et al. Ketamine kinetics in unmedicated and diazepam-premedicated subjects. Clin Pharmacol Ther. 1984;36(5):645–653.
17. Little B, Chang T, Chucot L, Dill WA, Enrile LL, Glazko AJ, et al. Study of ketamine as an obstetric anesthetic agent. Am J Obstet Gynecol. 2017;113(2):247–260.
18. Idvall J, Ahlgren I, Aronsen KF, Stenberg P. Ketamine infusions: pharmacokinetics and clinical effects. Br J Anaesth. 1979;51(12):1167–1173.
19. Bell RF. Low-dose subcutaneous ketamine infusion and morphine tolerance. Pain. 1999;83(1):101–103.
20. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesth Analg. 2003;96(3):789–795..
21. Burstal R, Danjoux G, Hayes C, Lantry G. PCA ketamine and morphine after abdominal hysterectomy. Anaesth Intensive Care. 2001;29(3):246–251.
22. Urban MK, Ya Deau JT, Wukovits B, Lipnitsky JY. Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. HSS J. 2008;4(1):62–65.
23. Guillou N, Tanguy M, Seguin P, Branger B, Campion JP, Mallédant Y. The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. Anesth Analg. 2003;97(3):843–847.
24. Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology. 1998;88(1):82–88.
25. Rolan P, Lim S, Sunderland V, Liu Y, Molnar V. The absolute bioavailability of racemic ketamine from a novel sublingual formulation. Br J Clin Pharmacol. 2014;77(6):1011–1016.
26. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. Br J Anaesth. 1981;53(8):805–810.
27. Fitzgibbon EJ, Hall P, Schroder C, Seely J, Viola R. Low dose ketamine as an analgesic adjuvant in difficult pain syndromes. J Pain Symptom Manage. 2002;23(2):165–170.

Brain / Neuro

Acute management of stroke

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INTRODUCTION

This chapter provides an overview of the current practice in the management of acute stroke, including its definition, epidemiology, pathophysiology and management of both ischaemic and haemorrhagic stroke. The last section describes the risks factors of peri-operative strokes and the pre-operative considerations.

DEFINITION

Stroke is a broad diagnostic concept, which refers to an acute brain insult of vascular origin. Typically stroke presents as an acute and focalised neurological deficit related to the affected brain area.

The current World Health Organization (WHO) defines stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin”[1].

There are two main types of stroke: ischaemic stroke, which is the most common, and haemorrhagic stroke. Haemorrhagic stroke includes subarachnoid and intracerebral haemorrhage. Subarachnoid haemorrhage has different pathophysiology and management, and is not covered in this chapter.

Recent definitions of stroke include not only clinical but also “tissue” criteria[2]. This allows the differentiation of ischaemic and haemorrhagic stroke.

According to these new definitions:

- Ischaemic stroke is characterised by “evidence of central nervous system infarction based on pathological, imaging, or other objective evidence or clinical evidence of focal ischaemic injury based on symptoms persisting ≥24 hours or until death, and the exclusion of other aetiologies”.
- Intracerebral haemorrhage corresponds to “rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma”.

The WHO definition is based on the duration of clinical symptoms and excludes patients with a brief neurological deficit (<24 hours), which were typically referred as transient ischaemic attack (TIA) instead of stroke. However, many of those patients will have demonstrable infarction or haemorrhage on imaging and will now be classified as stroke.

STROKE EPIDEMIOLOGY

Stroke is a major health burden. It accounts for 11.8 per cent of the total mortality worldwide[3]. Stroke is the second leading cause of death in people between 15 and 59 years and the fifth leading cause of death in people aged over 60 years[4]. There are 15 million people worldwide who suffer a stroke each year, and one in six people will have a stroke in their lifetime[4]. In 2017, there will be almost 56,000 new and recurrent strokes in Australia, equivalent to one stroke every nine minutes (Deloitte Access Economics). Two per cent of Australians have had a stroke at some stage in their lives and over one third of these have a disability resulting from their stroke (AIWH data).

The most common type of stroke in Western countries is ischaemic stroke which represents 80-90 per cent of strokes. In Asia, intracerebral haemorrhages are more common and tend to be of smaller size, representing up to 40 per cent of the strokes in some regions[5-7]. This difference has been attributed to diet, lifestyle or environmental factors rather than genetics but this remains uncertain.

PRINCIPLE OF MANAGEMENT OF STROKE

Successful management of stroke relies on a system of care that can detect and fast-track patients to the definitive treatment in the shortest possible time. Recovery and postoperative care areas should be protocolised to enable this objective.

"FAST" is a commonly used algorithm used to raise awareness about stroke in the community, and applied by para-medical staff. This is a reasonable screening procedure for monitoring in recovery areas. This stands for Face: unilateral facial weakness, Arm: unilateral arm weakness, Speech: speech disturbance and Time: known time of onset and time to call the emergency number. Unilateral symptoms should be regarded as possibly stroke related. Speech disturbance may require a more sophisticated examination as differentiating aphasias from post-operative confusion and delirium can be difficult. History and clinical examination remains the key to diagnosis because early first-line imaging is often normal or subtly abnormal. Long periods of observation of patients with suspected stroke are inappropriate as the yield for intervention is very high in the first hours and reduces rapidly after this.

The subsequent management requires a multidisciplinary team and stroke protocols to ensure early notification, recognition and treatment of stroke occurring in hospital or presenting to the emergency department. This has proven to improve patients' outcomes and most institutions have "stroke teams" in place.

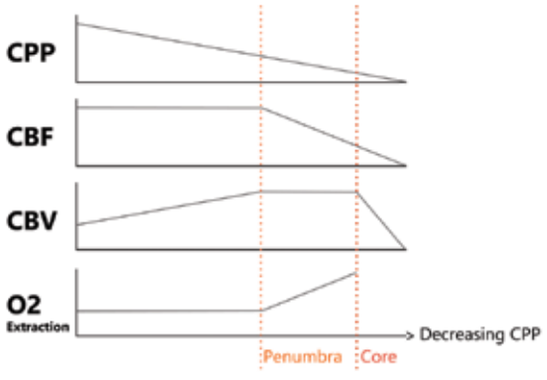
ISCHAEMIC STROKE

Pathophysiology

In its typical scenario, stroke results from an acute occlusion of a cerebral artery by a thrombotic embolus. This leads to an irreversible infarction of the supplied brain tissue (core), surrounded by an area of hypo-perfused brain (penumbra). The relative size of the core and penumbra depends on the performance of the collateral circulation.

Following vessel occlusion, cerebral perfusion pressure (CPP) decreases in the affected brain region. Physiological autoregulation can maintain cerebral blood flow via dilation of small vessels and recruitment of collaterals. There is a measurable increase in cerebral blood volume in this area. Beyond maximum autoregulation, cerebral perfusion falls from the normal level of 50 mL/100 g/min, and oxygen extraction increases. When the perfusion reaches a level around 18-20 mL/100 g/min, the brain tissue becomes electrically silent[8] but remains viable and salvageable if perfusion is restored[9]. This is the penumbra whose concept was first described by Astrup in 1981[8]. If cerebral perfusion further decreases below 10 mL/100 g/min, neuronal cell death occurs. Circulating cerebral blood volume in this area rapidly diminishes. This is the core infarction. The concept of mismatch relates to the volume difference between the core and penumbra. If reperfusion does not occur, the penumbra decreases in size, increasing the core. Figure 1 illustrates these concepts. Modern management of stroke is based upon urgent confirmation of acute ischaemia with salvageable tissue.

Figure 1. Cerebral physiology in stroke
CPP = cerebral perfusion pressure; CBF = cerebral blood flow; CBV = cerebral blood volume



Investigations

Whether a patient presents with a suspected stroke in the operating theatre, the recovery ward or the emergency department, eligibility for thrombolysis should be determined to ensure timely treatment.

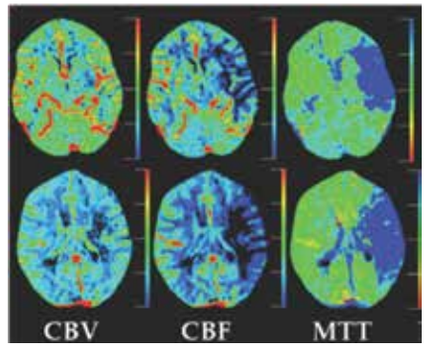
Following review of history and confirmation of timing, the initial non-contrast CT scan is primarily aimed at excluding an intracerebral haemorrhage which will appear as a hyperdensity. Patients with ischaemic stroke are likely to have a normal CT scan or show early ischaemic changes such as loss of the insular ribbon[10], attenuation of the lentiform nucleus[11], or subtle white matter hypodensity. A hyperdense vessel[12] is often suggestive of an intraluminal thrombus.

In the past few years, imaging techniques have evolved to image not only the ischaemic core of a stroke but also the surrounding penumbra. In a CT perfusion, continuous cine imaging of the brain is acquired following a bolus injection of contrast. Dynamic change in density of regions centered on arterial and tissue structures allows to derive a mapped cerebral blood volume (CBV: area under the curve in parenchymal pixels divided by area under the curve in arterial pixels) and mean transit time (MTT derived from the density curve of the arterial pixels). The cerebral blood flow can also be calculated (CBF=CBV/MTT).

The penumbra is the area with decreased CBF and normal or mildly increased CBV. These are sometimes described as area of CBV/MTT mismatch. The ischaemic core is the area with markedly decreased CBF and decreased CBV.

Similarly, MRI perfusion imaging can identify the penumbra. The ischaemic core is seen on MRI diffusion sequences (see figure 2).

Figure 2. CT perfusion of a patient with a left MCA stroke, showing a large area of potentially salvageable penumbra (CBF and MTT maps), with a small volume core infarction (CBV map)



It is important to outline that current perfusion imaging techniques have many limitations. Processing algorithms are non-standardised across vendors and reference diagnostic criteria cannot be firmly established. They have a high specificity, but the false negative rate is estimated at about 20-30 per cent and a negative study should not contraindicate thrombolysis. Those techniques have an important role in research and often have a value in the assessment of late presentations of strokes.

Delays in obtaining and processing sophisticated imaging techniques should not delay treatment. Where there is clinical evidence of a new focal neurological deficit and a normal non-contrast CT scan, IV thrombolysis is indicated and should be commenced without delay.

An intra-arterial thrombus can be visualised using CT angiography. MR angiography is an alternative technique but unless contrast is used, it has a poorer definition than CT angiography for medium and small intracranial vessels. These modalities are used to detect a potential target for interventional radiology procedures (thrombectomy). They are taking a larger place in the investigation of stroke.

After the acute phase, ischaemic stroke will require additional investigations to determine an underlying etiology and offer secondary prevention. Typically, these will include imaging of the extracranial vessels, imaging of the heart and in-hospital monitoring of heart rate in a stroke unit to detect atrial fibrillation. In the absence of confirmed cause, implantable loop recorders or external portable monitoring devices will often be considered as these provide a six-fold increase in the rate of detection of atrial fibrillation[13,14].

Treatment

Contrary to intracerebral haemorrhage, ischaemic stroke is a rapidly changing area of medicine that has witnessed important therapeutic advances over the last decade. For this reason, early identification and investigation of peri-operative and post-operative stroke is imperative.

The treatment options for acute ischaemic stroke include intravenous thrombolysis and thrombectomy. Patients with perioperative stroke are ineligible for thrombolysis but are still eligible for thrombectomy.

Thrombolysis

Acute stroke patients with no major bleeding risk identified on history, no proven coagulopathy and a brain CT scan that excludes a haemorrhage or a non-vascular cause are potentially eligible for intravenous thrombolysis.

Important contraindications include:

- Platelet count <100,000mm^3, INR >1.7 (including from warfarin) or novel anticoagulant therapy with the last dose within 48 hours unless a reversal agent is available.

However, thrombolysis is not delayed while waiting for coagulation testing results; practically, the history combined with point of care INR if needed is sufficient to initiate thrombolysis.

- Major surgery within the past 14 days, cranial or spinal surgery and major head trauma within three months are relative contraindications and the risks and benefits have to be assessed by the treating teams.

Recombinant tissue plasminogen (Actilyse® or Alteplase®) is given at 0.9 mg/kg with a maximum of 90 mg. Usually 10 per cent of the dose is administered as a bolus followed by a one-hour infusion of the remaining dose.

Current guidelines recommend initiation of thrombolysis within the first 4.5 hours[15] after onset of stroke for patients to benefit. The effect of Alteplase® is time-dependent with an average improvement in disability free survival of 10 per cent if treated early (within 3 hours) and 5 per cent if treated between 3 and 4.5 hours[16]. The number needed to treat (NNT) to return to independence rises rapidly, from 4.5 to 14 between 1.5 hours and 4.5 of onset. The risk of symptomatic intracerebral haemorrhage is approximately 7 per cent[17] and there are few, if any, therapeutic options in this event. Patients with diabetes, those with the presence of a hypodensity on the initial CT scan and a severe neurological deficit are at higher risk. The average absolute increase in risk of early death due to thrombolysis related intracerebral haemorrhage is 2 per cent[16].

Alteplase® is the only drug currently approved for intravenous thrombolysis in Australia. There are ongoing trials for Tenecteplase®[18,19], which is logistically easier to administer.

Alteplase® is potentially beneficial beyond 4.5 hours. The risk of haemorrhagic transformation does not increase further after 4.5 hours if strict inclusion criteria are applied[20]. This requires advanced imaging to confirm the presence of salvageable brain and limited size established infarction.

Thrombectomy

Patients with proximal intracranial occlusion of large blood vessels respond poorly to intravenous thrombolysis and have a poor prognosis with 69-80 per cent mortality at 90 days[21].

Endovascular clot retrieval is a novel approach in carefully selected patients. It can be safely done in large, highly resourced stroke centres which require a regional organisation of stroke services with inter-hospital transfer of patients to a thrombectomy centre. The basic principle of thrombectomy is aspiration of the clot with a retrieval device (e.g. Solitaire FR® and TREVO®). It sometimes also involves stenting of the affected vessel.

Current selection criteria replicate those used in clinical trials which have included patients with large anterior circulation vessel occlusions: middle cerebral artery occlusion, or intracranial carotid bifurcation occlusion with involvement of anterior cerebral artery and middle cerebral artery segments (also called “carotid T” occlusion).

Since 2015, nine positive trials have demonstrated the benefit of endovascular clot retrieval for large vessel ischaemic stroke up to six hours after symptom onset[22-30]. The NNT with endovascular therapy within six hours is three to reduce disability by one point or more on the modified Rankin scale (a scale of disability ranging from zero to six, no disability to death); a more powerful effect than most medical interventions today. The procedure does not lead to an excess of mortality when compared to thrombolysis.

A meta-analysis[31] of five of these trials suggested a benefit up to 7.3 hours. This has recently been confirmed in the DAWN trial, which demonstrates a benefit up to 12 hours after stroke onset in selected patients (unpublished at the time of redaction of this chapter, released at the European Stroke Organization Conference in May 2017).

Endovascular therapy should not prevent the initiation of intravenous thrombolysis where this is indicated, and intravenous thrombolysis should not delay clot retrieval.

Endovascular treatment of acute ischaemic stroke requires that patients are immobilised during the procedure; either with general anesthesia or sedation. Both techniques have potentials drawbacks. General anesthesia can introduce avoidable delays and additional risks. On the other hand, there are concerns about patients’ movements interfering with the procedure. Retrospective studies had suggested a worse outcome in the general anaesthesia group, perhaps due to peri-operative hypotension, hypocapnia and attenuated cerebral autoregulation[32]. However, this finding could also be explained by the larger proportion of severe strokes in the general anaesthesia group[33]. Two recent prospective clinical trials comparing conscious sedation with general anaesthesia showed no significant difference in terms of neurological outcomes[34,35]. This supports the choice of either technique, and conversion from sedation to general anaesthesia if required.

General measures

Prior to thrombolysis, blood pressure target should be <185/110 mmHg (consensus-based recommendation). There is no evidence to support acute lowering of blood pressure beyond these numbers. However, the question is being assessed by ongoing clinical trials.

There is no evidence to prescribe blood pressure parameters during endovascular procedure but maintaining within the physiological range (systolic 110-160 mmHg) appears reasonable and is recommended by some authors[36].

Following thrombolysis or thrombectomy, most patients will be admitted to a stroke unit or high-dependency unit for close observation during the first 24 hours. During this period, naso-gastric tube insertion and non-compressible arterial punctures are proscribed; venopuncture and compressible arterial puncture should be minimised and pressure should be applied for 30 minutes.

Antiplatelets drugs are usually initiated 24-48 hours after intravenous thrombolysis or thrombectomy but might be required earlier and with dual antiplatelet therapy if a stent is placed. A post-treatment CT scan is usually performed the next day. This will assess for haemorrhagic transformation and for large size established infarctions prior to starting antithrombotics.

Special case of malignant middle cerebral artery infarction

A middle cerebral artery stroke occupying at least two thirds of the middle cerebral artery territory and associated with brain oedema is defined as a malignant middle cerebral artery stroke. This type of stroke can lead to midline shift and herniation, and has a poor prognosis with ~80 per cent mortality[37,38]. None of the attempts to reduce edema such as hypothermia or mannitol have been successful in altering this outcome.

Decompressive craniectomy with removal of part of the skull to allow the expansion of the brain and prevent herniation has been shown to halve patients’ mortality. Those patients survive with at least a moderate disability[39,40]. The dominance or non-dominance of the affected hemisphere can be an important consideration in the decision making process.

Patients less than 60 years old should be considered for decompressive craniectomy within the first 48 hours of onset[41,42]. Surgery might be considered in elderly patients depending on premorbid status and patients’ preferences[39].

INTRACEREBRAL HAEMORRHAGE

Physiopathology

The rupture of a small diameter blood vessel is the cause of most intracerebral haemorrhages. Common mechanisms leading to vessel damage are hypertension and accumulation of amyloid protein in cerebral amyloid angiopathy. Less frequent causes include vascular malformation, drugs, trauma or malignancy.

In the first few hours after the initial haemorrhage, one third of the haemorrhages grow by ~30 per cent in size[43-45]. This growth is most likely to occur if haemorrhages are of large size[46], have an irregular shape, heterogeneous density[47,48] or the patient is on anticoagulants[49,50].

Expansion into the ventricles and the subarachnoid space can occur in haemorrhages located in the deep white matter or basal ganglion region or, in a cortical region of the brain, respectively. Expansion to these structures is associated with poor outcome related to chemical meningitis and risk of acute hydrocephalus[51-53].

On CT angiography, rapid extravasation of contrast[54] has led to the description of a “spot sign”[55,56], a tiny area of hyperdensity within the haemorrhage which is thought to relate to ongoing bleeding. This has been shown to be associated with poor outcome[57].

The mass effect of the haemorrhage is increased by the development of oedema secondary to injury to the brain parenchyma.

Management

Intracerebral haemorrhage is the most severe type of stroke. Therapeutic options are limited. Treatments strategies have attempted to reduce the haematoma size and growth, reduce the edema, and control the local or global mass effect.

In large haemorrhage and symptomatic large volume edema, hypertonic saline[58] and mannitol are commonly used[59], although the efficacy of the latter is not confirmed[60].

Surgery

Surgery is indicated to evacuate the haematoma in posterior fossa haemorrhages, and for acute hydrocephalus.

In other situations, surgery has not shown to improve patients’ outcome[61,62]. Procedures to evacuate superficial haemorrhages are sometimes performed as the operation appears potentially less invasive, but there is little evidence to support this management[63]. A minimally invasive surgery to evacuate the haematoma through a burr hole is currently investigated in a randomised controlled trial[64].

In larger haemorrhage complicated by mass effect, decompression and haematoma evacuation may be lifesaving but long term disability is a central consideration.

Haemostatic therapy

Despite hope to minimise the effect of haematoma growth, recombinant activated factor VIIa has not shown a benefit in terms of disability[65,66].

Platelet transfusion in patients on antiplatelet therapy has been found to be detrimental[67].

Blood pressure control
In the "Intensive blood pressure lowering trial in acute cerebral haemorrhage", INTERACT pilot trial, blood pressure lowering showed a promising effect on haematoma growth[68]. This effect was not confirmed in the main trial. Nonetheless, acute lowering of the blood pressure in the first six hours of onset of cerebral haemorrhage has shown a modest improvement in disability in survivors[69].

Reflecting this, the American Heart Association and American Stroke Association (AHA/ASA) management guidelines for ICH were updated in 2015[68] to support the safety and potential benefit of lowering systolic blood pressure to 140 mmHg.

PERI-OPERATIVE STROKE

Epidemiology
A perioperative stroke is defined as one that occurs either intra-operatively or in the post-operative period within 30 days[70]. Perioperative strokes are associated with an increased length of stay and a six-fold increased mortality[71,72].

Any combination of surgery and anaesthesia is associated with an increased risk of stroke irrespective of the type of surgery[73]. This may relate to coagulation changes[74,75].

The most common type of perioperative stroke is ischaemic stroke of embolic origin (heart or aorta). Hypotension is rarely the cause of perioperative stroke[76,77]. Haemorrhagic stroke is uncommon[70,78], which probably reflects the fact that severe hypertension during anaesthesia is a rare event, and anticoagulants have typically been withheld.

The risk of perioperative stroke varies depending on the type of the surgery and patients' risk factors.

Procedural risk
Urgent surgery is associated with an increased risk of stroke when compared to elective surgery[79].

Cardiac, vascular and brain surgeries are defined as "high-risk" as these have an increased risk of stroke when compared to other types of surgery. Valvular and aortic repair surgeries have a stroke risk as high as 8 to 10 per cent[70,72,79,80].

Perioperative strokes in non-high-risk surgery are relatively rare and are estimated to have an incidence of about 1/1000 cases[80].

Patients' risk factors
Age, a history of previous stroke or transient ischaemic attack, renal failure, atrial fibrillation and a history of cardiovascular diseases are identified risk factors for perioperative stroke[77,80-82]. Atrial fibrillation is associated with a two-fold increase in the risk of death and stroke after carotid endarterectomy[83,84].

Preoperative consideration
Modifiable risks mostly refer to adequate management of preoperative anticoagulants and antiplatelet drugs, and evaluation of large vessels atheromatous disease.

Anticoagulants and antiplatelet drugs
Many surgical procedures require withholding of anticoagulants. This decision should carefully consider the balance between risk of stroke and risk of bleeding.

Minor bleeding risk procedures such as cataract extraction, dental procedures[85], cutaneous procedures or selected cardiac procedures (pacemaker, defibrillator, endovascular procedures) can be done safely on antithrombotics with adequate local haemostasis.

In most other procedures, warfarin is stopped five days prior to the procedure. Novels anticoagulants have a shorter half-life and therefore can usually be stopped two to three days before the procedure.

The patient's thromboembolic risk determines the need to use bridging therapy with heparin (see table 1). In high risk thromboembolic groups, bridging is required. In the intermediate thromboembolic risk category, the incidence of thromboembolism appears low (~1 per cent)[86] irrespective of whether a bridging strategy is decided or not. Guidelines in this category are therefore less clear.

Table 1. Proposed risk groups for peri-operative stroke (adapted from Douketis et al)[68,86]. MVR: mitral valve replacement; AVR: aortic valve replacement, TIA: transient ischaemic attack, CHADS-2: congestive heart failure, hypertension, age≥75y, diabetes, stroke or TIA

RISK	MECHANICAL HEART VALVE	ATRIAL FIBRILLATION
High (>10%/year)	• All MVR • Cage ball & tilting disc AVR • Stroke / TIA <6months	• CHADS-2 is 5-6 • Rheumatic valvular disease • Stroke / TIA <3 months
Moderate (4-10%/year)	• Bileaflet AVR with at least one CHADS risk factor	• CHADS-2 is 3-4
Low (<4%/year)	• Bileaflet AVR without risk factor	• CHADS-2 is <3

Reintroduction of the bridging heparin and anticoagulants after the procedure is determined by the bleeding risk associated with the surgery: no early bridging in very high-risk situations (major neurosurgical and cardio-vascular surgeries), full 48-72 hours in high risk procedures and 24-48 hours in moderate risk.

Limited evidence exists to guide the perioperative management of antiplatelet therapy. Patients with a history of cerebrovascular disease are considered moderate to high risk for perioperative adverse events. Discontinuation of aspirin prior to surgery is usually not recommended. This might not be applicable to intracranial or prostate surgery, and in patients deemed at high risk of bleeding.

Clopidogrel and Prasugrel are associated with a higher risk of bleeding and preoperative interruption is usually recommended[86].

Large vessels disease
Patients with carotid stenosis are at risk of peri-operative stroke and treatable causes should be addressed prior to planning other surgery.

In stroke patients with a carotid stenosis of ≥70 per cent, carotid endarterectomy has shown to be beneficial[87] and is recommended within the first two weeks after the stroke[88].

Patients with no history of stroke or TIA are not normally candidates for a prophylactic carotid endarterectomy. However, patients in this group who require cardiac surgery may benefit from prior or concomitant revascularisation in high-grade, especially bilateral, stenosis. The preoperative evaluation should include brain imaging by CT scan or MRI in a context of significant carotid stenosis to exclude a silent stroke on the corresponding site, as this would strengthen the argument for carotid revascularisation. Perioperative complications are comparable when carotid endarterectomy is combined or done prior to cardiac surgery[87].

Preventative carotid surgery only prevents 40 to 50 per cent of perioperative stroke in CABG procedures[89]. Another common cause is embolisation from aortic plaques. Preoperative imaging of the aortic arch can help to grade this risk and influence the surgical technique (off-pump or peripheral cannulation).

Timing of surgery after stroke
In the acute phase of an ischaemic stroke, the capacity of the brain to auto-regulate is lowered[9]. Minor fluctuations in blood pressure secondary to anaesthesia, bleeding or haemodynamic fluctuations may lead to under or over perfusion of neurons.

There are sparse recommendations on the timing for elective surgery after a stroke. Some authors suggest that it should be delayed by three to six months after the initial event[90-92]. More recent data from the Danish National Patient Register suggest that patients should be considered at high risk of stroke up to nine months after the initial event. This register included 481,183 non-cardiac surgeries, of which 7137 surgeries (1.5 per cent) were performed in patients with a history of stroke[93].

CONCLUSION

Appropriate pre-operative assessment of stroke risk and safe management of anti-thrombotic medication are the keys to reducing perioperative stroke.

The recent advent of thrombolysis, and especially thrombectomy, have changed the potential outcome of patients with stroke. These therapeutic advances mean that early recognition of stroke symptoms, and timely and adequate management, are critical to offering these patients the best chance of disability free survival. Perfusion imaging techniques can enhance patient selection for interventions and further research.

REFERENCES

1. [No authors listed]. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol. 1988;41(2):105–114.
2. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064–2089.
3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-–e322.
4. Mendis S, Davis S, Norrving B. Organizational update: the World Health Organization global status report on noncommunicable diseases 2014: one more landmark step in the combat against stroke and vascular disease. Stroke. 2015;46(5):e121–e122.
5. Zhang LF, Yang J, Hong Z, Yuan GG, Zhou BF, Zhao LC, et al. Proportion of different subtypes of stroke in China. Stroke. 2003;34(9):2091–2096.
6. Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. Neurology. 2013;81(3):264–272.
7. Inagawa T, Ohbayashi N, Takechi A, Shibukawa M, Yahara K. Primary intracerebral hemorrhage in Izumo City, Japan: incidence rates and outcome in relation to the site of hemorrhage. Neurosurgery. 2003;53(6):1283–1297; discussion 97–98.
8. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. Stroke. 1981;12(6):723–725.
9. Markus HS. Cerebral perfusion and stroke. J Neurol Neurosurg Psychiatry. 2004;75(3):353–361.
10. Truwit CL, Barkovich AJ, Gean-Marton A, Hibri N, Norman D. Loss of the insular ribbon: another early CT sign of acute middle cerebral artery infarction. Radiology. 1990;176(3):801–806.
11. Tomura N, Uemura K, Inugami A, Fujita H, Higano S, Shishido F. Early CT finding in cerebral infarction: obscuration of the lentiform nucleus. Radiology. 1988;168(2):463–467.
12. Schuierer G, Huk W. The unilateral hyperdense middle cerebral artery: an early CT-sign of embolism or thrombosis. Neuroradiology. 1988;30(2):120–122.
13. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370(26):2478–2486.
14. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370(26):2467–2477.
15. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359(13):1317–1329.
16. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014;384(9958):1929–1935.
17. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet. 2012;379(9834):2364–2372.
18. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med. 2012;366(12):1099–1107.
19. Bivard A, Huang X, Levi CR, Spratt N, Campbell BCV, Cheripelli BK, et al. Tenecteplase in ischemic stroke offers improved recanalization: analysis of two trials. Neurology. 2017;89(1):62–67.
20. IST-3 Collaborative Group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379(9834):2352–2363.
21. Schneweis S, Grond M, Neveling M, Schmulling S, Rudolf J, Heiss WD. Intravenous thrombolysis in proximal middle cerebral artery occlusion. Cerebrovasc Dis. 2001;11(3):212–215.
22. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723–1731.
23. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11–20.
24. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within eight hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296–2306.
25. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009–1018.
26. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol. 2016;15(11):1138–1147.
27. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285–2295.
28. Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2017;88(1):38–44.
29. Mocco J, Zaidat OO, von Kummer R, Yoo AJ, Gupta R, Lopes D, et al. Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. Stroke. 2016;47(9):2331–2338.

30. Khoury NN, Darsaut TE, Ghostine J, Deschaintre Y, Daneault N, Durocher A, et al. Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: a randomized care trial. J Neuroradiol. 2017;44(3):198–202.
31. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA. 2016;316(12):1279–1288.
32. Hendén PL, Rentzos A, Karlsson JE, Rosengren L, Sundeman H, Reinsfelt B, et al. Hypotension during endovascular treatment of ischemic stroke is a risk factor for poor neurological outcome. Stroke. 2015;46(9):2678–2680.
33. Brinjikji W, Murad MH, Rabinstein AA, Cloft HJ, Lanzino G, Kallmes DF. Conscious sedation versus general anesthesia during endovascular acute ischemic stroke treatment: a systematic review and meta-analysis. AJNR Am J Neuroradiol. 2015;36(3):525–529.
34. Hendén PL, Rentzos A, Karlsson JE, Rosengren L, Leiram B, Sundeman H, et al. General anesthesia versus conscious sedation for endovascular treatment of acute ischemic stroke: the AnStroke trial (anesthesia during stroke). Stroke. 2017;48(6):1601–1607.
35. Simonsen CZ, Sørensen LH, Juul N, Johnsen SP, Yoo AJ, Andersen G, et al. Anesthetic strategy during endovascular therapy: general anesthesia or conscious sedation? (GOLIATH – general or local anesthesia in intra arterial therapy) A single-center randomized trial. Int J Stroke. 2016;11(9):1045–1052.
36. Evans MRB, White P, Cowley P, Werring DJ. Revolution in acute ischaemic stroke care: a practical guide to mechanical thrombectomy. Pract Neurol. 2017;17(4):252–265.
37. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996;53(4):309–315.
38. Huttner HB, Schwab S. Malignant middle cerebral artery infarction: clinical characteristics, treatment strategies, and future perspectives. Lancet Neurol. 2009;8(10):949–958.
39. Jüttler E, Unterberg A, Hacke W. Hemicraniectomy for middle-cerebral-artery stroke. Author reply. N Engl J Med. 2014;370(24):2347–2348.
40. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, et al. Surgical decompression for space-occupying cerebral infarction (the hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurol. 2009;8(4):326–333.
41. Cruz-Flores S, Berge E, Whittle IR. Surgical decompression for cerebral oedema in acute ischaemic stroke. Cochrane Database Syst Rev. 2012;1:CD003435.
42. Back L, Nagaraja V, Kapur A, Eslick GD. Role of decompressive hemicraniectomy in extensive middle cerebral artery strokes: a meta-analysis of randomised trials. Intern Med J. 2015;45(7):711–717.
43. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. Stroke. 1998;29(6):1160–1166.
44. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. Stroke. 1997;28(12):2370–2375.
45. Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, et al. Determinants of intracerebral hemorrhage growth: an exploratory analysis. Stroke. 2007;38(3):1072–1075.
46. Dowlatshahi D, Smith EE, Flaherty ML, Ali M, Lyden P, Demchuk AM, et al. Small intracerebral haemorrhages are associated with less haematoma expansion and better outcomes. Int J Stroke. 2011;6(3):201–206.
47. Delcourt C, Zhang S, Arima H, Sato S, Al-Shahi Salman R, Wang X, et al. Significance of hematoma shape and density in intracerebral hemorrhage: the intensive blood pressure reduction in acute intracerebral hemorrhage trial study. Stroke. 2016;47(5):1227–1232.
48. Barras CD, Tress BM, Christensen S, MacGregor L, Collins M, Desmond PM, et al. Density and shape as CT predictors of intracerebral hemorrhage growth. Stroke. 2009;40(4):1325–1331.
49. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. Neurology. 2004;63(6):1059–1064.
50. Cucchiara B, Messe S, Sansing L, Kasner S, Lyden P, CHANT Investigators. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. Stroke. 2008;39(11):2993–2996.
51. Chen G, Arima H, Wu G, Heeley E, Delcourt C, Zhang P, et al. Subarachnoid extension of intracerebral hemorrhage and 90-day outcomes in INTERACT2. Stroke. 2014;45(1):258–260.
52. Chan E, Anderson CS, Wang X, Arima H, Saxena A, Moullaali TJ, et al. Significance of intraventricular hemorrhage in acute intracerebral hemorrhage: intensive blood pressure reduction in acute cerebral hemorrhage trial results. Stroke. 2015;46(3):653–658.
53. Bhattathiri PS, Gregson B, Prasad KS, Mendelow AD, STICH Investigators. Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. Acta Neurochir Suppl. 2006; 96:65–68.
54. Goldstein JN, Fazen LE, Snider R, Schwab K, Greenberg SM, Smith EE, et al. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. Neurology. 2007;68(12):889–894.
55. Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, et al. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. Stroke. 2007;38(4):1257–1262.
56. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 1997;28(1):1–5.
57. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. Lancet Neurol. 2012;11(4):307–314.
58. Ziai WC, Toung TJ, Bhardwaj A. Hypertonic saline: first-line therapy for cerebral edema?. J Neurol Sci. 2007;261(1–2):157–166.

59. Hemphill 3rd, JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2015;46(7):2032–2060.
60. Wang X, Arima H, Yang J, Zhang S, Wu G, Woodward M, et al. Mannitol and outcome in intracerebral hemorrhage: propensity score and multivariable intensive blood pressure reduction in acute cerebral hemorrhage trial two results. Stroke. 2015;46(10):2762–2767.
61. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the international surgical trial in intracerebral haemorrhage (STICH): a randomised trial. Lancet. 2005;365(9457):387–397.
62. Prasad K, Mendelow AD, Gregson B. Surgery for primary supratentorial intracerebral haemorrhage. Cochrane Database Syst Rev. 2008(4):CD000200.
63. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet. 2013;382(9890):397–408.
64. Hanley DF, Thompson RE, Muschelli J, Rosenblum M, McBee N, Lane K, et al. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase two trial. Lancet Neurol. 2016;15(12):1228–1237.
65. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2005;352(8):777–785.
66. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2008;358(20):2127–2137.
67. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase three trial. Lancet. 2016;387(10038):2605–2613.
68. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood. 2012;120(15):2954–2962.
69. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368(25):2355–2365.
70. Mashour GA, Moore LE, Lele AV, Robicsek SA, Gelb AW. Perioperative care of patients at high risk for stroke during or after non-cardiac, non-neurologic surgery: consensus statement from the Society for Neuroscience in Anesthesiology and Critical Care. J Neurosurg Anesthesiol. 2014;26(4):273–285.
71. Axelrod DA, Stanley JC, Upchurch GR, Jr., Khuri S, Daley J, Henderson W, et al. Risk for stroke after elective noncarotid vascular surgery. J Vasc Surg. 2004;39(1):67–72.
72. Selim M. Perioperative stroke. N Engl J Med. 2007;356(7):706–713.
73. Wong GY, Warner DO, Schroeder DR, Offord KP, Warner MA, Maxson PM, et al. Risk of surgery and anesthesia for ischemic stroke. Anesthesiology. 2000;92(2):425–432.
74. Rem J, Feddersen C, Brandt MR, Kehlet H. Postoperative changes in coagulation and fibrinolysis independent of neurogenic stimuli and adrenal hormones. Br J Surg. 1981;68(4):229–233.
75. Modig J, Borg T, Bagge L, Saldeen T. Role of extradural and of general anaesthesia in fibrinolysis and coagulation after total hip replacement. Br J Anaesth. 1983;55(7):625–629.
76. Restrepo L, Wityk RJ, Grega MA, Borowicz Jr L, Barker PB, Jacobs MA, et al. Diffusion- and perfusion-weighted magnetic resonance imaging of the brain before and after coronary artery bypass grafting surgery. Stroke. 2002;33(12):2909–2915.
77. Limburg M, Wijdicks EF, Li H. Ischemic stroke after surgical procedures: clinical features, neuroimaging, and risk factors. Neurology. 1998;50(4):895–901.
78. Ng JL, Chan MT, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. Anesthesiology. 2011;115(4):879–890.
79. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, et al. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg. 2003;75(2):472–478.
80. Sharifpour M, Moore LE, Shanks AM, Didier TJ, Kheterpal S, Mashour GA. Incidence, predictors, and outcomes of perioperative stroke in noncarotid major vascular surgery. Anesth Analg. 2013;116(2):424–434.
81. Kikura M, Takada T, Sato S. Preexisting morbidity as an independent risk factor for perioperative acute thromboembolism syndrome. Arch Surg. 2005;140(12):1210–1217; discussion 8.
82. Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. Anesthesiology. 2009;110(2):231–238.
83. Harthun NL, Stukenborg GJ. Atrial fibrillation is associated with increased risk of perioperative stroke and death from carotid endarterectomy. J Vasc Surg. 2010;51(2):330–336.
84. Tu JV, Wang H, Bowyer B, Green L, Fang J, Kucey D, et al. Risk factors for death or stroke after carotid endarterectomy: observations from the Ontario Carotid Endarterectomy Registry. Stroke. 2003;34(11):2568–2573.
85. Dezsi CA, Dezsi BB, Dezsi AD. Management of dental patients receiving antiplatelet therapy or chronic oral anticoagulation: a review of the latest evidence. Eur J Gen Pract. 2017;23(1):196–201.
86. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e326S–e350S.
87. Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, et al. Carotid endarterectomy--an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2005;65(6):794–801.

88. Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev. 2011(4):CD001081.
89. Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. Eur J Vasc Endovasc Surg. 2002;23(4):283–294.
90. Blacker DJ, Flemming KD, Link MJ, Brown RD, Jr. The preoperative cerebrovascular consultation: common cerebrovascular questions before general or cardiac surgery. Mayo Clin Proc. 2004;79(2):223–229.
91. Landercasper J, Merz BJ, Cogbill TH, Strutt PJ, Cochrane RH, Olson RA, et al. Perioperative stroke risk in 173 consecutive patients with a past history of stroke. Arch Surg. 1990;125(8):986–989.
92. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10):1043–1049.
93. Jørgensen ME, Torp-Pedersen C, Gislason GH, Jensen PF, Berger SM, Christiansen CB, et al. Time elapsed after ischemic stroke and risk of adverse cardiovascular events and mortality following elective noncardiac surgery. JAMA. 2014;312(3):269–277.

Decompressive craniectomy in the management of neurological emergencies: An inconvenient truth?

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INTRODUCTION

It is becoming increasingly apparent that our climate is changing. Notwithstanding some of the ongoing scientific debate, it is difficult to detract from the observation that many of these changes have come about because of human activity. The term “an inconvenient truth” succinctly captures the sentiment that what we are observing is in fact the predictable consequences of what may retrospectively be viewed as a relatively short period of human history.

There are many parallels to be drawn within the field of modern medicine. Despite enormous technological advances that have occurred over recent years there may come a time when consideration must be given to the long-term consequences of an acute intervention because it may fail to provide significant clinical benefit and it may leave a person in a condition that the patient, as well as their family, may feel to be overly burdensome and even unacceptable. In these circumstances, the “inconvenient truth” is that not all lifesaving procedures are equal, and in certain circumstances, achieving mere survival at all cost may not be beneficial both to the patients and society as a whole. If this is the case, careful consideration must be given in balancing the benefits and risk of potentially “lifesaving” therapy for cogent ethical reasons. A contemporary example of this issue concerns the use of decompressive craniectomy in the management of neurological emergencies.

DECOMPRESSIVE CRANIECTOMY FOR NEUROLOGICAL EMERGENCIES – THE “RUB”

This is a technically straightforward procedure in which a large segment of the skull vault is temporarily removed, either unilaterally or bifrontally, in order to provide extra space into which the swollen brain can expand. The rationale is that death can be prevented because the brain is no longer confined within the rigid skull compartment and raised intracranial pressure (ICP) that is life threatening and unresponsive to the usual medical management can be successfully controlled.

The procedure first became popular in the early 1970s predominantly in the context of severe traumatic brain injury (TBI)[1-3] and ischaemic stroke[4]. However, the past four decades has seen its use expanded to include a variety of neurological emergencies[5]. Overall the results of these studies appear to provide clear evidence that decompressive surgery can reduce mortality. However, it will not reverse the effects of the pathological condition that precipitated the neurological crisis and although many patients make a good recovery, a significant number remain severely disabled and dependent[6-9]. The acceptability or otherwise of this outcome can difficult to determine however if the result of a “lifesaving” intervention is a young person with severe neurological impairment such that they are totally dependent and have limited ability to communicate a question must arise regarding the wisdom of the clinical decision. The chance of producing such a state has been called the “RUB” (Risk of Unacceptable Badness) and it has a satisfying resonance with its literary source in Shakespeare’s Hamlet[10,11].

In the crucial soliloquy, Hamlet muses: “To sleep, perchance to dream, Aye, there’s the rub”. He is worried about what he should do having been told by a ghost that his uncle (who has since married his mother) murdered his father. He is trying to decide whether he should take revenge based on this possibly suspect information or leave things as they are. He realises that if he acts on demonic information and commits a mortal sin he will of course be damned, but if he fails to avenge his father he cannot live with himself. He thinks about the possibility of suicide and the release of eternal sleep that that would promise, but then he contemplates the possibility that in death one dreams. The prospect of spending eternity dead, and therefore, impotent, but

wracked with the moral torments that have provoked his suicidal thoughts is, to him, an unacceptably bad prospect. He recognises that there is a risk of falling into this unacceptably bad state. He therefore faces the RUB.

The difficulties faced by Hamlet can be compared to the decision to offer a decompressive craniectomy to a young person with a severe head injury. Patients and relatives are often told that there is a probabilistic chance of surviving a serious catastrophe if a certain course of action is taken. The image created is a small chance of life on the one hand and death on the other. Faced with this stark choice many will say, "Any chance is better than none." But this decision is not always made in the light of the real probabilities, especially if the possibility (or in certain cases the probability) of survival with severe disability is not acknowledged.

The concept of converting death into an unacceptable level of disability is certainly "inconvenient" and has been a concern among neurosurgeons for many years[12]. This led to a number of randomised controlled trials investigating efficacy of the procedure initially in the context of the ischaemic stroke[13-15] and more recently in the context of severe traumatic brain injury[16,17].

Evidence for clinical efficacy

In the early 2000s three major trials were conducted in Europe that compared decompressive hemicraniectomy with standard medical therapy for patients under 60 years of age, who clinically deteriorated following the development of "malignant" middle cerebral infarction[13-15]. Due to difficulties with slow recruitment none of the trials were fully completed, however each trial independently demonstrated that mortality was significantly lower in patients randomised to surgical decompression. Thereafter a pooled analysis performed on the 93 patients in all three trials and it was concluded that there was an "increase in the number patients with a favourable functional outcome"[18]. On initial examination this would appear to provide unequivocal support to ongoing use of the procedure, however closer examination of the study design gave some cause for concern regarding the definition of a "favourable outcome".

For many years the modified Rankin Scale (mRS) has been the most commonly used tool with which to assess outcome following stroke. It does have some limitations in that it tends to focus on physical ability rather than the cognitive and emotional aspects of recovery. However it is a robust assessment tool that has stood the test of time. Traditionally, a favourable outcome has been defined as 0-3 on the mRS and the obvious implication of this dichotomy is that the aim of the procedure is to leave survivors with some degree of independence compatible with what most people would regard as an acceptable quality of life.

However, in the pooled analysis the favourable outcome category was redefined such that it included patients with a mRS of 4. This would therefore include those patients who could not walk and who could not attend to their bodily needs without assistance and were therefore, by definition, highly dependent, an outcome that most investigators have previously deemed unfavourable[5,19].

By way of justification it was stated that "on the basis of increasing experience of long term outcome in patients with a space occupying infarction most investigators feel obliged to define a score of 4 on the mRS as favourable". However, examining the literature shows no evidence to support this position and ethically it seems highly questionable in that we are not told the reasons for this change in attitude by the investigators[19,20]. An alternative interpretation would be to accept the "inconvenient truth" that a reduction in mortality achieved by surgical decompression comes at a cost of an increase in the numbers of survivors with severe disability and dependency.

These findings were even more striking in the DESTINY II trial that investigated decompressive hemicraniectomy for patients over 60 years of age[21]. The trial was stopped for reasons of proven efficacy after the reductions in deaths and severe disability at six months had become significant and it was concluded that "hemicraniectomy increased survival without severe disability". This again appears to favour ongoing use of the procedure on the basis of its lifesaving potential but is again not supported by closer examination of the basic data. There is certainly a reduction in mortality from 70 per cent at six months in those patients randomised to medical treatment down to 33 per cent randomised to surgical decompression. However of the 27 patients who survived following decompressive hemicraniectomy only two patients achieved a mRS score of 3 and therefore had some degree of independence. Of the remaining 25 patients, there was an equal distribution of patients between a mRS of 4 and 5, with 16 of these patients having such severe aphasia or neuropsychological deficits that they were unable to answer a relatively simple question regarding retrospective consent. These findings therefore appear to lend further support for the "inconvenient truth" that surgical intervention almost uniformly translates into an increase in the number of survivors with severe disability and dependency[19].

In the context of severe traumatic brain injury the results of recent randomised controlled trials have been similar.

Decompressive hemicraniectomy following severe traumatic brain injury

There have now been two large multicentre randomised controlled trials comparing surgical decompression with standard medical therapy in patients who have sustained a severe traumatic brain injury[16,17]. The DECRA study investigated the role of early bifrontal decompressive craniectomy in the context of diffuse cerebral swelling. The hypothesis upon which the trial was based was that early decompression would optimise cerebral perfusion and improve clinical outcome by reducing secondary insults. In order to examine this hypothesis,

patients were randomised at the relatively low ICP threshold of greater than 20 mmHg for more than 15 minutes in the hour after first-tier medical therapy. The findings of the study were that patients randomised to the surgical arm of the trial had a lower ICP and spent less time in intensive care, however, even though the same proportion survived in both arms of the trial the neurological outcomes at six months were worse in patients who had been randomised to the surgical arm.

Given the enrolment ICP threshold (which is a lower threshold than is usually used in clinical practice), it was unsurprising that there was no survival benefit for those patients randomised to the surgical arm of the trial. However, what the trial did clearly demonstrate was that at that particular ICP threshold, there was insufficient ongoing secondary brain injury to justify intervention and that any potential benefit obtained from improved cerebral perfusion was offset by surgical morbidity[22]. Prior to these findings, it was almost assumed that lowering the intracranial pressure would be beneficial[23] but the results highlighted the need for more considered judgement and a careful assessment of the risks of poor quality survival when making surgical decisions[24].

The results of the study evoked considerable debate and one of the key criticisms was that the ICP threshold at which patients were randomised was not representative of current clinical practice (which is to intervene at higher ICP thresholds)[29,31]. With the benefit of hindsight this is a valid observation. However, if the trial had shown benefit the patients in the trial would have come to represent the clinical practice of the future and this would have had a significant impact on neurosurgery if survival (regardless of quality of life or the probable wishes of the patients) were the only valued outcome[13].

It is in this regard the results of the recent RESCUEicp Trial are particularly pertinent given the higher ICP threshold at which patients because this more reflective of the type of practice in most neurotrauma centres[17]. The trial was conducted over a 10 year period between 2004 and 2014 and 409 patients were randomised amongst 2008 eligible patients, at 52 centres in 20 countries. The enrolment threshold was an ICP greater than 25mmHg for one to 12 hours despite maximal medical treatment, except barbiturate therapy. Patients were then randomised to ongoing medical therapy with the addition of barbiturates or surgical decompression with the actual technique being at the discretion of the treating surgeon. The results of the study were consistent with the stroke trials in that a clear survival benefit was demonstrated in those patients randomised to surgical decompression. There were further similarities in that this reduction in mortality came as an almost direct result of an increase in the number of survivors in either a vegetative state or with severe disability. At 12 month follow up there was a small increase, albeit statistically insignificant in the number of patients with a favourable outcome from 34.6 per cent in the medical arm of the trial to 42 per cent ($p = 0.12$) in the surgical arm of the trial. However, this small increase was only seen when one included in the favourable category patients with upper levels of severe disability in a similar fashion to the stroke trials that deemed a mRS of 4 as favourable. Without this re-categorisation the number of patients who survived with lower moderate disability or better (traditionally regarded as a genuinely favourable outcome) was very similar (32 per cent favourable in the surgical arm of the trial and 28.5 per cent favourable in the medical arm).

Overall the evidence of these trials seems to overwhelmingly support the ethically problematic "inconvenient truth" that decompressive surgery reduces mortality at the expense of survival with severe disability. However this in itself does not necessarily mean that the procedure should be abandoned. In the same way that climate change is requiring society to re-examine some aspects of our everyday lifestyle the time may have come for a nuanced examination of the value society places on an individual life and the acceptability or otherwise of performing a procedure that converts death into survival with severe disability.

The future role of decompressive craniectomy in the management of neurological emergencies

Given the significant reduction in mortality demonstrated in the aforementioned trials it would seem reasonable to consider lifesaving surgical intervention for a young person with a catastrophic neurological condition such as "malignant" middle cerebral infarction or a severe TBI. This is especially the case if a person's prior wishes are unknown because they may learn to adapt to a level of disability that they may previously have thought to be unacceptable[27,28].

This position is reinforced by the ethical concept of the rule of rescue that describes the powerful human proclivity to rescue identified endangered lives, regardless of cost or risk[29]. The classic examples of this concept are heroic searches for a sailor lost at sea or daring attempts to rescue someone in a burning building. In such cases the cost to the community or the risk to those attempting the rescue is extremely high. However, the psychological and moral imperatives are difficult to resist. In the context of medical care there is always a strong ethical imperative to save an individual already identified life even when it could be argued from a utilitarian viewpoint that the money and resources might be more efficiently used to prevent deaths in the wider community. People obtain social utility and a feeling of security knowing that they live in a compassionate society which cares for the needs of each constituent member and where those in most desperate need will not be ignored or abandoned merely on the basis of resource allocation. However, that security is threatened if the rescue system is seen to be a juggernaut that is insensitive to the way people actually value their lives because there will always be circumstances where serious consideration must be given to withholding surgical intervention.

In the context of ischaemic stroke it is difficult to invoke the rule of rescue for patients more than 60 years of age given that most survivors will be immobile, unable to communicate and be fully dependent on nursing care.

In the context of severe traumatic brain injury, age is one of a number of important prognostic factors that is included in some recently developed prediction models that provide a prediction of unfavourable outcome at six months (defined by the Glasgow outcome scale as severe disability, vegetative or dead)[30,31]. A number of studies have used these models to stratify patients according to injury severity and compared the *prediction* of unfavourable outcome with the *observed* long term outcome (figures 1 and 2)[32-34]. Presenting data in this manner provides an objective assessment of outcome following surgical intervention and can perhaps form the basis of more rational and informed discussions among stakeholders when considering surgical intervention. It must of course be acknowledged that all prognostic models have their limitations and from a purist perspective, should never be used to guide medical decision-making for individual patients. In addition there will always be those patients that defy the odds and make a miraculous recovery despite seemingly desperate circumstances. However as with patients more than 60 years of age with ischaemic stroke, for patients with a severe traumatic brain injury and a prediction of unfavourable outcome greater that 80 per cent the most likely outcome for survivors is either severe disability or survival in a vegetative state.

Prior to surgically intervening in these circumstances a surgeon has an obligation to try and establish that this outcome would be acceptable for that individual and the larger community has to determine the value we place on life at any cost[35]. There will always be a delicate balance between an individual's right to survive with severe disability and the cost to the wider community where healthcare resources may be limited. However, similar to the arguments for urgent actions to reduce the impact of climate change on our future generations, we have a moral responsibility to consider the long term implications of what is in many cases an acute and emotionally charged clinical decision. The considerations here are not only financial but also personal and ethical and they require us to exercise well-considered judgment about our actions

Figure 1. The CRASH collaborators prediction model. The prediction of an unfavorable outcome at six months (x axis) and the observed outcome at 18 months among the 319 patients on whom 18 month follow up was available. Numbers within the bar chart represent absolute patient numbers
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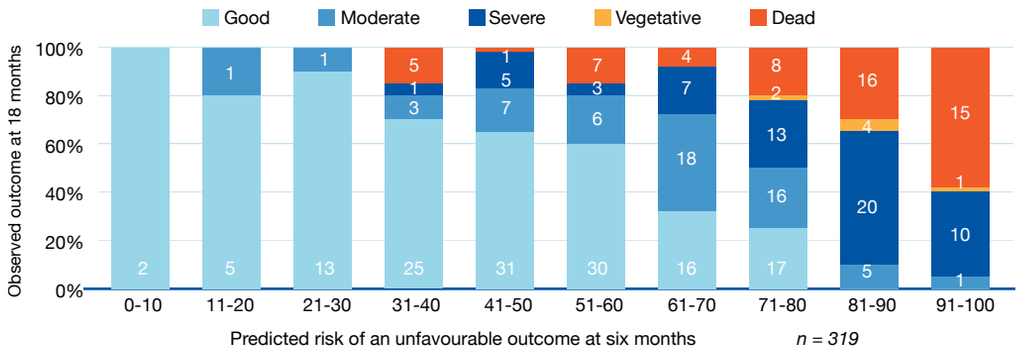
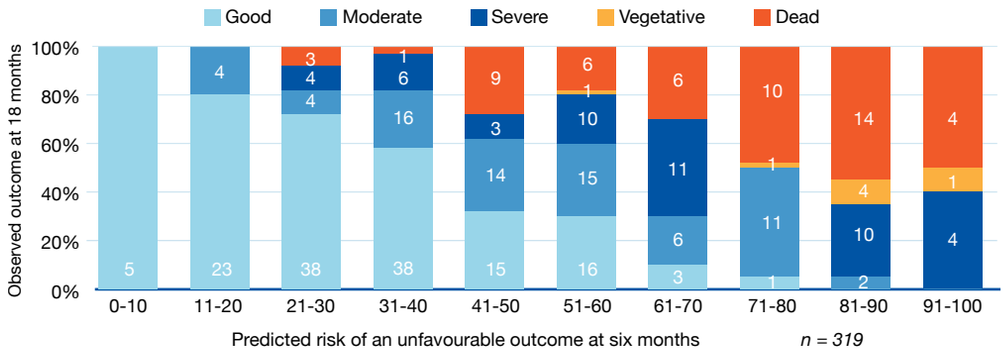


Figure 2. The IMPACT investigators model. The prediction of an unfavorable outcome at six months (x axis) and the observed outcome at 18 months among the 319 patients on whom 18 month follow up was available. Numbers within the bar chart represent absolute patient numbers
(Reproduced with kind permission by Elsevier)



CONCLUSION

There is now clear evidence that surgical intervention can be a lifesaving intervention that converts death into survival with disability and we can predict this outcome with some degree of accuracy. Is this an "inconvenient truth"? It is inconvenient in the sense that we do, in rescue medicine, have to act decisively and often quickly and we certainly have an ethical and legal obligation to act in what we feel to be the patient's best interests. But feeling is not enough. What we have highlighted is the need for our actions to be reasonable and informed by the evidence. In most jurisdictions, the clinician who acts with clearly stated intentions, having carefully considered the ethical aspects of what they are doing, will not be subject to the "damned if you do and damned if you don't" mentality that many of us fear that the courts may show in these fraught areas of decision-making. In fact neither the courts nor ethicists are in the business of making reasonable care more difficult, they are only concerned that it be truly reasonable.

REFERENCES

1. Kjellberg RN, Prieto A Jr. Bifrontal decompressive craniotomy for massive cerebral edema. J Neurosurg. 1971;34(4):488-493.
2. Ransohoff J, Benjamin V. Hemicraniectomy in the treatment of acute subdural haematoma. J Neurol Neurosurg Psychiatry. 1971;34(1):106.
3. Venes JL, Collins WF. Bifrontal decompressive craniectomy in the management of head trauma. J Neurosurg. 1975;42(4):429-433.
4. Greenwood J Jr. Acute brain infarctions with high intracranial pressure: surgical indications. Johns Hopkins Med J. 1968;122(5):254-260.
5. Honeybul S, Ho KM. The current role of decompressive craniectomy in the management of neurological emergencies. Brain Inj. 2013;27(9):979-991.
6. Aarabi B, Hesdorffer DC, Ahn ES, Aresco C, Scalea TM, Eisenberg HM. Outcome following decompressive craniectomy for malignant swelling due to severe head injury. J Neurosurg. 2006;104(4):469-479.
7. Holtkamp M, Buchheim K, Unterberg A, Hoffmann O, Schielke E, Weber JR, et al. Hemicraniectomy in elderly patients with space occupying media infarction: improved survival but poor functional outcome. J Neurol Neurosurg Psych. 2001;70(2):226-228.
8. Leonhardt G, Wilhelm H, Doerfler A, Ehrenfeld CE, Schoch B, Rauhut F, et al. Clinical outcome and neuropsychological deficits after right decompressive hemicraniectomy in MCA infarction. J Neurol. 2002;249(10):1433-1440.
9. Polin RS, Shaffrey ME, Bogaev CA, Tisdale, N, Germanson T, Bocchicchio B, et al. Decompressive bifrontal craniectomy in the treatment of severe refractory posttraumatic cerebral oedema. Neurosurgery. 1997;41(1):84-94.
10. Gillett GR. The RUB. Risk of unacceptable badness. N Z Med J. 2001;114(1130):188-189.
11. Gillett GR, Honeybul S, Ho KM, Lind CR. Neurotrauma and the RUB: where tragedy meets ethics and science. J Med Ethics. 2010;36(12):727-730.
12. Cooper PR, Rovit RL, Ransohoff J. Hemicraniectomy in the treatment of acute subdural hematoma: a re-appraisal. Surg Neurol. 1976;5(1):25-28.
13. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, et al. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurol. 2009;8(4):326-333.
14. Jüttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, et al. DESTINY Study Group: Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. Stroke. 2007;38(9):2518-2525.
15. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). Stroke. 2007;38(9):2506-2517.
16. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, et al. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med. 2011;364(21):1493-1502.
17. Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, Timothy J, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. N Engl J Med. 2016;375(12):1119-1130.
18. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol. 2007;6(3):215-222.
19. Honeybul S, Ho KM, Gillett G. Outcome following decompressive hemicraniectomy for malignant cerebral infarction: ethical considerations. Stroke. 2015;46(9):2695-2698.
20. Puetz V, Campos CR, Eliasziw M, Hill MD, Demchuk AM, Calgary Stroke Program. Assessing the benefits of hemicraniectomy: what is a favourable outcome? Lancet Neurol. 2007;6(7):580-81.
21. Jüttler E, Unterberg A, Woitzik J, Bösel J, Amiri H, Sakowitz OW, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med. 2014;370(12):1091-1100.
22. Honeybul S, Ho KM, Lind CR. What can be learned from the DECRA study. World Neurosurg. 2013;79(1):159-161.
23. Vashu R, Sohail A. Decompressive craniectomy is indispensable in the management of severe traumatic brain injury. Acta Neurochir (Wien). 2011;153(10):2065-2066.
24. Honeybul S, Ho KM. The surgical management of intracranial hypertension following traumatic brain injury. Anaesth Intensive Care. 2012;40(3):558-559.
25. Servadei F. Clinical value of decompressive craniectomy. N Engl J Med. 2011;364(16):1558-9.
26. Timmons SD, Ullman JS, Eisenberg HM. Craniectomy in diffuse traumatic brain injury. N Engl J Med. 2011;365(4):373.
27. Honeybul S, Gillett GR, Ho KM, Janzen C, Kruger K. Is life worth living? Decompressive craniectomy and the disability

paradox. J Neurosurg. 2016;125(3):775-778.
28. Larach DR, Larach DB, Larach MG. A life worth living: seven years after craniectomy. Neurocrit Care. 2009;11(1):106-111.
29. Jonsen AR. Bentham in a box: technology assessment and health care allocation. Law Med Health Care. 1986;14(3-4):172-174.
30. Perel P, Arango M, Clayton T, Edwards P, Komolafe E, Poccock S, et al. Predicting outcome after brain injury: practical prognostic models based on a large cohort of international patients. BMJ. 2008;336(7641):425-429.
31. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 2008;5(8):e165.
32. Honeybul S, Ho KM, Lind CR, Gillett GR. The retrospective application of a prediction model to patients who have had a decompressive craniectomy for trauma. J Neurotrauma. 2009;26(12):2179-2183.
33. Honeybul S, Ho KM, Lind CR, Gillett GR. Observed versus predicted outcome for decompressive craniectomy: a population-based study. J Neurotrauma. 2010;27(7):1225-1232.
34. Honeybul S, Ho KM. Predicting long-term neurological outcomes after severe traumatic brain injury requiring decompressive craniectomy: a comparison of the CRASH and IMPACT prognostic models. Injury. 2016;47(9):1886-1892.
35. Ho KM, Honeybul S, Lind CR, Gillett GR, Litton E. Cost-effectiveness of decompressive craniectomy as a lifesaving rescue procedure for patients with severe traumatic brain injury. J Trauma. 2011;71(6):1637-1644.

Adenosine for transient cardiac standstill in neurovascular surgery: A heart-stopping moment

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INTRODUCTION

Anaesthetists are infrequent users of adenosine. Many of us may have administered it as a junior doctor, perhaps in an emergency department to terminate supraventricular tachycardia (SVT). Those who undertake regular lists in electrophysiology suites may occasionally administer a dose to test the successful ablation of an accessory tract or atrial fibrillation. Mostly, though, it is one of many drugs about which we memorise a paragraph or two for our examinations, then mentally shelve all but the most fundamental rules of thumb.

In the past decade or so, another clinical use of adenosine has emerged for anaesthetists. You may be a staff specialist who seldom practises neuroanaesthesia, substituting on a list for an absent colleague, or perhaps a regular neuroanaesthetist whose surgeon has just returned from an overseas conference. They are now enthusiastic to try a technical approach increasingly used by their international colleagues. Before a routine aneurysm clipping, the surgeon asks “Do you have adenosine in theatre? The approach to this aneurysm may be difficult, and I need you to induce a short period of cardiac standstill if I can’t apply a temporary clip.” You wonder: How much should I give? What precautions should I take before giving it? Which patients will tolerate it? Is there any evidence for its use in this manner?

This paper will briefly review the pharmacology of adenosine, then examine the evidence for its use in neurovascular surgery. Reports about the adverse effects of adenosine come largely from the cardiology literature, but have significant implications for anaesthetists. A summary of practice points will conclude the review.

PHARMACOLOGY

Adenosine is an endogenous purine nucleoside found both intracellularly and in plasma. It has a simple molecular structure: a ribose attached to adenine. It acts as an extracellular signalling molecule, produced from precursors such as adenosine tri-, di- and monophosphate (AMP)[1]. There are four G-protein-coupled adenosine receptors, A_1, A_{2A}, A_{2B} and A_3; their widespread distribution in various organ systems and tissues explains adenosine’s broad range of physiological and pathophysiological roles[2]. The A_1, A_{2A} and A_3 receptors are activated by physiological concentrations of extracellular adenosine, but A_{2B} activation requires higher (pathological) adenosine levels, present in hypoxia, ischaemia, or inflammation[3]. Thus there are numerous potential therapeutic applications for exogenous adenosine, many of which have only recently undergone investigation[2,3].

Adenosine’s intravascular half-life is 5-10 seconds due to its rapid uptake into endothelial cells and erythrocytes, where it is metabolised and inactivated by adenosine deaminase or adenosine kinase to inosine or AMP respectively. It enters cells freely and swiftly down a concentration gradient, via a transporter expressed on many cell types[3].

Adenosine mediates vasodilation in most vascular beds, including the coronary circulation, but is a vasoconstrictor in the kidney, spleen and hepatic veins. It has both pro- and anti-inflammatory actions, and inhibits platelet aggregation[2]. It is widely distributed in the brain and spinal cord, where it acts as a neuromodulator, tonically active in the cerebral cortex and hippocampus. It is considered neuroprotective due to its inhibition of glutamate release[4,5]. Table 1 summarises adenosine receptor distribution and the diversity of its functions.

Table 1. Adenosine receptor subtypes and their mediated functions[2-5]

A_1	A_{2A}	A_{2B}	A_3
Negative chronotropy, inotropy, dromotropy	Decreased platelet aggregation	Cardiac preconditioing	Mast cell activation, white cell chemotaxis
Vasoconstriction	Vasodilation	Vascular integrity	Inflammatory pain
Bronchoconstriction	Immunosuppression	Pro-inflammation (in acute injury)	Chronic neuropathic pain
Inhibition: lipolysis, insulin and glucagon release, neurotransmitter release	Regulation of motor activity, psychiatric behaviours, sleep-wake cycle, neuronal cell death	Anti-inflammation (chronic disease)	Anti-cancer (melanoma)
Decreased renal blood flow and tubuloglomerular feedback, inhibition of renin release	Angiogenesis		Airway contraction
Reduced respiration			
Cardiac preconditioning			
Analgesia			
Sleep			

Adenosine has been used for decades for the termination of re-entrant SVTs involving the atrioventricular (AV) node. It acts as a negative chronotrope and dromotrope, slowing heart rate and prolonging AV nodal conduction[6,7]. It may help to differentiate between broad-complex SVT and ventricular tachycardia. In SVTs which are AV node-dependent, an adenosine-induced temporary conduction delay can reveal underlying flutter. Adenosine also reduces the refractory period of atrial myocytes. It terminates only a subset of SVTs because its effect on any accessory tract depends on whether the tract cells are nodal or atrial myocytes. Mostly, adenosine does not slow conduction in bypass tracts, and therefore it may unmask hidden accessory pathways in patients with Wolf-Parkinson-White syndrome. This is the rationale for adenosine's use after SVT ablation and pulmonary vein isolation for elimination of atrial fibrillation[8,9].

Adenosine is widely administered as an infusion during myocardial perfusion scans as a pharmacological stressor. It mimics the vasodilatory effect of exercise on coronary vessels, thereby inducing as much as a four- or five-fold increase in intracoronary blood flow in healthy coronary arteries[8,10]. Theoretically, in patients with severe coronary artery disease and well-developed collateral vessels, adenosine can cause sufficient vasodilation of larger coronary arterioles to divert blood from collateral vessels. This potentially causes ischaemia in the collateral-dependent myocardium, but fortunately this is rarely seen[11]. Thus adenosine is also used in coronary fractional flow reserve testing, a method of identifying the culprit stenotic lesion when there is diffuse stenotic disease, and has been shown to reduce ischaemic-reperfusion injury in ST-elevation myocardial infarction[8].

Clinically, peripherally administered intravenous adenosine followed by a saline flush takes effect within seconds. The heart rate slows over 20 to 30 seconds, and if a sufficient dose for a particular individual is given, a variable period of asystole ensues, after which the heart rate returns to baseline over 20 to 30 seconds. There is a subsequent period of marked hypotension usually lasting up to two minutes, due to a reduced systemic vascular resistance (SVR) and a parallel increase in cardiac output (CO). Adenosine's short intravascular half-life means that the brief asystole and hypotension is typically self-limited. There is a large inter-individual difference in the dose required to achieve cardiac standstill[13-15].

Following standstill, adenosine causes a reflex increase in circulating catecholamines, inducing a brief sympathetically mediated sinus tachycardia as well as atrial and ventricular ectopics. These in turn can trigger conduction via a re-entrant pathway, particularly after the temporary shortening of the atrial myocyte refractory period. It is this combination of factors which can lead to atrial fibrillation in susceptible individuals[9,16].

ENDOVASCULAR SURGERY

Adenosine has been used since 1996 to reduce aortic blood flow briefly during the deployment of endovascular stent grafting for thoracic aortic aneurysms[17]. Although other drugs and pacing-induced ventricular fibrillation can also produce the brief cardiac standstill required, adenosine is preferred by proceduralists due to its rapid onset, predictable duration, relatively linear dose-response relationship, the reliability of return of baseline haemodynamics and a lower imbalance of cardiac demand and supply[14].

NEUROSURGERY

Early applications of adenosine in neurosurgery

Adenosine was first used in neurosurgery in the mid-1980s for the induction of profound hypotension during cerebral aneurysm manipulation[18]. The rationale was that the reduction in aneurysm wall tension would minimise the risk of rupture and bleeding. Previously, deep hypothermic circulatory arrest under extracorporeal perfusion was used to secure giant aneurysms or those with difficult anatomical approaches, but the complication rate and resources required meant that adenosine was an attractive alternative. Sodium nitroprusside (SNP) was also used to induce hypotension during aneurysm surgery, although tachyphylaxis and rebound hypertension were significant disadvantages[19].

In early studies, adenosine was infused intravenously until mean arterial pressure (MAP) was 40-50 mm Hg. Typically, this induced hypotension was maintained for approximately 30 minutes[18]. Intraoperative cardiac catheterisation revealed the expected marked decrease in SVR and equivalent increase in CO. Cardiac filling pressure and acid-base status were unchanged[18,20]. When glomerular filtration rate and renal blood flow were measured during adenosine infusion, a profound but rapidly reversible renal afferent arteriolar vasoconstriction occurred, leading the authors to suggest that adenosine-induced hypotension should be kept relatively brief, and avoided in patients with impaired renal function. Creatinine levels, however, remained unchanged[21].

In 1999, a case report by Groff and colleagues was the first to describe the use of bolus doses of adenosine to induce transient asystole to facilitate aneurysm ligation. They employed an SNP infusion to maintain hypotension during the dissection of a basilar aneurysm, then added 6- and 12 mg boluses of adenosine to achieve asystolic periods of eight and 13 seconds respectively. The consequent collapse of the aneurysm dome meant that no temporary clip was required, and the aneurysm was secured without neurological consequences[22]. In the same year, transient cardiac standstill with adenosine was also used during embolisation of a cerebral arteriovenous malformation (AVM)[23].

Intraoperative aneurysm rupture

The first description of adenosine used emergently during aneurysm rupture was in 2000[24]. The patient was unlucky enough to have both a large parietal AVM and a fusiform, multilobulated anterior communicating artery aneurysm. During the procedure, significant aneurysmal bleeding remained uncontrolled, despite application of a temporary clip and barbiturate-induced hypotension. A single 12 mg bolus of adenosine provided a 25-second period of asystole, during which the aneurysm was satisfactorily secured.

In 2010, a Finnish group published a review of 16 cases where adenosine was used to assist with haemostasis during intraoperative rupture, from a total of 1014 aneurysm surgeries over five years. The dose range was 6-18 mg, with most patients receiving 12 mg. Only four patients required repeat dosing; one patient, however, received a total of 89 mg of adenosine. The duration of asystole achieved in each case was not reported, but there were no adverse neurological outcomes or cardiac events in this series[25].

Adenosine as an adjunct in elective aneurysm surgery

Since 2010, several case series have described adenosine's elective use during aneurysm surgery[13,26,28-33]. The commonest indication is to decrease aneurysm turgor and bulk in order to facilitate clip application, thus reducing the risk of intraoperative rupture. Some aneurysms are in unfavourable anatomical locations, leading to a narrow corridor of approach and an inability to apply a temporary clip: for example, paraclinoid or basilar apex aneurysms. Applying a temporary clip to some vessels may induce an unacceptably high risk of ischaemia, or impede vision of important structures. Adenosine then provides an alternative means of 'softening' the aneurysm sac. Other indications for adenosine include a broad aneurysm neck, a thin wall, atheroma in the aneurysm neck, adjustment of a clip, or previous coiling[13,26].

All the case series have much in common. The absolute numbers of patients given adenosine were low: six patients in the smallest series[26], 72 in the largest[28]. Not all studies provided a denominator (the total number of aneurysm surgeries during the relevant study period). In those that did, adenosine was used in about 17-21 per cent of aneurysm surgeries. Occasional patients within some series received adenosine for intraoperative rupture[13,27,29,31], but in most patients, the decision to give adenosine was made either preoperatively or early in the procedure. Patients received a standard general anaesthetic with propofol or volatile (or both) plus remifentanil. Central venous access was typically in situ and was used for adenosine administration. When adenosine use was planned, precordial pads were placed before the patient was draped, in case of the requirement for transcutaneous pacing or defibrillation.

Adenosine dosing strategies

Clinical experience with adenosine has shown that the duration of cardiac standstill or extreme bradycardia achieved with a given dose is reasonably consistent within individuals, but exhibits considerable interindividual difference[6,25,34]. Three case series attempted to clarify dose-response relationships. The first reviewed five patients undergoing endovascular glue embolisation of cerebral AVMs. Each patient received escalating bolus doses of adenosine, starting with 0.25-0.35 mg/kg. The inter-bolus interval was three to 10 minutes, and the desired endpoint was 20-30 seconds with MAP below 30 mm Hg. Patients also received a low-rate background infusion of SNP. The authors found a linear relationship between adenosine dose and duration of both asystole and hypotension. The mean dose required to achieve the endpoint was 1 mg/kg, or 6 to 90 mg (one patient was a four-year-old). This dose provided asystole for an average of eight seconds, MAP <30 for an average of 18 seconds, and MAP < 50 for 50 seconds[35].

Bebawy and colleagues retrospectively assessed the dose-response relationship in 24 patients given adenosine for aneurysm surgery[28]. Fourteen patients required multiple doses to achieve successful ligation. The authors' clinical aim was to keep systolic blood pressure below 60 mm Hg, and dosing was calculated for ideal body weight (IBW). A dose of 0.3-0.4 mg/kg IBW enabled successful aneurysm clipping in all patients. As the authors suggested, adenosine titration to a haemodynamic endpoint is not feasible when an aneurysm requires imminent control during intraoperative rupture. Titration also exposes patients to repeated episodes of relative hypotension or flow arrest and the potential for detrimental cardiac or neurological consequences. They concluded that 0.3-0.4 mg/kg IBW (e.g. 18-24 mg in a 60-70 kilogram patient) was a reasonable empirical dose for appropriate surgical conditions in intraoperative rupture[28].

A third study in 27 patients described an escalating dose technique, starting with 3-6 mg then gradually increasing the dose to attain 30 seconds of bradycardia (defined as heart rate < 40 bpm). This was performed at a point in the operation "when it was determined that adenosine cardiac arrest was needed to facilitate aneurysm clipping"[29]. After the initial dose, further doses were administered only when haemodynamics had returned to baseline. Once the optimal dose was identified, it was administered as many times as required during dissection, vessel identification and clip application. The median dose providing up to 30 seconds of bradycardia was 12 mg (0.16 mg/kg). To achieve 30-60 seconds of bradycardia, the median dose was 30 mg (0.42 mg/kg). However, the inter-patient range was 3 mg to 90 mg, and patients required anywhere between a single dose and eight doses. One patient received a total of 285 mg before the aneurysm was secured[29].

A South Korean group took advantage of an institutional change in their adenosine dosing strategy to compare strategy effectiveness. Twenty-two patients received adenosine in a four-year period.

The first 11 patients received an initial dose of 6-12 mg, with doses escalated until a satisfactory period of asystole was achieved. Eight patients required multiple doses. The final dose ranged from 0.16 to 2.67 mg/kg, and this provided between three and 30 seconds of asystole. With the next 11 patients, a pre-calculated dose of 0.3-0.4 mg/kg IBW was administered, resulting in only one patient requiring a further dose. This dose regimen provided a range of 13-41 seconds of asystole. The authors concluded that for convenience and safety, the pre-calculated dose method was preferable[32].

Adenosine and outcomes after neurosurgery

Bebawy and colleagues performed a retrospective case-control study to determine whether repeated flow arrest from adenosine had neurological consequences in the early postoperative period. Intraoperative adenosine (in 72 patients, compared with 341 patients not given adenosine) was not associated with a poor neurological outcome at 48 hours after surgery or at hospital discharge, as measured by a modified Rankin scale score >2. The only modifiable risk factor in their study that led to a worse neurological outcome was temporary arterial occlusion[30].

A second retrospective case-control study assessed whether there was a relationship between adenosine use during cerebral aneurysm surgery and morbidity and mortality. The outcome of interest was a composite of cardiac complications in the immediate postoperative period and 30-day mortality. Of the 326 patients undergoing aneurysm surgery, 64 were given adenosine, and these were compared with the remaining 262 patients. Cardiac complications were defined as myocardial infarction or arrhythmias, (the latter being non-sinus rhythm lasting over an hour or requiring cardioversion). Cardiac complications were included if they occurred within seven days of surgery. The composite outcome occurred in 4.6 per cent of patients in the no-adenosine group and 9.4 per cent of patients who received adenosine. Although this trend was non-significant, the study was probably underpowered to detect a difference. The two groups were adjusted for their different incidence of coronary artery disease, but the odds of the composite outcome were still not significantly different between the groups[31]. Given that patients with the worst disease were excluded from adenosine use, the influence of adenosine on cardiac complications may have been underestimated.

Adverse effects and patient selection

The frequency of adenosine use in cardiac settings is far higher than in neurosurgery, and has given clinicians a more representative idea of the incidence of major side effects, almost all of which are brief and self-terminating. Most minor side effects are subjective and masked by anaesthesia. The incidence of atrial fibrillation after adenosine is 8 to 12 per cent[36,37], and occurs even in children[38].

There are numerous case reports of other arrhythmias ranging from complete heart block to ventricular fibrillation, and bronchospasm in both healthy and diseased lungs[16,39-43]. Coronary artery spasm occurs rarely; its mechanism is poorly understood[44-46]. There are no reports of death.

A registry of adenosine use during myocardial perfusion imaging in over 9000 patients reported the frequency of a variety of adverse effects; once again, no deaths occurred. This study, like many of the case reports, involved a 6-minute infusion of adenosine at 140 mcg/kg/min via a peripheral line, with a total dose of approximately 0.8 mg/kg. Table 2 summarises the frequency of side effects in this study.[47]

Table 2. Frequency of adverse effects with adenosine infusion in the Adenoscan Multicenter Trial Registry[47]

SIDE EFFECT	APPROXIMATE INCIDENCE
Flushing	36%
Dyspnea	35%
Chest pain	35%
Gastrointestinal discomfort	14%
Headache	11%
AV block	7%
ST-T changes	6%
Arrhythmias	3%
Bronchospasm	0.1%

Most of the neurosurgical studies excluded patients with certain comorbidities from receiving adenosine: patients with severe coronary artery disease, AV block greater than first degree, and severe reactive airway disease (active wheezing or hospitalisation in the previous six months)[28,32,33]. It is therefore unsurprising that there were very few complications in the 239 neurosurgical patients included. Thirteen patients developed transient arrhythmias, two had minor troponin elevations without apparent clinical sequelae, one developed myocardial ischaemia in the postoperative period, and one required chest compressions for refractory severe hypotension. With the latter patient, adenosine had been rapidly re-dosed to attain control of haemorrhage during an intraoperative rupture with a 500 mL blood loss. Prolonged hypotension requiring chest compressions and low-dose adrenaline ensued, with spontaneous return of circulation after three minutes. Tracheal extubation was achieved uneventfully without troponin positivity[29].

Precautions with adenosine

Patients taking dipyridamole or those with a cardiac transplant are likely to be more sensitive to adenosine. Dipyridamole, a phosphodiesterase inhibitor, potentiates the effect of adenosine by blocking the nucleoside transporter by which adenosine enters erythrocytes and endothelial cells, and by inhibiting its metabolism within cells[48]. In a cardiac transplant, the denervated SA and AV nodes have a three- to five-fold greater response to adenosine[49,50]. Central venous delivery of adenosine is likely to lower the required dose, by reducing the opportunity for uptake and metabolism before the drug reaches the site of action[23]. Carbemazepine can potentiate adenosine-induced bradycardia[51].

Methylxanthines include caffeine, theobromine (in chocolate), and theophylline. All are adenosine receptor antagonists. Caffeine has been shown to significantly reduce the efficacy of adenosine if ingested within four hours of its administration. An increased dose of adenosine may be required for therapeutic efficacy if patients have recently taken methylxanthines[52].

Adenosine is not contraindicated in atrial fibrillation, but if the patient has underlying Wolf-Parkinson-White syndrome, adenosine's AV nodal blockade can permit antegrade conduction from atria to ventricles in a 1:1 ratio down the accessory tract, potentially causing ventricular fibrillation. Any clinician using adenosine has to be prepared for this possibility. In fact, given the high morbidity and mortality of intraoperative rupture, the only absolute contraindication to adenosine should probably be a confirmed hypersensitivity reaction. That notwithstanding, careful consideration of adenosine use is warranted in patients with a number of conditions and taking certain drugs. Table 3 lists the precautions to consider when administering adenosine.

Table 3. Precautions with adenosine use

HIGH DEGREE OF CAUTION	MODERATE DEGREE OF CAUTION
Severe coronary artery disease (>80% stenosis)	Atrial fibrillation
AV block greater than first degree	Dipyridamole (consider reduced dose)
Pacemaker	Cardiac transplant (consider reduced dose)
Wolf-Parkinson-White syndrome	
Atrial flutter	
Verapamil, digoxin, carbamazepine	
Sinus node disease	
Afterload-dependent patients	

PRACTICE TIPS

1. In Australia, the intraoperative use of adenosine for transient cardiac standstill is not listed as an indication by the Australian Register of Therapeutic Goods[53].
2. If adenosine use is anticipated, defibrillator pads should be applied to the patient, either for transcutaneous pacing in the event of refractory bradyarrhythmias, or for cardioversion of malignant tachyarrhythmias. For transcutaneous pacing, a semiautomatic/manual defibrillator will be required, and the defibrillator's ECG electrodes should be attached for successful capture.
3. As any period of flow arrest is short, the surgeon should be prepared for the desired neurosurgical manoeuvre when adenosine is given. Excellent communication between surgeon and anaesthetist to coordinate timing is required.
4. Bradycardia with adenosine is unlikely to be reversed by anticholinergics such as atropine[39].
5. In the event of aneurysm rupture, a starting dose of 0.3-0.4 mg/kg seems reasonable, but all neurosurgical case series to date have administered adenosine via a central venous line. If using a peripheral intravenous line, higher doses will probably be required.
6. A repeat dose of adenosine should be given only when the patient's blood pressure and heart rate have returned to baseline.
7. Where intraoperative adenosine administration is in use, departments of anaesthesia should consider developing a local guideline, in consultation with departments of neurosurgery and the local drug and therapeutic committee.

CONCLUSION

Transient cardiac standstill or extreme hypotension induced by adenosine is a well-described neurosurgical technique to facilitate the clipping of anatomically challenging cerebral aneurysms. Although used relatively infrequently, the strategy is increasing in popularity. Anaesthetists should be aware of the requirement for doses of adenosine that are larger than those traditionally used for SVT termination. The brevity of adenosine's half-life means it is a remarkably safe drug, but rare cases of malignant tachyarrhythmias, refractory bradycardias, coronary spasm or bronchospasm can occur. Where possible defibrillator pads and linked ECG electrodes should be applied before administration of adenosine, and its use should be avoided in patients with severe coronary artery disease, higher-grade heart block, and severe reactive airway disease.

REFERENCES

1. Skrabanja AT, Bouman EA, Dagnelie PC. Potential value of adenosine 5'-triphosphate (ATP) and adenosine in anaesthesia and intensive care medicine. Br J Anaesth. 2005;94(5):556-562.
2. Chen JF, Eltzschig HK, Fredholm BB. Adenosine receptors as drug targets – what are the challenges? Nat Rev Drug Discov. 2013;12(4):265-286.
3. Eltzschig HK. Adenosine: an old drug newly discovered. Anesthesiology. 2009;111(4):904-915.
4. Masino SA, Dulla CG. Adenosine, glutamate and pH: interactions and implications. Neurol Res. 2005;27(2):149-152.
5. Stockwell J, Jakova E, Cayabyab FS. Adenosine A1 and A2A receptors in the brain: current research and their role in neurodegeneration. Molecules. 2017;22(4):676.
6. Camm JA, Wood AJ. Adenosine and supraventricular tachycardia. N Engl J Med. 1991;325(23):1621-1628.
7. Link MS. Evaluation and initial treatment of supraventricular tachycardia. N Engl J Med. 2012;367(15):1438-1448.
8. Layland J, Carrick D, Lee M, Oldroyd K, Berry C. Adenosine: physiology, pharmacology and clinical applications. JACC Cardiovasc Interv. 2014;7(6):581-591.
9. Dallaglio PD, Betts TR, Ginks M, Bashir Y, Anguera I, Rajappan K. The role of adenosine in pulmonary vein isolation: a critical review. Cardiol Res Pract. 2016;2016:8632509.
10. Patel RN, Arteaga RB, Mandawat MK, Thornton JW, Robinson VJ. Pharmacologic stress myocardial perfusion imaging. South Med J. 2007;100(10):1006-1014.
11. van der Hiel B, Scholte AJ, Stokkel MP. Intermittent ST-segment depressions during adenosine stress test. Clin Nucl Med. 2007;32(12):927-929.
12. Bulluck H, Sirker A, Loke YK, Garcia-Dorado D, Hausenloy DJ. Clinical benefit of adenosine as an adjunct to reperfusion in ST-elevation myocardial infarction patients: an updated meta-analysis of randomized controlled trials. Int J Cardiol. 2016;202:228-237.
13. Bendok BR, Gupta DK, Rahme RJ, Eddleman CS, Adel JG, Sherma AK, et al. Adenosine for temporary flow arrest during intracranial aneurysm surgery: a single-center retrospective review. Neurosurgery. 2011;69(4):815-821.
14. Plaschke K, Boeckler D, Schumacher H, Martin E, Bardenheuer HJ. Adenosine-induced cardiac arrest and EEG changes in patients with thoracic aorta endovascular repair. Br J Anaesth. 2006 96(3):310–316.
15. Lippmann M, Kakazu C, Fang TD, Bui H, Donayre C, White RA. Adenosine's usefulness in vascular surgery. Tex Heart Inst J. 2007;34(2):258.
16. Pelleg A, Pennock RS, Kutalek SP. Proarrhythmic effects of adenosine: one decade of clinical data. Am J Ther. 2002;9(2):141-147.
17. Baker AB, Bookallil MJ, Lloyd G. Intentional asystole during endoluminal thoracic aortic surgery without cardiopulmonary bypass. Br J Anaesth. 1997;78(4):444-448.
18. Öwall A, Gordon E, Lagerkranser M, Lindquist C, Rudehill A, Sollevi A. Clinical experience with adenosine for controlled hypotension during cerebral aneurysm surgery. Anesth Analg. 1987;66(3):229-234.
19. Wright JM, Huang CL, Sharma R, Manjila S, Xu F, Dabb B, et al. Cardiac standstill and circulatory flow arrest in surgical treatment of intracranial aneurysms: a historical review. Neurosurg Focus. 2014;36(4):1-8.
20. Öwall A, Lagerkranser M, Sollevi A. Effects of adenosine-induced hypotension on myocardial hemodynamics and metabolism during cerebral aneurysm surgery. Anesth Analg. 1988;67(3):228-232.
21. Zäll S, Edén E, Winsö I, Volkmann R, Sollevi A, Ricksten SE. Controlled hypotension with adenosine or sodium nitroprusside during cerebral aneurysm surgery: effects on renal hemodynamics, excretory function and renin release. Anesth Analg. 1990;71(6):631-636.
22. Groff MW, Adams DC, Kahn RA, Kumbar UM, Yang BY, Bederson JB. Adenosine-induced transient asystole for management of a basilar artery aneurysm. J Neurosurg. 1999;91(4):687-690.
23. Pile-Spellman J, Young WL, Joshi S, Duong H, Vang MC, Hartmann A, et al. Adenosine-induced cardiac pause for endovascular embolization of cerebral arteriovenous malformations: technical case report. Neurosurgery. 1999;44(4):881-887.
24. Nussbaum ES, Sebring LA, Ostanny I, Nelson WB. Transient cardiac standstill induced by adenosine in the management of intraoperative aneurysmal rupture: technical case report. Neurosurgery. 2000;47(1):240-243.
25. Luostarinen T, Takala RS, Niemi TT, Katila AJ, Niemelä M, Hernesniemi J, et al. Adenosine-induced cardiac arrest during intraoperative cerebral aneurysm rupture. World Neurosurg. 2010;73(2):79-83.
26. Powers CJ, Wright DR, McDonagh DL, Borel CO, Zomorodi AR, Britz GW. Transient adenosine-induced asystole during the surgical treatment of anterior circulation cerebral aneurysms: technical note. Neurosurgery. 2010;67(ONS Supplement 2):461-470.
27. Vealey R, Koht A, Bendok B. Multidose adenosine used to facilitate microsurgical clipping of a cerebral aneurysm complicated by intraoperative rupture: a case report. Anesth Analg Case Reports. 2017;8(5):109-112.
28. Bebawy JF, Gupta DK, Bendok BR, Hemmer LB, Zeeni C, Avram MJ, et al. Adenosine-induced flow arrest to facilitate intracranial aneurysm clip ligation: dose-response data and safety profile. Anesth Analg. 2010;110(5):1406-1411.
29. Guinn NR, McDonagh DL, Borel CO, Wright DR, Zomorodi AR, Powers CJ, et al. Adenosine-induced transient asystole for intracranial aneurysm surgery: a retrospective review. J Neurosurg Anesthesiol. 2011;23(1):35-40.
30. Bebawy JF, Zeeni C, Sharma S, Kim ES, DeWood MS, Hemmer LB, et al. Adenosine-induced flow arrest to facilitate intracranial aneurysm clip ligation does not worsen neurologic outcome. Anesth Analg. 2013;117(5):1205-1210.
31. Khan SA, McDonagh DL, Adogwa O, Gokhale S, Toche UN, Verla T, et al. Perioperative cardiac complications and 30-day mortality in patients undergoing intracranial aneurysmal surgery with adenosine-induced flow arrest: a retrospective comparative study. Neurosurgery. 2014;74(3):267-272.
32. Lee SH, Kwun BD, Kim JU, Choi JH, Ahn JS, Park W, et al. Adenosine-induced transient asystole during intracranial aneurysm surgery: indications, dosing, efficacy, and risks. Acta Neurochir (Wien). 2015;157(11):1879-1886.
33. Andrade-Barazarte J, Luostarinen T, Goehre F, Kivelev J, Jahromi BR, Ludtka C, et al. Transient cardiac arrest induced by adenosine: a tool for contralateral clipping of internal carotid artery-ophthalmic segment aneurysms. World Neurosurg. 2015;84(6):1933-1940.
34. Bailey AM, Baum RA, Rose J, Humphries RL. High-dose adenosine for treatment of refractory supraventricular tachycardia in an emergency department of an academic medical center: a case report and literature review. J Emerg Med. 2016;50(3):477-481.
35. Hashimoto T, Young WL, Aagaard BD, Joshi S, Ostopkovich ND, Pile-Spellman J. Adenosine-induced ventricular asystole to induce transient profound systemic hypotension in patients undergoing endovascular therapy dose-response characteristics. Anesthesiology. 2000;93(4):998-1001.
36. Strickberger SA, Man C, Daoud EG, Goyal R, Brinkman K, Knight BP, et al. Adenosine-induced atrial arrhythmia: a prospective analysis. Ann Intern Med. 1997;127(6):417-422.
37. Glatter KA, Cheng J, Dorostkar P, Modin G, Talwar S, Al-Nimri M, et al. Electrophysiologic effects of adenosine in patients

with supraventricular tachycardia. Circulation. 1999;99(8):1034-1040.
38 Kaltman JR, Tanel RE, Shah MJ, Vetter VL, Rhodes LA. Induction of atrial fibrillation after the routine use of adenosine. Pediatr Emerg Care. 2006;22(2):113-115.
39. El-Menyar A, Gehani A. Adenosine-induced tachyarrhythmia and cardiac arrest. Future Cardiol. 2010;6(4):433-436.
40. Harvey MG, Safih S, Wallace M. Adenosine-induced complete heart block: not so transient. Emerg Med Australas. 2007;19(6):559-562.
41. Rajkumar CA, Qureshi N, Ng FS, Panoulas VF, Lim PB. Adenosine induced ventricular fibrillation in a structurally normal heart: a case report. J Med Case Rep. 2017;11(1):21.
42. Coli S, Mantovani F, Ferro J, Gonzi G, Zardini M, Ardissinoo D. Adenosine-induced severe bronchospasm in a patient without pulmonary disease. Am J Emerg Med. 2012;30(9): 2082.e3-5.
43. Salter B, O'Donnell T, Weiner M, Fischer G. Adenosine and bronchospasm: vigilance in the electrophysiology suite. J Cardiothorac Vasc Anesth. 2015;29(2):410-411.
44. Nakayama M, Morishima T, Chikamori T, Aiga M, Takazawa K, Yamashina A. Coronary arterial spasm during adenosine myocardial perfusion imaging. J Cardiol. 2009;53(2):288-292.
45. Montaser I, Asaad N, Al-Suwaidi. Adenosine-induced coronary artery spasm: a case report. Med Princ Pract. 2012;21(2):82-85.
46. Arora P, Bhatia V, Arora M, Kaul U. Adenosine induced coronary spasm - a rare presentation. Indian Heart J. 2014;66(1):87-90.
47. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial Registry. J Am Coll Cardiol. 1994;23(2):384-389.
48. Gamboa A, Abraham R, Diedrich A, Shibao C, Paranjape SY, Farley G, et al. Role of adenosine and nitric oxide on the mechanisms of action of dipyridamole. Stroke. 2005;36(10):2170-2175.
49. Ellenbogen KA, Thames MD, DiMarco JP, Sheehan H, Lerman BB. Electrophysiological effects of adenosine in the transplanted human heart: evidence of supersensitivity. Circulation. 1990;81(3):821-828.
50. Koglin J, Stäblein A, Von Scheidt W. Supersensitivity mismatch of adenosine in the transplanted human heart: chronotropy and dromotropy versus inotropy. Transpl Int. 1996;9(1):9-14.
51. Mallet ML. Proarrhythmic effects of adenosine: a review of the literature. Emerg Med J. 2004;21(4):408-410.
52. Cabalag M, Taylor DM, Knott JC, Buntine P, DeVilliers S, Meyer A. Recent caffeine ingestion reduces adenosine efficacy in the treatment of paroxysmal supraventricular tachycardia. Acad Emerg Med. 2010;17(1):44-49.
53. Department of Health, Therapeutic Goods Administration. ARTG Public Summary ARTG ID 49439 [Internet]. 1994. From: http://www.tga.gov.au. Accessed 28 June 2017.

Liver / Metabolic

Anaesthesia for patients with liver disease

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INTRODUCTION

Patients with liver disease represent a growing proportion of presentations for surgery. Liver disease arises from a variety of aetiologies varying in severity from stable sub-clinical disease to End Stage Liver Disease (ESLD). Treatment advances have led to increased survival in these patients. This will result in a growing number undergoing surgery with diagnosed, as well as undiagnosed, yet stable disease. This patient population requires special consideration perioperatively due to increased risk of infection, organ dysfunction and morbidity and mortality. This article focuses on the impact to the anaesthetist of adult patients with chronic liver disease.

EPIDEMIOLOGY

With the increasing prevalence of obesity and weight gain, Non-Alcoholic Fatty Liver Disease (NAFLD) has become the leading cause of liver disease in Australia and New Zealand. An estimated 5.5 million Australians are affected by NAFLD including 40 per cent of all adults aged over 50[1]. Pharmacotherapy currently in development may change the future for these patients[2]. Alcohol-related liver disease, hepatitis B and hepatitis C predominate as the next most common causes of chronic liver disease with hepatitis B being the leading cause of liver-related mortality. Hepatitis is a major risk factor for the development of hepatocellular carcinoma (HCC) – the most rapidly rising cause of cancer death in Australia[3]. Viral hepatitis B or C is linked to 30 per cent of cases of liver cancer in Australia[4]. Novel direct-acting antivirals are now available which halt the progression of Hepatitis B and in the case of Hepatitis C may offer cure. Other causes of chronic liver disease include toxins, metabolic, autoimmune, vascular and biliary disease (see table 1).

CIRRHOSIS

Cirrhosis represents the end point of chronic liver disease with fibrosis and scarring of liver tissue leading to significant liver dysfunction. It is independently associated with increased morbidity and mortality. Cirrhotics often have concomitant organ dysfunction with portal hypertension, splenomegaly, varices and possible thrombocytopenia. They are fragile and decompensate easily with higher blood transfusion requirements, longer lengths of stay, and increased risk of infection and perioperative complications. Del Olmo et al found a significant increase in 30-day mortality between cirrhotics (16.3 per cent) and controls (3.5 per cent) undergoing non-hepatic operative procedures[5]. The great majority of patients with cirrhosis are actually unaware of its presence. A high degree of clinical suspicion is therefore required. Diagnosis is difficult and relies on investigations. The presence of concomitant hypoalbuminaemia, thrombocytopenia and elevated INR should raise suspicion for cirrhosis. Historically, diagnostic confirmation was through ultrasound and biopsy. It can now be obtained through use of a Fibroscan (Echosens, Paris) which utilises low frequency ultrasound and elastography to measure liver elasticity or stiffness. The Fibroscan is portable, painless, rapid and useful for staging hepatitis along with the degree of liver fibrosis and cirrhosis[6]. In all cirrhotics undergoing surgery, careful consideration should be given to the necessity of the procedure, whether it should be performed in a tertiary hepatobiliary centre and whether high dependency unit (HDU) care is required. It is therefore important to estimate risk and consider risk modification, postoperative placement and hepatology input.

Table 1. Causes of liver failure

CHRONIC	ACUTE
Infection • Viral hepatitis • Cytomegalovirus • Epstein Barr Virus	**Infection** • Viral hepatitis
Alcohol	**Drugs** • Paracetamol • Antibiotics • Phenytoin • Halogenated volatiles • Rifampicin • MDMA (Ecstasy) • Idiosyncratic
Biliary obstruction • Congenital • Biliary stones	**Toxins** • Amanita phalloides
Autoimmune • Primary biliary cholangitis • Primary sclerosing cholangitis	**Miscellaneous** • Sepsis • HELLP • Reye's Syndrome • Lymphoma
Metabolic disease • NAFLD • Wilson's Disease • Haemochromatosis	
Vascular • Budd-Chiari • Thromboses	

ESTIMATING RISK

Risk stratification in patients with liver disease is an important consideration prior to embarking on surgery. It is particularly necessary for this patient group as peri-operative outcome is linked closely to the severity of underlying liver dysfunction.

Child-Pugh Score

Historically, the Child-Pugh Score was used to predict mortality in patients with liver disease undergoing surgery. It subsequently became a general overall prognostic tool in patients with liver disease. Developed in 1964, it calculates a score from the patient's bilirubin, INR, albumin, degree of ascites and encephalopathy[7] (see table 2). Scores are then stratified into three groups (A-C) based on increasing severity with A being a score <7 and C >9. Child-Pugh A, B, and C predict a perioperative mortality risk of 10, 30 and 80 per cent respectively[8]. Criticism of the Child-Pugh score relates to its subjective nature, limited discriminatory capacity and subsequent lack of accuracy. It places any patient into one of three classes rather than displaying a spectrum of severity[9]. A bilirubin score of 55 µmol/L, for example would be scored the same as a bilirubin score of 155 µmol/L – even though the degree of elevation in serum bilirubin level is known to be an important prognostic indicator in patients with cirrhosis[9]. The Child-Pugh has largely been surpassed by the Model for End Stage Liver Disease (MELD) score.

Table 2. Child Pugh Score[7]

CLINICAL/LAB MEASUREMENT	POINTS SCORED		
	1	2	3
Encephalopathy grade	None	1-2	3-4
Ascites	Absent	Mild	Moderate to severe
Albumin (g/L)	>35	28-35	<28
INR	< 1.7	1.7-2.3	>2.3
Bilirubin (mmol/L)	<35	36-60	>60

The Model for End Stage Liver Disease (MELD)

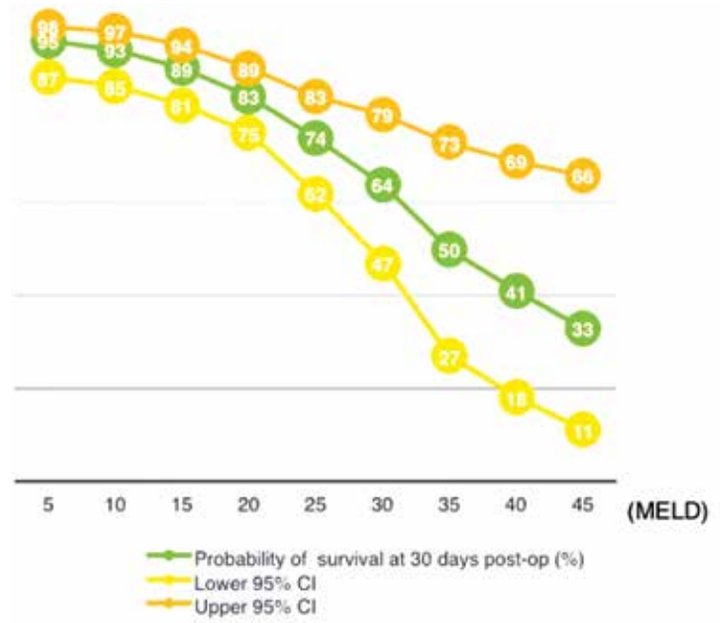
The MELD was originally developed in 2000 at the Mayo Clinic as a tool to predict three-month mortality in patients following Transjugular Intrahepatic Portosystemic Shunt (TIPS) procedures[10]. The score actually turned out to be predictive of prognosis in chronic liver disease in general. It has become the leading prognostic tool for estimating disease severity and survival in patients with chronic liver disease. In 2002 following modifications, it was adopted by the United Network for Organ Sharing (UNOS) and Organ Procurement Transplantation Network (OPTN) as an objective tool in assigning need for liver transplant. Its principal role is ranking patient's mortality risk on the transplant waiting list to aid allocation. It is also shown to have predictive value for mortality in patients with cirrhosis undergoing a variety of non-transplant surgical procedures[11,12]. The score ranges from six to 40 and is calculated from serum bilirubin, creatinine and INR[13].

MELD Score = 10 * ((0.957 * ln(Creatinine)) + (0.378 * ln(Bilirubin)) + (1.12 * ln(INR))) + 6.43

For patients who have had dialysis twice within the past week, or 24 hours of Continuous Veno-Veno-Haemodialysis (CVVHD), the creatinine value will automatically be set to 4 mg/dl. The inclusion of serum creatinine is an important contribution highlighting the importance of renal function in disease severity for patients with ESLD. A higher MELD score corresponds to a higher preoperative mortality risk. Patients with scores >15 should avoid elective surgery; 30-day post-operative survival decreases exponentially beyond MELD scores of 10 (see figure 1).

Figure 1. Probability of post-operative survival versus MELD (redrawn[11])

Weaknesses of the MELD score include the variability in measurement of INR and that serum creatinine is an



inaccurate marker of renal function in cirrhosis (influenced by muscle mass, protein dietary intake, age, ethnicity, and gender). Overall, the MELD score is based on widely available objective lab values, and is hence a more objective and robust predictor of perioperative outcome and mortality than the Child-Pugh score[14]. Modifications to the MELD have also arisen over time. The delta MELD (change in MELD score) has shown that an increasing MELD score predicts a higher mortality risk than a decreasing or stable MELD, even if the overall score is the same[14]. Hyponatraemia is a strong predictor of early mortality independent of the MELD score[15]. Its inclusion improves the accuracy of MELD particularly in patients with low MELD coupled with severe hyponatraemia[16].

PRE-OPERATIVE ASSESSMENT

Liver disease involves multi-system organ dysfunction with secondary manifestations and complications. A careful preoperative assessment adopting a thorough systems approach is therefore required. History, examination and investigations should be targeted towards disease aetiology, severity and its stability or progression. The routine use of liver function tests in the general population is not advised. Testing should instead be on the basis of history and examination. Deferring surgery is not necessary for mild elevations of transaminases, however, moderate to severe elevations warrant further evaluation. As always, determination of the necessity and timing of surgery must be confirmed. Pre-operative consultation with a hepatologist or medical gastrointestinal team should be considered in patients with advanced or moderately severe disease to facilitate assistance in the event of peri-operative decompensation. In adopting a systems approach to the patient, anaesthetists should recall the underlying pathophysiology of liver disease and take this into account when assessing the patient.

Neurological

Patients with severe or ESLD display altered brain metabolism and are at risk of developing encephalopathy with potential cerebral oedema and intracranial hypertension. Presentation ranges from mild confusion with impaired memory or psychomotor function to complete coma. Assessment can be performed utilising Glasgow Coma Scale or Conn Score (West Haven Criteria)[17]. The inappropriate use of sedatives or narcotics can exacerbate CNS depression. Gastrointestinal bleeds, dietary protein overload and sepsis can also precipitate altered neurological function. Normal bowel function with adequate emptying avoids elevations in gut ammonia and nitrogenous levels. Lactulose promotes reduction in soluble ammonia due to reduced gut pH along with direct removal. Rifaximin (an oral antimicrobial agent) also has a protective effect in reducing nitrogen producing enteric bacteria[18].

Respiratory

The respiratory system is rarely affected in early liver disease. Involvement may occur in severe ESLD when ascites contributes to atelectasis or hepatic hydrothorax. Both conditions reduce the functional residual capacity (FRC) placing patients at risk of desaturation. Patients with advanced liver disease and severe portal hypertension may also be at risk of pulmonary vascular complications such as portopulmonary hypertension (elevated mean pulmonary artery pressure secondary to increased pulmonary vascular resistance), and hepatopulmonary syndrome (HPS), (hypoxaemia due to pulmonary vasodilatation and shunting)[19]. HPS is diagnosed when portal hypertension, arterial hypoxaemia (age-corrected alveolar-arterial oxygen gradient of >2-2.7 kPa) and intrapulmonary vascular vasodilation are present in the absence of cardiopulmonary disease[20]. Desaturation occurs due to ventilation-perfusion mismatch and worsens in the upright position (platypnoea and orthodeoxia). Treatment is supportive with resolution seen following liver transplantation. The timing of transplantation prioritises early treatment as severe hepatopulmonary syndrome is a contra-indication. Medical treatment is disappointing, and transplantation offers improvement or cure in 85 per cent of patients.[21].

Cardiovascular

ESLD patients display a hyperdynamic circulation with tachycardia, increased cardiac output and low SVR. These compensatory cardiovascular changes may occur due to splanchnic vasodilation, sodium and fluid retention and increased production coupled with decreased hepatic clearance of vasodilating substances such as nitric oxide, carbon monoxide, endogenous cannabinoids and Tumor Necrosis Factor alpha[22]. Clinically, patients mimic the haemodynamic profile of sepsis. The presence of underlying cirrhotic cardiomyopathy or ventricular dysfunction can be masked. Patients are often beta blocked to aid reduction in portal pressures and reduce the risk of variceal bleeding. For major surgery in those unable to provide satisfactory exertional history a transthoracic echocardiogram should be considered to assess overall systolic and diastolic ventricular function and exclude pulmonary hypertension. QT prolongation is also common and worsens in parallel with severity of disease[23]. Hypomagnesaemia is common and may need correction.

Portopulmonary hypertension (PPHTN) is defined by right heart catheterisation showing a mean pulmonary artery pressure (MPAP) >25 mmHg at rest, Pulmonary Capillary Wedge pressure <15 mmHg and pulmonary vascular resistance >240 dynes.sec.cm-5 (or three Woods units)[24]. If present, patients can develop subsequent right ventricular (RV) dysfunction. These patients pose a high perioperative mortality risk with challenging haemodynamic management and fluid balance. Surgery should be undertaken only when absolutely necessary. Liver transplantation itself is contraindicated where MPAP exceeds 50 mmHg; is associated with significant RV dysfunction or where pulmonary vasodilator therapy fails to reduce MPAP below 35 mmHg[24,25].

Renal and electrolytes

Renal dysfunction is common in patients with advanced liver disease and cirrhosis. Its presence represents a higher perioperative risk of mortality and morbidity than liver dysfunction alone. Causation is multifactorial and contributed to by low SVR states leading to an altered renin-angiotensin-aldosterone system and subsequent ascites, oedema, renal intravascular vasoconstriction and hypoperfusion[26]. Attention must be given to adequate preoperative fluid balance, avoidance of nephrotoxins and highlighting patients at risk of requiring renal replacement therapy in the postoperative period. With progressive reductions in renal function and advanced hepatic failure, consideration must be given to the presence of hepatorenal syndrome (HRS). Divided into two types, criteria for the syndrome are shown in table 3[27].

Table 3. Criteria for hepatorenal syndrome

(i)	Cirrhosis with ascites.
(ii)	Serum creatinine greater than 133 µmol/L over days to weeks or an increase of greater than 26.5 µmol/L within 48h.
(iii)	No improvement of creatinine after 2 days of diuretic withdrawal and volume expansion with albumin.
(iv)	Absence of shock.
(v)	No current or recent treatment with nephrotoxic drugs.
(vi)	Absence of parenchymal kidney disease.

Management of HRS is complex, ideally involving improvement of underlying liver dysfunction. Medical therapy with terlipressin, octreotide or noradrenaline to elevate mean arterial pressure may be required[27]. TIPS procedures can provide short-term benefit, though are considered high risk and utilised only as a last resort. Where a reversible liver insult is present or liver transplantation is possible, dialysis may provide bridging therapy whilst awaiting improvement in liver function. When assessing patients with concomitant renal and hepatic dysfunction the help of nephrologists should be sought early to aid assistance postoperatively.

Electrolyte and fluid disturbances are common in patients with advanced disease. Ascites, peripheral oedema, hypoalbuminaemia, hyponatraemia, hypomagnesaemia and hypo-phosphataemia are frequently encountered. Attention should be given to correction of the “intravascularly deplete, yet extravascularly full” state. Magnesium and phosphate depletion should be corrected to improve overall cellular function and avoid risk of dysrhythmias. Hyponatraemia is a common finding in patients with cirrhosis. The degree of severity correlates to that of cirrhosis and contributes to encephalopathy[28]. If present, sodium levels should be monitored with avoidance of rapid over-correction due to risk of precipitating central pontine myelinolysis. For a full description of acid-base and electrolyte disorders in liver disease see Scheiner et al[29].

Gastrointestinal

The gastrointestinal features of advanced liver disease include the development of portal hypertension and its sequelae along with global malnutrition states. Portal hypertension arises principally due to increased vascular resistance within the portal system. Cirrhosis and scarring is the most common contributor though portal thrombotic disease may also be responsible. It is often exacerbated by splanchnic vasodilatation due to the production of endogenous vasodilators. Principal manifestations are; oesophageal, gastric and haemorrhoidal varices, splenomegaly with thrombocytopenia, and the development of ascites. Oesophageal and gastric varices are predisposed to rupture and haemorrhage. Severity should be determined preoperatively in any patient with severe portal hypertension or history of haematemesis. Endoscopic ligation, sclerotherapy and nonselective beta-blocker therapy are undertaken as prophylaxis against bleeding. Sengstaken tube placement and TIPS procedures are reserved for those with haemorrhage where endoscopic and pharmacological therapies fail[30].

The presence of tense ascites is associated with a 50 per cent mortality at five years[31]. It predisposes patients to aspiration, spontaneous bacterial peritonitis and haemodynamic instability arising from impaired venous return. FRC may be reduced increasing risk of rapid desaturation following induction of anaesthesia. Consideration should be given to paracentesis preoperatively or immediately following induction of anaesthesia. Treatment reduces the likelihood of renal impairment and electrolyte derangement. Volume replacement with albumin solutions should be given to avoid post-paracentesis circulatory dysfunction.

Many patients with liver disease are malnourished with sarcopenia, increasing the risk of sepsis. Patients with ascites often require low sodium diets. Pre- and postoperative nutritional plans should be established in consultation with dieticians to aid overall recovery.

Coagulation system

The coagulation system of patients with liver disease is perceived as being associated with clinical bleeding due to deficiency in pro-coagulant factors. The reality is more complex involving a balance between coagulopathy

and prothrombotic states. The majority of coagulation proteins are reduced with the exception of Factor VIII and von Willebrand factor[32,33]. Reduced levels do not impair thrombin generation until their concentration is extremely low. Preoperative assessment of coagulation should be clinically based and will vary with severity of disease. Laboratory investigations should be supportive of clinical decision making rather than directive. Hypersplenism and platelet consumption result in thrombocytopenia, while abnormal platelet and endothelial function, dysfibrinogenaemia, excessive fibrinolysis and renal failure add to the complicated picture[33]. While the majority of patients with liver disease have mild to moderate thrombocytopenia and platelet dysfunction, platelet transfusion is rarely required as platelet counts of 50-60 × 10 9/L are sufficient to trigger coagulation and high levels of von Willebrands Factor are protective[34]. The INR and APTT are measures of secondary haemostasis that do not correlate directly with bleeding tendency. Assessment of preoperative bleeding risk using these parameters alone is unreliable as they do not take into account other key components of the coagulation system such as Protein C and S and vascular endothelium. Normal to high levels of factor VIII can also normalise APTT despite multiple deficiencies of procoagulant factors[35]. Preoperative INR has no predictive value in relation to intraoperative blood loss and the administration of fresh frozen plasma (FFP) solely on the basis of abnormal INR is not advised.

INTRAOPERATIVE CONSIDERATIONS

As with any patient, the choice of anaesthetic and level of monitoring should be tailored to the nature of surgery and overall patient assessment. Patients with mild liver disease, Child-Pugh A classification or low and stable MELD differ little from other patients in intra-operative management. Appropriate care and monitoring should be exercised postoperatively to ensure no decompensation or deterioration in liver function.

Patients with moderate to severe and ESLD warrant special consideration. Intraoperative management is influenced by the surgical procedure, risk stratification, disease severity and underlying organ dysfunction.

Airway and ventilation

In patients with severe ascites, rapid sequence induction should be considered due to risk of aspiration resulting from raised intra-abdominal pressure. Where tense ascites is present, a longer period of preoxygenation in a slight head-up position helps off-set the impact on FRC.

In cases of respiratory impairment due to severe ascites or hepatic hydrothorax, preoperative drainage should be considered. Post-paracentesis complications of infection, circulatory dysfunction and electrolyte/renal derangement may arise. Hypoxia, hypercarbia, acidosis and hypothermia increase pulmonary vascular resistance, worsening pulmonary hypertension and RV dysfunction. Hypocarbia and hypoxia lead to hepatic vasoconstriction, reduction in hepatic blood flow and subsequent liver ischaemia.

Circulation

Reductions in mean arterial pressure (MAP) lead to a reduction in portal venous and hepatic arterial blood flow. These changes are exacerbated by IPPV, pneumoperitoneum, head-up position and direct compression during surgery in and around the liver. A relative fluid restriction is important to preserve the glycocalycx and reduce fluid extravasation.

In liver resection, fluid requirement is balanced against the potential for liver congestion and blood loss. The use of low central venous pressure (CVP) to avoid bleeding is a standard of practice to decrease blood loss[36]. Techniques for reduction include head up position, fluid restriction during the resection phase, glyceryl trinitrate (GTN) and furosemide to help maintain a state of hypovolaemia and vasodilation. This reduces hepatic vein back pressure and venous bleeding. Haemodynamic instability with reduced cardiac output and an increased risk of air embolism may be exacerbated by hypovolaemia[37,38]. Appropriate open communication between surgeon and anaesthetist is critical in obtaining optimal conditions through reduction in CVP while ensuring judicious fluid replacement and monitoring end-tidal CO_2. In a meta-analysis and systematic review, Hughes et al found that while a low CVP technique reduced blood loss and transfusion rates after liver resection, this did not correspond to improvements in overall terms of morbidity or length of hospital stay[39].

Surgical methods for haemostatic control during liver resection have improved greatly over time. Devices such as the Cavitron Ultrasonic Surgical Aspirator (CUSA, Valleylab), Harmonic Scalpel, Bipolar vessel sealing device (LigaSure) and Argon beam coagulator have led to faster transection times with more effective haemostasis[40]. Use of intraoperative ultrasound aids delineation of proper transection planes. Radiofrequency-assisted liver resection and ablation techniques are other relatively new modalities allowing resection of certain tumors with reduced blood loss[41]. As a result, the use of vessel occlusion techniques such as the Pringle manoeuvre (clamping of the hepatoduodenal ligament to cease hepatic artery and portal vein flow) and inferior vena cava (IVC) clamp are less commonly utilised. If such manoeuvres are performed, the anaesthetist must be aware of the potential for iatrogenic liver injury, liver ischaemia, increased portal/splanchnic pressures, reperfusion injury and thrombo-embolic phenomena.

Access and monitoring

Access and monitoring is influenced by the nature of surgery, severity of disease, comorbidities and associated organ dysfunction. For major surgeries, arterial blood gas monitoring is recommended to enable assessment

of haemoglobin, electrolytes and acid base status. The clearance of lactate postoperatively is a useful surrogate indicator of volume status and underlying liver function. In situations of elevated lactate care must be given to fully investigate all causes before attributing elevations to liver disease alone[42].

Thromboelastography (TEG) and Thromboelastometry (ROTEM) are viscoelastic tests providing point-of-care information on clot formation, strength, and stability. Their use reduces transfusion requirements in liver transplantation and currently is the gold standard for displaying fibrinolysis and hypercoagulability[43]. Intraoperative inspection of the wound edges and surgical field is essential in determining the need for administration of coagulation products. TEG allows guidance and direction of which products are required.

Where significant blood loss is possible large bore IV access must be established with consideration of rapid infusion devices and cell salvage. Central venous lines (CVL) are standard of care for major liver surgery at many institutions. Abnormal laboratory coagulation parameters do not require correction prior to CVL placement[44], especially when inserted by experienced clinicians utilising ultrasound guidance. In robust patients undergoing minimally invasive and less complex resections a CVL is not always necessary[44]. In centers with extensive experience, this is also the case, as fluid restriction may be implemented independently of CVP monitoring[37].

Patients with severe PPHTN are a significant clinical challenge requiring intraoperative monitoring via TOE or pulmonary artery catheter (PAC). The use of a PAC can however result in serious complications including PA rupture, arrhythmias, and death[45]. Placement should only be performed in appropriate patients by experienced practitioners. Despite being a poor predictor of fluid responsiveness[46] their ability to measure cardiac output and provide a direct measure of pulmonary artery and capillary wedge pressures guides management. TOE provides a more useful dynamic assessment of the effects of pulmonary pressures on the right ventricle. Valuable information on volume status, ventricular/valvular function and the presence of air or clot may be obtained. Numerous retrospective studies have demonstrated safe placement in the presence of varices and coagulopathy and this should not be viewed as a contraindication[47,48].

PHARMACOLOGICAL CONSIDERATIONS

Sedatives

Sedatives (for example, benzodiazepines) are generally avoided in this patient population due to decreased metabolism, prolonged clinical effect and the possibility of worsening encephalopathy.

Opioids

The liver is the major site of biotransformation and metabolism of opioids. In patients with cirrhosis the elimination half-life of morphine is prolonged which can lead to the exacerbation of sedative or respiratory depressant effects, especially with repeated administration[49]. If opioids are utilised, appropriate O_2 saturation monitoring should be in place with consideration for dose reduction and longer dosing intervals for increased safety. The use of intrathecal morphine is increasingly being used following liver resection for its effective analgesia and avoidance of epidural-related sequelae[50]. Postoperatively, patients are often monitored in HDU due to the potential for respiratory depression. Numerous studies have shown this is rare at doses <5μg/kg (max 400μg)[51,52]. Pethidine should be avoided due to the potential accumulation of norpethidine, a metabolite that causes seizures. The half-life and bioavailability of oxycodone is increased, hence dose reduction or a longer dosing interval should also be applied. Methadone is metabolised in the liver resulting in reduced clearance. It does not however have toxic metabolites and is well tolerated in patients with mild to moderate liver failure if standard doses are used[48]. In severe liver failure the half-life increases and it should be used cautiously[53]. Tramadol is metabolised to active metabolites in the liver. While the risk of respiratory depression is less than with morphine, dose reduction and care should still be exercised due to its significant side effect profile (seizures, serotonergic syndrome)[49,53]. The disposition of fentanyl and remifentanil remain unchanged in severe liver disease and these can be used in the same manner as in patients without liver disease[49].

Paracetamol

Paracetamol overdose is one of the leading causes of acute liver failure in many parts of the western world including Australia[54]. This association has led to many practitioners avoiding the drug in patients with liver impairment. It is, however, a safe and useful analgesic for this patient population and free of sedative or nephrotoxic effects. The majority of paracetamol's metabolism is via sulfation and glucuronidation. A small proportion is oxidised via the CYP system to a hepatotoxic intermediate, N-acetyl-p-benzoquinone imine (NAPQI), which is then rendered non-toxic by conjugation to glutathione[53]. While the half-life of paracetamol may be prolonged in liver disease, CYP activity is not increased (with subsequent less NAPQI formation). Glutathione stores are also generally sufficient to avoid paracetamol hepatotoxicity. Current recommendations including those of the FDA are to limit long-term (>14d) doses to 2-3 g/day. Short-term dosing is safe at 4 g/day for adults[53,55].

Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are generally avoided in patients with liver disease due to possible gastrointestinal bleeds, worsening platelet dysfunction and renal impairment. There is limited study data available for recommendation on the use

of COX-2 selective NSAIDs in the liver disease population. Despite a lower side effect profile than COX-1 inhibitors the potential for renal dysfunction still exists so their use is not recommended[56].

Regional/local anaesthetics

The use of regional anaesthesia allows a decrease in patient exposure to sedatives and opioid analgesia avoiding potential respiratory depression, worsening encephalopathy and other opioid related side effects. Correction of underlying coagulopathy to facilitate neuraxial approach is not recommended. Where coagulopathy is present, peripheral techniques may be adopted. The use of continuous bilateral transversus abdominis plexus (TAP) and rectus sheath blocks have been shown to provide effective analgesia and an alternative to epidurals[57,58,59]. Plasma local anaesthetic (LA) levels are higher in patients with liver dysfunction due to altered distribution and impaired metabolism[60]. The safe amount of long-acting LA in liver disease either by wound instillation or epidural is unknown. If liver dysfunction is present postoperatively, a limitation of 48h infusion and ropivacaine concentration no greater than 0.25 per cent has been recommended in order to avoid accumulation and toxicity[61].

Muscle relaxants

Atracurium and cis-atracurium are the preferred relaxants for patients with liver disease due to their organ independent elimination through Hoffman degradation. Plasma cholinesterase levels are decreased in severe liver failure prolonging the duration of action of suxamethonium though this is rarely a problem clinically. Rocuronium and vecuronium are metabolised by the liver requiring dose reduction but may be an alternative since the introduction of sugammadex. A neuromuscular monitor should be utilised in all patients with significant liver dysfunction to aid clinical decision making for extubation.

Sugammadex

Sugammadex is neither metabolised nor excreted by the liver. The data sheet however advises caution for use in patients with hepatic impairment accompanied by coagulopathy[62] due to changes in coagulation profiles following administration[63,64]. None of the studies have shown a clinically significant difference in bleeding between the control groups and sugammadex groups[65,66] and studies have been performed in patients with liver disease demonstrating its safety[67].

Propofol/volatile agents

Liver function after resection or transplantation may be better after propofol TIVA[68,69] than volatile agents but there is little evidence for relative benefit in cirrhosis. Drug hapten-induced hepatitis following exposure to volatile agents is rare. The move from halothane to newer volatile agents has not eliminated the possibility of an idiosyncratic reaction and this has been described for all halogenated volatile agents including desflurane[70].

Thromboprophylaxis

Cirrhosis may be associated with an increase in venous thromboembolic events (VTE) due to an imbalance between thrombotic and antithrombotic proteins. Enhanced thrombin in association with partial deficiency in endogenous anticoagulants may be responsible[71]. Studies range between 0.5-6.3 per cent for incidence of new deep vein thrombosis (DVT) or pulmonary embolus (PE) in patients with cirrhosis[72,73]. Søgaard et al found a higher relative risk of venous thromboembolism compared to the general population[74]. In addition, patients are at high risk of portal vein and other splanchnic thromboses. Patients with cirrhosis having undergone surgery should receive thromboprophylaxis to mitigate this risk. This is often neglected due to the presence of underlying coagulopathy and varices. The decision on which prophylactic anticoagulant to utilise should be on a case by case basis. Options include unfractionated and low molecular weight heparin (LMWH), vitamin K antagonists (Warfarin) and direct acting oral anticoagulants (Dabigatran). This is complicated by a lack of adequate studies or established guidelines, the absence of an ideal lab monitoring test and the presence of pre-existing elevations in INR or APTT. Where risk of surgical bleeding is high mechanical therapy should be used. The ability to reverse unfractionated heparin (protamine), warfarin (prothrombin complex concentrates) or dabigatran (idarucizumab) is an advantage of these agents over LMWH.

Drug Induced Liver Injury

Drug Induced Liver Injury (DILI) is the commonest cause of acute liver failure (ALF) in Australasia. In most cases this is an idiosyncratic and unpredictable reaction. Aside from paracetamol overdose, commonly implicated drugs are antibiotics (particularly amoxicillin/clavulanate), anti-tuberculosis therapies, sulpha-containing drugs, nitrofurantoin, phenytoin and sodium valproate[75]. Herbal/dietary medicines are also increasingly implicated. DILI includes a spectrum from asymptomatic elevation in liver transaminases to acute liver failure. It most commonly presents with unexpected jaundice. Management involves cessation of causative agent and early referral to a hepatologist. In cases progressing to ALF liver transplantation may be required.

NEW CONSIDERATIONS FOR PATIENTS WITH HEPATITIS

Australia has embarked on an ambitious path to eradicate hepatitis C disease. This is thought possible due to high cure rates (>90 per cent) achieved by short duration (12 weeks) direct-acting antiviral (DAA) combinations. Sustained virological response is associated with improvement in liver function, reduced rates of HCC[76], reduced portal venous pressure, decreased oesophageal varices and fewer liver transplantations[77]. Cost estimates show effectiveness, though barriers to eradication do exist[78]. Patients presenting for elective surgery with newly diagnosed hepatitis C should have antiviral treatment considered prior to surgery for risk mitigation. Treatment regimens are based on the viral genotype which varies with region[79]. Unfortunately, some trials have reported a high recurrence rate for HCC after HCV eradication and further studies are in progress to address the controversy surrounding this[80]. Sustained virological response rates for hepatitis B infection are lower and lifelong therapy is required for control.

POSTOPERATIVE CARE

Postoperatively patients require ongoing monitoring and management due to potential for decompensation with sepsis, encephalopathy and renal dysfunction. An HDU area with access to physicians experienced in dealing with these patients is important for successful outcomes in patients undergoing major surgeries and those with moderate to severe disease. Decompensation is life-threatening requiring early referral to hepatologists and intensive care for prompt diagnosis and treatment of the underlying cause.

CONCLUSION

In this article we have described the important considerations for the anaesthetist when faced with patients with liver disease. Approaches to management include risk stratification and a systems based pre-operative assessment cognisant of the pathophysiological implications of the disease. Intraoperative care involves planning of monitoring, fluid therapy and anaesthetic technique, tailored to the severity of disease and nature of surgery. Careful consideration should be given to post-operative drug selection with cautious use of agents undergoing hepatic metabolism and avoidance of nephrotoxins. Appropriate postoperative placement is paramount with patients with moderate to severe disease better cared for in tertiary hepatobiliary centres. Decompensated liver disease is life-threatening requiring multidisciplinary input in consultation with hepatology and intensive care physicians.

REFERENCES

1. Gastroenterological Society of Australia (GESA) and Australian Liver Association (ALA). Economic cost and health burden of liver disease in Australia [Internet]. 2013. From: http://www.gesa.org.au/resources/economic-cost-and-health-burden-of-liver-disease-in-australia/. Accessed 1 July 2017.
2. Townsend SA, Newsome PN. New treatments in non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2017;46(5):494–507.
3. Strasser S. Hepatocellular carcinoma: the most rapidly rising cause of cancer death in Australia. Med Today. 2013;14(12):55–57.
4. Amin J, Dore GJ, O'Connell DL, Bartlett M, Tracey E, Kaldor JM, et al. Cancer incidence in people with hepatitis B or C infection: a large community-based linkage study. J Hepatol. 2006;45(2):197–203.
5. Del Olmo JA, Flor-Lorente B, Flor-Civera B, Rodriguez F, Serra MA, Escudero A, et al. Risk factors for nonhepatic surgery in patients with cirrhosis. World J Surg. 2003;27(6):647–652.
6. Nakamura Y, Aikata H, Fukuhara T, Honda F, Morio K, Morio R, et al. Liver fibrosis assessment by FibroScan compared with pathological findings of liver resection specimen in hepatitis C infection. Hepatol Res. 2017;47(8):767–772.
7. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg. 1964;1:1–85.
8. Mansour A, Watson W, Shayani V, Pickleman, J. Abdominal operations in patients with cirrhosis: still a major surgical challenge. Surgery. 1997;122(4):730–735.
9. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from child to MELD. Mayo End-stage Liver Disease. Hepatology. 2001;33(2):473–475.
10. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31(4):864–871.
11. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for end-stage liver disease (MELD) predicts non-transplant surgical mortality in patients with cirrhosis. Ann Surg. 2005;242(2):244–251.
12. Kamath PS, Kim WR, Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology. 2007;45(3):797–805.
13. Bambha K, Kamath PS. Model for End Stage Liver Disease (MELD) [Internet]. 2016. From: www.uptodate.com/contents/model-for-end-stage-liver-disease-meld. Accessed 2 September 2017.
14. Merion RM, Wolfe RA, Dykstra DM, Leichtman AB, Gillespie B, Held PJ. Longitudinal assessment of mortality risk among candidates for liver transplantation. Liver Transpl. 2003;9(1):12–18.
15. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359(10):1018–1026.
16. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology. 2006;130(6):1652–1660.
17. Nabi E, Bajaj JS. Useful tests for hepatic encephalopathy in clinical practice. Curr Gastroenterol Rep. 2014;16(1):362.
18. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362(12):1071–1081.
19. Porres-Aguilar M, Altamirano JT, Torre-Delgadillo A, Charlton MR, Duarte-Rojo A. Portopulmonary hypertension and hepatopulmonary syndrome: a clinician-oriented overview. Eur Respir Rev. 2012;21(125):223–233.
20. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome – a liver-induced lung vascular disorder. N Engl J Med. 2008;358(22):2378–2387.
21. Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome: impact of liver transplantation. Hepatology. 2005;41(5):1122–1129.

22. Hennenberg M, Trebicka J, Sauerbruch T, Heller J. Mechanisms of extrahepatic vasodilation in portal hypertension. Gut. 2008;57(9):1300–1314.
23. Bernardi M, Maggioli C, Dibra V, Zaccherini G. QT interval prolongation in liver cirrhosis: innocent bystander or serious threat?. Expert Rev Gastroenterol Hepatol. 2012;6(1):57–66.
24. Krowka MJ, Wiesner RH, Heimbach JK. Pulmonary contraindications, indications and MELD exceptions for liver transplantation: a contemporary view and look forward. J Hepatol. 2013;59(2):367–374.
25. Bozbas SS, Bozbas H. Portopulmonary hypertension in liver transplant candidates. World J Gastroenterol. 2016;22(6):2024–2029.
26. Kiamanesh D, Rumley J, Moitra VK. Monitoring and managing hepatic disease in anaesthesia. Br J Anaesth. 2013;111(Suppl 1):i50–61.
27. Runyon BA. Hepatorenal syndrome [Internet]. 2016. From: https://www.uptodate.com/contents/hepatorenal-syndrome. Accessed 16 July 2017.
28. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology. 2004;40(4):802–810.
29. Scheiner B, Lindner G, Reiberger T, Schneeweiss B, Trauner M, Zauner C, et al. Acid-base disorders in liver disease. J Hepatol. pii:S0168-8278(17)32131–1.
30. Hilzenrat N, Sherker AH. Esophageal varices: pathophysiology, approach, and clinical dilemmas. Int J Hepatol. 2012;2012:795063–2.
31. Planas R, Montoliu S, Ballesté B, Rivera M, Miquel M, Masnou H, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol. 2006;4(11):1385–1394.
32. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365(2):147–156.
33. Tripodi A, Primignani M, Mannucci PM, Caldwell SH. Changing concepts of cirrhotic coagulopathy. Am J Gastroenterol. 2017;112(2):274–281.
34. Refaii, M. Haemostasis disorders in liver disease [Internet]. n.d. From: http://www.clinicalpainadvisor.com/labmed/hemostasis-defects-associated-with-liver-disease/article/614627/?utm_source=TrendMD&DCMP=OTC-CPA_trendmd&dl=0. Accessed 1 September 2017.
35. Blasi A. Coagulopathy in liver disease: lack of an assessment tool. World J Gastroenterol. 2015;21(35):10062–10071.
36. Melendez JA, Arslan V, Fischer ME, Wuest D, Jarnagin WR, Fong Y, et al. Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood loss, blood transfusion, and the risk of postoperative renal dysfunction. J Am Coll Surg. 1998;187(6):620–625.
37. Niemann CU, Feiner J, Behrends M, Eilers H, Ascher NL, Roberts JP. Central venous pressure monitoring during living right donor hepatectomy. Liver Transpl. 2007;13(2):266–271.
38. Poznanzsk G, Durczynski P, Gaszynski W. Venous air embolism during major liver surgery: far more common than we think. Eur J Anaesthesiol. 2014;31(2):120–121.
39. Hughes MJ, Ventham NT, Harrison EM, Wigmore SJ. Central venous pressure and liver resection: a systematic review and meta-analysis. HPB (Oxford). 2015;17(10):863–887.
40. Romano F, Garancini M, Uggeri F, Degrate L, Nespoli L, Gianotti L. Bleeding in hepatic surgery: sorting through methods to prevent it. HPB Surg. 2012;2012:169351–12.
41. Weber JC, Navarra G, Jiao LR, Nicholls JP, Jensen SL, Habib NA. New technique for liver resection using heat coagulative necrosis. Ann Surg. 2002;236(5):560–563.
42. Kruse JA, Zaidi SA Carlson RW. Significance of blood lactate levels in critically ill patients with liver disease. Am J Med. 1987;83(1):77–82.
43. Weeder PD, Porte RJ, Lisman T. Hemostasis in liver disease: implications of new concepts for perioperative management. Transfus Med Rev. 2014;28(3):107–113.
44. Mumtaz H, Williams V, Hauer-Jensen M, Rowe M, Henry-Tillman S, Heaton K, et al. Central venous catheter placement in patients with disorders of hemostasis. Am J Surg. 2000;180(6):503–505.
45. Dalen JE. The pulmonary artery catheter – friend, foe, or accomplice?. JAMA. 2001;286(3):348–350.
46. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest. 2002;121(6):2000–2008.
47. Myo Bui CC, Worapot A, Xia W, Delgado L, Steadman RH, Busuttil RW, et al. Gastroesophageal and hemorrhagic complications associated with intraoperative transesophageal echocardiography in patients with model for end-stage liver disease score 25 or higher. J Cardiothorac Vasc Anesth. 2015;29(3):594–597.
48. Leung C, Yeoh SW, Lim LY, Boyapati R, Testro AG, Vaughan R, et al. To TOE or not to TOE? That is the question in patients with portal hypertension and varices. Gut. 2013;62(4):655–656.
49. Soleimanpour H, Saeid S, Shahsavari Nia K, Sanaie S, Alavian SM. Opioid drugs in patients with liver disease: a systematic review. Hepatol Mon. 2016;16(4):e32636.
50. Tzimas P, Prout J, Papadopoulos G, Mallett SV. Epidural anaesthesia and analgesia for liver resection. Anaesthesia. 2013;68(6):628–635.
51. Kasivisivanathan R, Abbassi-Ghadi N, Prout J, Clevenger B, Fusai GK, Mallett SV. A prospective cohort study of intrathecal versus epidural analgesia for patients undergoing hepatic resection. HPB (Oxford). 2014;16(8):768–775.
52. De Pietri L, Siniscalchi A, Reggiani A, Masetti M, Begliomini B, Gazzi M, et al. The use of intrathecal morphine for postoperative pain relief after liver resection: a comparison with epidural analgesia. Anesth Analg. 2006;102(4):1157–1163.
53. Dwyer JP, Jayasekera C, Nicoll A. Analgesia of the cirrhotic patient: a literature review and recommendations. J Gastroenterol Hepatol. 2014;29(7):1356–1360.

54. Gow PJ, Jones RM, Dobson JL, Angus PW. Etiology and outcome of fulminant hepatic failure managed at an Australian liver transplant unit. J Gastroenterol Hepatol. 2004;19(2):154–159.
55. Chandok N and Watt KD. Pain management in the cirrhotic patient: the clinical challenge. Mayo Clin Proc. 2010;85(5):45–-458.
56. Coulter D. COX-2 inhibitors and hepatotoxicity [Internet]. Prescriber Update. 2003;24(1):2. From: http://www.medsafe.govt.nz/profs/puarticles/cox2liver.htm. Accessed 1 September 2017.
57. Hebbard PD, Barrington MJ, Vasey C. Ultrasound-guided continuous oblique subcostal transversus abdominis plane blockade: description of anatomy and clinical technique. Reg Anesth Pain Med. 2010;35(5):436–441.
58. Bell R, Pandanaboyana S, Prasad KR. Epidural versus local anaesthetic infiltration via wound catheters in open liver resection: a meta-analysis. ANZ J Surg. 2014;85(1–2):16–21.
59. Sandeman DJ, Dilley AV. Ultrasound-guided rectus sheath block and catheter placement. ANZ J Surg. 2008;78(7):621–623.
60. Yokoyama M, Mizobuchi S, Nagano O, Fujii H, Yamashita M, Hirakawa M. The effects of epidural insertion site and surgical procedure on plasma lidocaine concentration. Anesth Analg. 2001;92(2):470–475.
61. Chan, SK, Lai, PB, Li PT, Wong J, Karmakar MK, Lee KF, et al. The analgesic efficacy of continuous wound instillation with ropivacaine after open hepatic surgery. Anaesthesia. 2010;65(12):1180–1186.
62. U.S. Food and Drug Administration. Bridion (sugammadex) injection [Internet]. 2015. From: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022225lbl.pdf. Accessed 10 September 2017.
63. De Kam PJ, Grobara P, Prohn M, Höppener F, Kluft C, Burggraaf J, et al. Effects of sugammadex on activated partial thromboplastin time and prothrombin time in healthy subjects. Int J Clin Pharmacol Ther. 2014;52(3);227–236.
64. Carron M, Bertini D, Prandini T, Fanton F, Foletto M, Ori C, et al. Effect of sugammadex on coagulation as detected by rotational thromboelastometry in morbidly obese patients. Minerva Anesthesiol. 2017;Jul 13: [ePub ahead of print].
65. Carron M. Effects of sugammadex on coagulation: it does not represent a bleeding risk in surgical patients. Int J Clin Pharmacol Ther. 2014;52(9):824.
66. Abrishami A, Ho J, Wong J, Yin L, Chung F. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. Cochrane Database Syst Rev. 2009;7:CD007362.
67. Fujita A, Ishibe N. Rapid reversal of neuromuscular blockade by sugammadex after continuous infusion of rocuronium in patients with liver dysfunction undergoing hepatic surgery. Acta Anaesthesiol Taiwan. 2014;52(2):54–58.
68. Laviolle B, Basquin C, Aguillon D, Compagnon P, Morel I, Turmel V, et al. Effect of an anesthesia with propofol compared with desflurane on free radical production and liver function after partial hepatectomy. Fundam Clin Pharmacol. 2012;26(6):735–742.
69. Xu Z, Yu J, Wu J, Qi F, Wang H, Wang Z, et al. The effects of two anesthetics, propofol and sevoflurane, on liver ischemia/reperfusion injury. Cell Physiol Biochem. 2016;38(4):1631–1642.
70. Chin MW, Njoku DB, MacQuillan G, Cheng WS, Kontorinis N. Desflurane-induced acute liver failure. Med J Aust. 2008;189(5):293–294.
71. Dhar A, Mullish BH, Thursz MR. Anticoagulation in chronic liver disease. J Hepatol. 2017;66(6):1313–1326.
72. Northup PG, McMahon MM, Ruhl AP, Altschuler SE, Volk-Bednarz A, Caldwell SH, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. Am J Gastroenterol. 2006;101(7):1524–1528.
73. Gulley D, Teal E, Suvannasanka A, Chalasani N, Liangpunsakul S. Deep vein thrombosis and pulmonary embolism in cirrhosis patients. Dig Dis Sci. 2008;53(11):3012–3017.
74. Søgaard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol. 2009;104(1):96–101.
75. Katarey D, Verma S. Drug-induced liver injury. Clin Med (Lond). 2016;16(Suppl 6):s104–s109.
76. Teng W, Hsieh Y-C, Lui K-W, Chen W-T, Hung C-F, Huang C-H, et al. Eradication of hepatitis C virus profoundly prolongs survival in hepatocellular carcinoma patients receiving transarterial chemoembolization. J Viral Hepat. 2017;00:1–8..
77. Afdhal N, Everson GT, Calleja JL, McCaughan GW, Bosch J, Brainard DM, et al. Effect of viral suppression on hepatic venous pressure gradient in hepatitis C with cirrhosis and portal hypertension. J Viral Hepat. 2017;24(10):823–831.
78. Scott N, Iser DM, Thompson AJ, Doyle JS, Hellard ME. Cost-effectiveness of treating chronic hepatitis C virus with direct-acting antivirals in people who inject drugs in Australia. J Gastroenterol Hepatol. 2016;31(4):872–882.
79. Lim SG, Aghemo A, Chen P-J, Dan YY, Gane E, Gani R, et al. Management of hepatitis C virus infection in the Asia-Pacific region: an update. Lancet Gastroenterol Hepatol. 2017;2(1):52–62.
80. Colombo M, Bruno S, Lleo A. Hepatitis C virus eradication with direct antiviral agents and liver cancer recurrence: is the best the enemy of the good?. Liver Int. 2017;37(8):1110–1112.

Perioperative hyperglycaemia – epiphenomenon or therapeutic target?

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INTRODUCTION

Perioperative hyperglycaemia is increasingly recognised as a common occurrence in surgical patients and there is concern as to its significance and how best to manage it[1]. This increased recognition is attributable to multiple factors; awareness of the prevalence of insulin resistance and diabetes in the community (often associated with increasingly sedentary lifestyles and an epidemic of obesity), an increase in the frequency of perioperative laboratory testing, and emerging concern that perioperative hyperglycaemia may be a marker of higher risk and adverse outcome. The critical care community has been examining these issues with large trials over the past 16 years, primarily involving patients undergoing cardiac surgery and patients with critical illnesses[2-6]. The consensus appears to be that intensive blood glucose control can cause more harm than benefit and is not therefore recommended for these patients[7]. However, we are only now turning our attention to this issue in the broader context of non-critically ill patients undergoing non-cardiac surgery. This chapter limits its discussion principally to this group of patients.

EPIDEMIOLOGY OF PERIOPERATIVE HYPERGLYCAEMIA

The epidemiology of perioperative hyperglycaemia is clearly dictated by the patient groups examined. Two main factors; the type of surgery that the patients are undergoing, and the co-existence of diabetes mellitus dictate the patterns observed. Among patients undergoing general surgery, perioperative hyperglycaemia can be seen in 20 to 40 per cent of patients at some point during their hospital stay[8-10]. In one study, clinically significant hyperglycemia (defined as blood glucose >10 mmol/L)[11] was observed in 7.9 per cent of non-cardiac surgical patients before surgery, in 17.2 per cent of subjects on the day of surgery, and in 9.9 per cent of patients during the postoperative period (days 2-10)[8]. Forty per cent of those patients had a blood glucose concentration >7.8 mmol/L, with 25 per cent of those patients having a blood glucose concentration >10.0 mmol/L. This figure rises to 80 per cent among patients undergoing cardiac surgery[4,5]. Umpierrez et al have reported a 38 per cent incidence of hyperglycemia (26 per cent known diabetics, 12 per cent undiagnosed diabetes) in a sample of 2000 hospital admissions[12] – the undiagnosed diabetics had a longer length of stay and ICU admission rate[13,14]. In one study after major colorectal surgery, 66 per cent of non-diabetic patients developed postoperative hyperglycaemia during their hospital stay[1]. Hence, perioperative hyperglycemia is very common, and is not restricted to patients with diabetes mellitus.

PREVALENCE OF DIABETES MELLITUS

Glucose regulation is a complicated process and highly orchestrated, involving principally the liver, pancreas, muscle, brain, adipose tissues and sensors in the hepatoportal area and in the kidneys. This has been extensively reviewed and summarised elsewhere[15]. Type 1 diabetes mellitus (T1DM) is caused by autoimmune-mediated destruction of pancreatic beta cells. Type 2 diabetes mellitus (T2DM) is initially characterised by tissue insensitivity to insulin. The longer the duration of T2DM, the less responsive the beta cells become, and over time are no longer able to release enough insulin. Hence, at a certain point in the progression of diabetes, insulin therapy may be necessary to control blood glucose levels.

Diabetes mellitus is the most common metabolic disorder and although there are international variations in the prevalence of diabetes, it is estimated that it has a global prevalence of 9 per cent of the population. Approximately 90-95 per cent of those individuals have T2DM, and 46.5 per cent of adults with diabetes are undiagnosed. In 2011 it was estimated that 366 million people on earth had diabetes, projected to increase to 522 million by 2030. The majority of this increase is an increase in the prevalence of T2DM, attributable to an ageing population, increased in obesity levels, lack of exercise, and migration of susceptible populations. Patients with T2DM can expect a 10-year reduction in life expectancy. In 2010, 6.8 per cent of all deaths globally were due to diabetes (Types 1 and 2), and it is one of the top five global causes of premature death[16].

UNDIAGNOSED DIABETES MELLITUS IN HOSPITAL PATIENTS

In one small study, it was determined that almost 20 per cent of hospitalised patients had undiagnosed diabetes mellitus, based on a $HbA1_C$ cut off value of 6.1 per cent[17]. In other studies, comprising non-cardiac surgical patients, 14-19 per cent were known diabetic patients[9,18], 10 per cent had undiagnosed diabetes mellitus while 11 per cent had undiagnosed impaired glucose tolerance[18]. The prevalence of hyperglycaemia in hospital

patients has been estimated at 40 per cent[19], and among surgical patients, 25 per cent of patients presenting for elective surgery were diabetic based on fasting blood sugar concentrations[20]. An Australian study has identified the prevalence of diabetes in hospital patients at 24.7 per cent[21]. Overall, therefore, up to a quarter of all hospital patients will be diabetic, and in the perioperative period, up to 40 per cent will have deranged glucose metabolism, attributable either to diabetes (diagnosed or undiagnosed), impaired glucose tolerance, or pure stress hyperglycaemia (see below). Hence, diabetes is a very common comorbidity in hospital patients, and those patients that are undiagnosed diabetics represent a further cohort that will experience greater risk.

PATHOPHYSIOLOGY OF STRESS HYPERGLYCAEMIA

Stress hyperglycemia (SH) is the term that has been coined to describe what used to previously be called "hospital hyperglycaemia". It is now defined as the development of (clinically significant) transient hyperglycemia in association with an acute illness which resolves with resolution of the acute illness, and it is implicit that these patients do not have previous evidence of diabetes[22,23].

The stress response to surgery is mediated largely by the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenal system. In general, there is a graded response to the degree of stress. Adrenal cortisol output increases up to 10-fold with severe stress. In patients with shock, plasma concentrations of epinephrine increase 50-fold and norepinephrine levels increase 10-fold. The adrenal medulla is the major source of these released catecholamines. The increased release of stress hormones results in multiple effects (metabolic, cardiovascular and immune) aimed at restoring homeostasis during stress. The HPA axis, sympatho-adrenal system and proinflammatory cytokines (TNF-α, IL-1 and IL-6) act collectively and synergistically to induce stress hyperglycaemia.

The endocrine response to stress is characterised by excessive gluconeogenesis, glycogenolysis and insulin resistance. Postoperative insulin resistance can persist for up to 21 days postoperatively[24]. Stress hyperglycaemia, however, appears to be caused predominantly by increased hepatic output of glucose rather than impaired tissue glucose extraction. The metabolic effects of cortisol include an increase in blood glucose concentration through the activation of key enzymes involved in hepatic gluconeogenesis and inhibition of glucose uptake in peripheral tissues such as the skeletal muscles. Both epinephrine and norepinephrine stimulate hepatic gluconeogenesis and glycogenolysis; norepinephrine has the added effect of increasing the supply of glycerol to the liver via lipolysis. Inflammatory mediators, specifically the cytokines TNF-α, IL-1, IL-6, and C-reactive protein, also induce peripheral insulin resistance. In addition, the altered release of adipokines (increased zinc-alpha2 glycoprotein and decreased adiponectin) from adipose tissue during acute illness is thought to play a key role in the development of insulin resistance.

Perioperative hyperglycaemia may thus be encountered in three broad categories of patient:[22]

1. Hyperglycaemia in a patient known to be diabetic.
2. In these patients, the hyperglycaemia is due to a combination of SH, and alteration of the patients diabetes medication or insulin regimen.
3. Hyperglycaemia in a patient who is not known to be diabetic (but subsequent testing identifies either impaired glucose tolerance or diabetes mellitus).
4. In these patients, the hyperglycaemia is due to a combination of SH and their underlying untreated insulin resistance/deficiency. This group of patient represents an "occult" group of high risk. They may already have started to develop some of the chronic complications of diabetes, and they are likely to have more extreme excursions in blood glucose values in the perioperative period. They also run the risk of developing diabetic crises. These crises may be well advanced before suspected by clinicians since the patients are not known to have deranged glucose homeostasis.
5. Hyperglycaemia in patients who are not known to be diabetic and on testing are found to have normal glucose metabolism.
6. In these patients, the hyperglycaemia is often an incidental finding, tends not to reach dangerous levels, and resolves in tandem with resolution of the acute surgical insult.

The prevalence of perioperative hyperglycaemia has led to calls for all patients undergoing major surgery to undergo HbA1c testing prior to surgery[25], and this is particularly relevant for those in category 2 above. Paradoxically, however, there is evidence that this perioperative hyperglycaemia may have greater clinical relevance for non-diabetic patients than for patients with established diabetes[9,10,18]. Hence, all episodes of in-patient hyperglycaemia, particularly perioperative hyperglycaemia, in patients not known to be diabetic must be followed up with further testing.

MECHANISMS OF HARM THROUGH HYPERGLYCAEMIA

The adverse consequences of chronic hyperglycaemia, and the benefits of treatment, are unquestionable, and the mechanism has been attributed to overproduction of superoxide radicals by the mitochondrial electron chain[26]. The typical chronic complications of diabetes take several years to develop; therefore, the explanation for a rise in harm that is related to stress hyperglycaemia needs further consideration. Diabetic patients are overrepresented in the hospital population, and are more likely to undergo surgery. They often have extensive comorbidities, including atherosclerosis, renal impairment, coronary artery disease, peripheral vascular disease and cerebrovascular disease. In comparison to non-diabetic patients, the surgical patient with diabetes demonstrates an increase in associated costs and more adverse outcomes in virtually every surgical specialty in which this question has been examined[8,20,27-33]. Patients with diabetes should therefore be considered as high-risk patients, with higher overall risks of morbidity and mortality, longer length of stay and death[34,35]. Whether this risk is further modified by the acute changes of stress hyperglycaemia is unknown.

Stress hyperglycaemia is mediated by much greater inflammatory and neuroendocrine derangements than are expected in chronic hyperglycaemia associated with diabetes. Possible mechanisms of harm from acute hyperglycaemia are impaired leukocyte functions[36,37], poor wound healing[38], increased proinflammatory activation with increased endothelial permeability and platelet activation and these actions appear to be worse with surges of hyperglycaemia rather than sustained hyperglycemia[15]. Some evidence suggests that chronic hyperglycaemia sets up a pattern of cellular conditioning that might actually be protective of acute hyperglycaemia-mediated damage during critical illness. One mechanism for this effect might be the preferential downregulation of glucose transporters under conditions of chronic rather than intermittent hyperglycaemia. GLUT-1 and GLUT-3 are facilitative glucose transporters that allow glucose to enter cells independently of insulin. Several factors that upregulate these transporters are elaborated during critical illness, potentially allowing glucose to enter cells unchecked by normal down regulatory responses. Thus, a wide range of tissues might be susceptible to enhanced glucose toxicity as a result of acute illness. Whether patients with chronic hyperglycaemia are able to compensate by downregulating glucose transporters is unknown. Various oxidative stressors prevent the downregulation of GLUT-1 transporters in vascular endothelial cells.

Acute fluctuations in glucose concentrations are associated with mortality in acutely ill patients, independently of mean glucose concentration. Repetitive acute glucose fluctuations induce more endothelial apoptosis and greater endothelial dysfunction and oxidative stress responses compared with the less variable excursions both in vitro and in patients with or without known diabetes. Furthermore, oxidative stress seems to have a unifying causal role in the stimulation of classic intracellular pathways that mediate chronic complications of hyperglycaemia. Therefore, increased oxidative stress during acute hyperglycaemia (by contrast with chronic hyperglycaemia or diabetes) would seem to be a plausible mechanism for additive adverse effects of stress hyperglycaemia.

STRESS HYPERGLYCAEMIA – AN EVOLUTIONARY PROTECTIVE RESPONSE?

There is an emerging view that SH may be an evolutionarily preserved survival mechanism to maximise immune system energetics and protein synthesis in the setting of acute stress[23]. In order for glucose to reach a cell with reduced blood flow such as in the setting of ischaemia or sepsis, it must diffuse down a concentration gradient. Stress hyperglycaemia results in a new glucose balance, allowing a higher blood glucose diffusion gradient to maximise cellular glucose uptake in the face of maldistributed microvascular flow. Acute hyperglycaemia may protect against cell death following ischaemia by promoting anti-apoptotic pathways and favouring angiogenesis. In a murine model, Malfitano and colleagues demonstrated that hyperglycaemia increased cell survival factors[39]. Other studies have shown that cardiomyocytes exposed to insulin free medium supplemented with high glucose concentration are resistant to ischaemia, hypoxia and calcium overload. Macrophages play a central role in the host response to injury, infection and sepsis. Metabolism of glucose provides metabolic intermediates necessary for this process. Additionally, these mechanisms ensure adequate glucose uptake by neuronal tissue in the setting of decreased microvascular flow. Iatrogenic normalisation may therefore impair immune and cerebral function during periods of stress. Most of these theories remain highly speculative and have not been tested in the human clinical domain. They do, however, provide useful caveats to overzealous correction of deranged blood glucose concentrations unless it is clearly safe to do so.

EVIDENCE OF HARM IN STRESS HYPERGLYCAEMIA

SH in critical illness

The clinical relevance and correct approach to dealing with SH is both topical and contentious[40,41]. Much of our understanding of the adverse consequences of hyperglycaemia in the hospital population comes from the extensive critical care and cardiac surgical literature on the topic. The results of some of the salient studies now frame much of the thinking in the field of perioperative hyperglycaemia. The association between high blood glucose concentrations and adverse outcomes (mortality, infection and length of stay) in both ICU and non-ICU hospital patients[42,43] led to the belief that the relationship was causal, and provoked a series of trials that examined the effects of intensive insulin therapy (IIT) to control blood glucose concentrations in a variety of ICU populations. Despite initially promising results[3,13], a subsequent definitive high-quality randomised controlled trial found that tight glycaemic control was associated with an increased risk of mortality[44], and that

this was strongly linked to hypoglycaemia in a dose-response fashion[2]. Hence, it is now generally accepted that admission hyperglycaemia in the critically ill is a marker of adverse prognosis[45], and that aggressive treatment to normalise blood glucose may actually cause harm. Most blood glucose therapeutic targets have now been relaxed to reduce the risk of harmful hypoglycaemia, but there remain many unknowns in this group, particularly as to whether there is a blood-glucose treatment sweet spot[40].

SH in other patient groups

Whether hyperglycaemia in the non-critically ill, non-cardiac surgical, perioperative or trauma patient causes harm, or whether it is simply a marker of severity of inflammatory response is unknown. However, the putative harm from acute hyperglycaemia, particularly in the surgical non-critically ill population, and whether these effects are different for diabetic patients, has been the subject of recent work. Although diabetes mellitus is a confounding factor, it does appear that hyperglycaemia has an effect upon morbidity and mortality independent of diabetes status[46]. It also appears perioperative hyperglycaemia may be more harmful for non-diabetics than for those with established diabetes mellitus – the so-called "diabetes paradox"[8,9]. The relationship is therefore complex, and some of the data is quite compelling. However, causality has been difficult to demonstrate, and without a large-scale randomised controlled trial, it is unlikely that we can unravel these relationships.

While the worst outcome associated with hyperglycaemia occurs in critically ill and cardiac surgical patients, as mentioned previously[3,4,28,47,48], the medical and non-cardiac surgery literature also indicates that medical admissions, surgical and trauma patients may also be at risk. Post-hoc analysis of the IHAST patient population by Pasternak revealed that patients having a blood glucose in the upper quartile (> 152 mg/dL) at the time that a cerebral aneurysm clip was being applied, had a greater three-month adverse neuropsychological outcome than those having blood glucose in the upper two quartiles (> 129 mg/dL)[49]. Hyperglycaemia on admission is associated with greater mortality[8], particularly in trauma patients[50,51], and these patients also suffer higher infection rates[52]. Orthopaedic trauma patients have a seven-fold higher risk of infection if they develop in-patient hyperglycemia[53]. In a retrospective case-control study, Noordzij et al examined the relationship between admission blood sugar and mortality in non-cardiac, non-vascular surgery patients, and identified that preoperative blood glucose concentrations > 11.1 $mmoll^{-1}$ were associated with a 2.1-fold increased risk of overall mortality and a fourfold increased risk of cardiovascular mortality[54]. In general and vascular surgery patients, Ramos et al calculated that the risk of mortality was directly related to blood sugar in the range 6.1-11.1 $mmoll^{-1}$ and for every 1 $mmoll^{-1}$ rise in glucose concentration, the mortality risk increased 19 per cent[55]. This study observed that every 2.2 mmol/L rise in postoperative blood glucose concentration above 6.1 mmol/L resulted in an increase in the infection rate by 30 per cent[55]. Hence, the actual degree of perioperative elevation of blood sugar may determine the increase in risk.

The influence of diabetes status in stress hyperglycaemia and the "diabetes paradox"

As indicated above, diabetes status confounds the relationship between perioperative hyperglycaemia and outcome. However, the nature of this confounding is not clear and there are trials with contradictory results. Non-diabetic general medical patients with admission hyperglycaemia have an increased length of stay, 28-day mortality and readmission rate[56]. In the study by Ramos, increased postoperative blood glucose was associated with increased infection rates independent of diabetic status of the patient[55]. In major orthopaedic surgical patients, preoperative hyperglycaemia was associated with postoperative pulmonary embolism (risk increase by four in elective joint replacement patients), and not affected by the diabetic status of the patient[57]. Kerby specifically addressed the interaction of diabetic status and blood glucose in trauma patients, and concluded that SH rather than diabetic hyperglycaemia was responsible for the increase in mortality[51]. Conversely, in the study by Frisch et al, multivariate analysis showed that mortality risk was related to hyperglycaemia only in the non-diabetic patients[8].

Three large retrospective observational studies, totalling 114,005 patients (21,597 patients with diabetes – 18.9 per cent) have confirmed many of the findings of Frisch. Kwon demonstrated the relationship between perioperative hyperglycaemia and mortality, infection and operative complications in both patients with diabetes and those without[10]. The occurrence of blood glucose >10$mmoll^{-1}$ increased mortality by 2.7, and increased both operative reinterventions and anastomotic failures. The effect of hyperglycaemia in non-diabetic patients was twice that for patients without diabetes, but treatment of hyperglycaemia with insulin in both those with and without diabetes mitigated these effects, particularly the infection risk. In a large retrospective analysis of abdominal, vascular and surgical patients, Kotagal identified that perioperative adverse event risk was increased by 33 per cent for diabetics, but that PH increased the risk of adverse outcomes only in the non-diabetic patients. In the largest study of its kind, Abdelmalak et al examined the records of more than 61,000 patients, and established that one year mortality in non-cardiac surgical patients was strongly associated with preoperative blood glucose, and was greater for patients with diabetes[58]. At euglycaemia, patients with diabetes had a higher one year mortality than non-diabetic patients. However, at hyperglycaemic blood glucose concentrations, the mortality in non-diabetic patients rose compared to the diabetic patients, further underlining the "diabetes paradox".

There are several tentative conclusions that can be drawn from this literature:

1. The association between admission blood glucose and adverse outcomes seems to be substantial and it may in fact represent a modifiable risk factor for adverse outcomes. Even a single elevation of postoperative blood glucose in non-diabetic surgical patients increases the risk of death and complications – this risk appears to be proportional[1].
2. These episodes in patients not known to be diabetic are under-investigated and poorly followed up[56].
3. It is also theorised that at the same degree of hyperglycaemia, non-diabetic patients are experiencing greater systemic stress than their diabetic counterparts, which may explain the worse outcomes for non-diabetic patients at a given blood glucose concentration.
4. We cannot therefore consider perioperative hyperglycaemia to be a benign entity[59], and the endocrinology community is actively urging perioperative clinicians not to underestimate it[41].

UNANSWERED QUESTIONS

There are many questions in this area of relatively recent research. The most important of these are outlined below. Most of them concern the perioperative management of blood glucose in patients with diabetes mellitus. These key questions will only be answered with high quality trial data.

1. Is there a preoperative blood glucose level above which one should postpone elective surgery?

Insufficient data exist to provide a pre-operative fasting blood glucose, or HbA1c above which surgery should be postponed. Elective surgery should be postponed in patients demonstrating significant complications from hyperglycaemia such as dehydration, impending ketoacidosis or hyperosmolar non-ketotic states.

2. Should glycaemic control be optimised before elective surgery?

It has been suggested that the quality of preoperative glycaemic control positively influences outome[29,30]. However, the evidence to support this is at best very weak. Although some observational studies have pointed to an association between HbA1c level and postoperative outcomes[29,30], a meta-analysis of the current literature has indicated that this evidence is also weak, largely due to the heterogeneity and retrospective nature of the currently available studies[60]. In chronically poorly controlled diabetic patients, the decision to proceed with ambulatory surgery should be made in conjunction with the surgeon while taking into consideration the presence of other comorbidities and the potential risks of surgical complications (e.g., delayed wound healing and wound infection). Nonetheless, the current recommendation is that patient with a HbA1c level in excess of 9.0 per cent (69 mmol/L) should have their elective surgery deferred until preoperative glycaemic control can be improved[61].

3. What is the optimal intraoperative period blood glucose level?

Again there is a lack of evidence regarding optimal perioperative blood glucose values. Blood glucose targets are based on consensus guidelines. Most guidelines now recommend an upper target of 10mmol/l. National Health Service Diabetes Guideline recommends blood glucose concentrations between 6.0-10.0 $mmoll^{-1}$, while accepting 4.0-12.0 $mmoll^{-1}$ [34]. The Australian Diabetes Society currently recommends a blood glucose target of 5.0-10.0 $mmoll^{-1}$ in both the ICU and non-ICU settings. The American Diabetes Association currently recommend commencing insulin therapy for critically ill patients with persistent hyperglycaemia (>10.0 $mmoll^{-1}$), and to aim for a blood glucose target range between 7.8-10.0 $mmoll^{-1}$ in all hospitalised patients[62] while the American College of Physicians recommends 7.8-11.1 mmol/L for critically ill patients. All documents do however acknowledge that the evidence for a specific range is weak, and for the moment these targets seem to sensibly balance potential risks and benefits.

For poorly controlled diabetics, blood glucose levels should be maintained around their normal rather than temporarily lowering them to "normal" levels. Patients with poorly controlled type 2 diabetes have an altered counter-regulatory response (i.e., release of epinephrine, norepinephrine, growth hormone, cortisol, and pancreatic polypeptide), resulting in hypoglycaemic symptoms at normal blood glucose levels. Also, significant fluctuations in blood glucose levels caused by acute reduction in chronically elevated blood glucose levels can lead to detrimental biochemical effects including increased oxidative stress response and may increase perioperative morbidity and mortality. In the critically ill and surgical patients, tight in-hospital glycaemic control does not appear to confer advantage, and may cause harm, as detailed above[63].

4. Is SH in non-diabetic patients harmful and should it be treated?

This is an intriguing question. It appears that perioperative hyperglycaemia in non-diabetic patients is a physiological epiphenomenon, and indeed some believe that it may be protective. It is unknown whether it confers protection, causes harm, and whether it should be treated. These are important questions that will require data from large registries and larger RCTS to answer.

5. How do we maintain optimal blood glucose levels?

There is insufficient evidence to recommend a method of insulin administration. Most consensus guidelines still advocate the use of a variable rate insulin infusion (VRII) to treat hyperglycaemia. The SAMBA guidelines state that subcutaneous insulin may be used in patients undergoing ambulatory surgery and as the benefits of being less labour intensive, more cost effective, reduced duration of post-operative observation required.

6. Should an insulin-naive patient receive insulin to optimise blood glucose levels?
There is again insufficient evidence in this area to guide practise. Patients with T2DM who do not usually require insulin to control blood glucose, may require the short-term use of insulin while the SH response is subsiding. However, if perioperative blood glucose values are very high in a patient not known to be diabetic, then it would seem prudent to check a HbA1c (if not already performed) to establish the patient's status. If the patient is then confirmed as non-diabetic, it would seem prudent to measure blood glucose mores frequently, ensure that there is no ketonuria, and in the face of persistent and potentially dangerous hyperglycaemia (i.e., if there are concerns of severe dehydration, ketoacidosis, and hyperosmolar non-ketotic states) to commence low dose short acting insulin in these patients to control blood glucose until it starts to resolve.

7. What are the areas for future research?
The following are a list of as yet unanswered questions, many of which relate to ambulatory surgery, and which are currently guided by consensus opinion and best practice guidelines:

- Does scheduled time of the surgery (i.e., early versus late) have any significant influence on outcomes, and if so, is there a patient subpopulation for which it does particularly?
- What is the impact of use of various preoperative regimens on short-term (e.g., morbidities and duration of recovery room, hospital stay and quality of recovery) and long-term (e.g., unplanned hospital admission, 30-day unexpected hospitalisation, morbidity, and mortality) outcome in the ambulatory setting?
- What is the effect of preoperative insulin therapy on outcome after ambulatory surgery?
- Is there any benefit to aggressive preoperative glycaemic control?
- Are there differences in optimal target blood glucose levels for high-risk outpatients versus low risk outpatients?
- Are there differences in optimal blood glucose management in T1DM versus T2DM in the ambulatory setting?
- Are there differences in patient outcome between the various routes of administration of insulin?
- Are there any predictors (e.g., blood glucose levels, HbA1c levels, and other comorbidities) that suggest avoidance of ambulatory surgery or need for overnight hospital admission?
- What is the impact of anaesthetic technique (local/regional anaesthesia, sedation/analgesia technique, general anaesthesia) on blood glucose control?

CONCLUSION

Perioperative hyperglycaemia is very much more common than previously expected, and carries serious implications for risk of adverse outcome. It is expected to occur in patients with diabetes, but it should be anticipated in all patients. However, patients with elevated blood glucose levels peri-operatively and who are diabetic or have impaired glucose tolerance, but are not yet diagnosed, represent a very high risk group. Stress hyperglycaemia should no longer be considered a benign entity and protocolised management of hyperglycaemia should exist as it does for diabetic patients. Follow up and further investigation with HbA1c will be required. Consideration should be given to checking HbA1c in all patients pre-operatively to identify this high risk group. Once identified, appropriate glucose management plans can be undertaken with the aim of reducing perioperative risk. It remains unknown whether it should be treated, at what level of blood glucose intervention should be initiated, and what exactly that intervention should be. Until high quality RCTs are performed is seems prudent to follow best practice and consensus guidelines.

REFERENCES

1. Kiran RP, Turina M, Hammel J, Fazio V. The clinical significance of an elevated postoperative glucose value in nondiabetic patients after colorectal surgery: evidence for the need for tight glucose control?. Ann Surg. 2013;258(4):599–604;discussion 604–605.
2. Investigators N-SS, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367(12):1108–1118.
3. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–1367.
4. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2003;125(5):1007–1021.
5. Umpierrez G, Cardona S, Pasquel F, Jacobs S, Peng L, Unigwe M, et al. Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: Gluco-cabg trial. Diabetes Care. 2015;38(9):1665–1672.
6. Desai SP, Henry LL, Holmes SD, Hunt SL, Martin CT, Hebsur S, et al. Strict versus liberal target range for perioperative glucose in patients undergoing coronary artery bypass grafting: a prospective randomized controlled trial. J Thorac Cardiovasc Surg. 2012;143(2):318–325.
7. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45(3):486–552.

8. Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, Gatcliffe C, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care. 2010;33(8):1783–1788.
9. Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET, et al. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg. 2015;261(1):97–103.
10. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: A report from the surgical care and outcomes assessment program. Ann Surg. 2013;257(1):8–14.
11. Levy N, Penfold N, Mythen M. Perioperative management of diabetes and the emerging role of anaesthetists as perioperative physicians. Br J Anaesth. 2016;116(4):443–447.
12. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87(3):978–982.
13. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449–461.
14. Ishizuka K, Usui I, Kanatani Y, Bukhari A, He J, Fujisaka S, et al. Chronic tumor necrosis factor-alpha treatment causes insulin resistance via insulin receptor substrate-1 serine phosphorylation and suppressor of cytokine signaling-3 induction in 3T3-L1 adipocytes. Endocrinology. 2007;148(6):2994–3003.
15. Akhtar S, Barash PG, Inzucchi SE. Scientific principles and clinical implications of perioperative glucose regulation and control. Anesth Analg. 2010;110(2):478–497.
16. Roglic G, Unwin N. Mortality attributable to diabetes: estimates for the year 2010. Diabetes Res Clin Pract. 2010;87(1):15–19.
17. Wexler DJ, Nathan DM, Grant RW, Regan S, Van Leuvan AL, Cagliero E. Prevalence of elevated hemoglobin a1c among patients admitted to the hospital without a diagnosis of diabetes. J Clin Endocrinol Metab. 2008;93(11):4238–4244.
18. Abdelmalak B, Abdelmalak JB, Knittel J, Christiansen E, Mascha E, Zimmerman R, et al. The prevalence of undiagnosed diabetes in non-cardiac surgery patients, an observational study. Can J Anaesth. 2010;57(12):1058–1064.
19. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care. 2004;27(2):553–591.
20. Hatzakorzian R, Bui H, Carvalho G, Shan WL, Sidhu S, Schricker T. Fasting blood glucose levels in patients presenting for elective surgery. Nutrition. 2011;27(3):298–301.
21. Bach LA, Ekinci EI, Engler D, Gilfillan C, Hamblin PS, MacIsaac RJ, et al. The high burden of inpatient diabetes mellitus: the Melbourne public hospitals diabetes inpatient audit. Med J Aust. 2014;201(6):334–338.
22. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–1807.
23. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response!. Crit Care. 2013;17(2):305.
24. Thorell A, Efendic S, Gutniak M, Haggmark T, Ljungqvist O. Insulin resistance after abdominal surgery. Br J Surg. 1994;81(1):59–63.
25. Aldam P, Levy N, Hall GM. Perioperative management of diabetic patients: new controversies. Br J Anaesth. 2014;113(6):906–909.
26. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615–1625.
27. Smiley DD, Umpierrez GE. Perioperative glucose control in the diabetic or nondiabetic patient. South Med J. 2006;99(6):580–589; quiz 590–581.
28. Thourani VH, Weintraub WS, Stein B, Gebhart SS, Craver JM, Jones EL, et al. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. Ann Thorac Surg. 1999;67(4):1045–1052.
29. Gustafsson UO, Thorell A, Soop M, Ljungqvist O, Nygren J. Haemoglobin A1c as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery. Br J Surg. 2009;96(11):1358–1364.
30. Underwood P, Askari R, Hurwitz S, Chamarthi B, Garg R. Preoperative A1c and clinical outcomes in patients with diabetes undergoing major noncardiac surgical procedures. Diabetes Care. 2014;37(3):611–616.
31. Marchant MH, Jr., Viens NA, Cook C, Vail TP, Bolognesi MP. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. J Bone Joint Surg Am. 2009;91(7):1621–1629.
32. Tsang ST, Gaston P. Adverse peri-operative outcomes following elective total hip replacement in diabetes mellitus: a systematic review and meta-analysis of cohort studies. Bone Joint J. 2013;95-B(11):1474–1479.
33. Carson JL, Scholz PM, Chen AY, Peterson ED, Gold J, Schneider SH. Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol. 2002;40(3):418–423.
34. Dhatariya K, Levy N, Kilvert A, Watson B, Cousins D, Flanagan D, et al. NHS diabetes guideline for the perioperative management of the adult patient with diabetes. Diabet Med. 2012;29(4):420–433.
35. Sampson MJ, Dozio N, Ferguson B, Dhatariya K. Total and excess bed occupancy by age, specialty and insulin use for nearly one million diabetes patients discharged from all english acute hospitals. Diabetes Res Clin Pract. 2007;77(1):92–98.
36. Bagdade JD, Root RK, Bulger RJ. Impaired leukocyte function in patients with poorly controlled diabetes. Diabetes. 1974;23(1):9–15.
37. Perner A, Nielsen SE, Rask-Madsen J. High glucose impairs superoxide production from isolated blood neutrophils. Intensive Care Med. 2003;29(4):642–645.
38. Edwards FH, Grover FL, Shroyer AL, Schwartz M, Bero J. The society of thoracic surgeons national cardiac surgery database: current risk assessment. Ann Thorac Surg. 1997;63(3):903–908.
39. Malfitano C, Alba Loureiro TC, Rodrigues B, Sirvente R, Salemi VM, Rabechi NB, et al. Hyperglycaemia protects the heart after myocardial infarction: aspects of programmed cell survival and cell death. Eur J Heart Fail. 2010;12(7):659–667.
40. Abdelmalak BB, Lansang MC. Revisiting tight glycemic control in perioperative and critically ill patients: when one size may not fit all. J Clin Anesth. 2013;25(6):499–507.
41. Dhatariya K. Should inpatient hyperglycaemia be treated?. BMJ. 2013;346:f134.

42. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, et al. Admission glucose level and clinical outcomes in the NINDS rt-PA stroke trial. Neurology. 2002;59(5):669–674.
43. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355(9206):773–778.
44. Finfer S, Heritier S, NICE Study Management Committee, SUGAR Study Executive Committee. The NICE-SUGAR (normoglycaemia in intensive care evaluation and survival using glucose algorithm regulation) study: statistical analysis plan. Crit Care Resusc. 2009;11(1):46–57.
45. Park BS, Yoon JS, Moon JS, Won KC, Lee HW. Predicting mortality of critically ill patients by blood glucose levels. Diabetes Metab J. 2013;37(5):385–390.
46. Lipshutz AK, Gropper MA. Perioperative glycemic control: an evidence-based review. Anesthesiology. 2009;110(2):408–421.
47. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78(12):1471–1478.
48. Zhang X, Wu Z, Peng X, Wu A, Yue Y, Martin J, et al. Prognosis of diabetic patients undergoing coronary artery bypass surgery compared with nondiabetics: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth. 2011;25(2):288–298.
49. Pasternak JJ, McGregor DG, Schroeder DR, Lanier WL, Shi Q, Hindman BJ, et al. Hyperglycemia in patients undergoing cerebral aneurysm surgery: its association with long-term gross neurologic and neuropsychological function. Mayo Clin Proc. 2008;83(4):406–417.
50. Kreutziger J, Wenzel V, Kurz A, Constantinescu MA. Admission blood glucose is an independent predictive factor for hospital mortality in polytraumatised patients. Intensive Care Med. 2009;35(7):1234–1239.
51. Kerby JD, Griffin RL, MacLennan P, Rue LW 3rd. Stress-induced hyperglycemia, not diabetic hyperglycemia, is associated with higher mortality in trauma. Ann Surg. 2012;256(3):446–452.
52. Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma. 2004;56(5):1058–1062.
53. Karunakar MA, Staples KS. Does stress-induced hyperglycemia increase the risk of perioperative infectious complications in orthopaedic trauma patients?. J Orthop Trauma. 2010;24(12):752–756.
54. Noordzij PG, Boersma E, Schreiner F, Kertai MD, Feringa HH, Dunkelgrun M, et al. Increased preoperative glucose levels are associated with perioperative mortality in patients undergoing noncardiac, nonvascular surgery. Eur J Endocrinol. 2007;156(1):137–142.
55. Ramos M, Khalpey Z, Lipsitz S, Steinberg J, Panizales MT, Zinner M, et al. Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. Ann Surg. 2008;248(4):585–591.
56. Evans NR, Dhatariya KK. Assessing the relationship between admission glucose levels, subsequent length of hospital stay, readmission and mortality. Clin Med. 2012;12(2):137–139.
57. Mraovic B, Hipszer BR, Epstein RH, Pequignot EC, Parvizi J, Joseph JI. Preadmission hyperglycemia is an independent risk factor for in-hospital symptomatic pulmonary embolism after major orthopedic surgery. J Arthroplasty. 2010;25(1):64–70.
58. Abdelmalak BB, Knittel J, Abdelmalak JB, Dalton JE, Christiansen E, Foss J, et al. Preoperative blood glucose concentrations and postoperative outcomes after elective non-cardiac surgery: an observational study. Br J Anaesth. 2014;112(1):79–88.
59. Dhatariya K, Levy N, Hall GM. The impact of glycaemic variability on the surgical patient. Curr Opin Anaesthesiol. 2016;29(3):430–437.
60. Rollins KE, Varadhan KK, Dhatariya K, Lobo DN. Systematic review of the impact of HbA1c on outcomes following surgery in patients with diabetes mellitus. Clin Nutr. 2016;35(2):308–316.
61. Membership of the Working Party, Barker P, Creasey PE, Dhatariya K, Levy N, Lipp A, et al. Peri-operative management of the surgical patient with diabetes 2015: association of anaesthetists of great britain and ireland. Anaesthesia. 2015;70(12):1427–1440.
62. American Diabetes Association. 13. Diabetes care in the hospital. Diabetes Care. 2016;39(Suppl 1):S99–104.
63. Buchleitner AM, Martínez-Alonso M, Hernández M, Solà I, Mauricio D. Perioperative glycaemic control for diabetic patients undergoing surgery. Cochrane Database Syst Rev. 2012;9:CD007315.

Malignant hyperthermia – "Keeping things cool"

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INTRODUCTION

Malignant hyperthermia (MH) is a rare, potentially fatal, pharmacogenetic inherited disease of skeletal muscle. It can manifest as a hypermetabolic crisis on exposure to halogenated volatile inhalational agents, including halothane, isoflurane, sevoflurane, desflurane, methoxyflurane, and/or the depolarising neuromuscular blocking agent, suxamethonium[1]. Case fatality was as high as 70 per cent in the 1970s, however, with the introduction of dantrolene sodium and increased understanding of clinical manifestations with more modern anaesthetic techniques, this has fallen to <6 per cent[2].

Prior to 1960, death under general anaesthesia was not uncommon. In 1960 at the Royal Melbourne Hospital, anaesthetist Dr Jim Villiers cared for a patient, in whom 10 members of his family had died under general anaesthesia, attributing the cause to ether. The patient developed a hypermetabolic crisis on exposure to halothane, but with due care survived the ordeal. Dr Villiers' medical colleagues, Dr (later Professor) Michael Denborough and Dr Richard Lovell published a letter in *The Lancet* in 1960, titled "Anaesthetic deaths in a family", describing the clinical picture, postulating an autosomal dominant inheritance and requesting the journal's readers for any knowledge of cases similar to the one reported in the letter[3]. Subsequently, the condition has become known as malignant hyperthermia and today, their work continues under the auspices of the research and testing group MHANZ (Malignant Hyperthermia Australia New Zealand)[4].

Epidemiology

Malignant hyperthermia affects all ethnic groups, with males twice as likely to have a reaction than females, and children less than 19 years of age accounting for 45-52 per cent of reported cases[2]. Given the variable and incomplete penetrance of this rare condition, the actual incidence is difficult to quantify and varies geographically depending on the concentration of malignant hyperthermia families in a given area. It is reported that the incidence of MH reactions ranges from 1:10,000 to 1:250,000 anaesthetics[1], and prevalence rates at 1 in 100,000 in-patient operations.

Pathophysiology

Dysregulated, excessive cytoplasmic Ca^{2+} in skeletal muscle, on exposure to a halogenated volatile agent and/or depolarising neuromuscular agent, is pathognomonic of MH. The aetiology of the mechanism is still under investigation[2]. However, what is known is that under the above conditions, there is a gain of function and proclivity of the receptors involved in Ca^{2+} homeostasis, which maintains their release of calcium from the sarcoplasmic reticulum into the cytoplasm, and impedes Ca^{2+} re-uptake. This results in sustained excitation-contraction coupling, with exhaustion of oxygen and adenosine triphosphate stores, heat production, and conversion to an anaerobic metabolic state, that is, the hypermetabolic crisis. There is widespread striated muscle cell death/rhabdomyolysis[6], consequent to the loss of cell membrane integrity with release of potassium and creatine kinase.

Clinical

There is variability in the clinical manifestations from no reaction to mild, atypical or fulminant hypermetabolic syndrome with multi-organ failure. This is as a result of variable expressivity and the advent of more modern anaesthetic techniques. Thus, uneventful anaesthesia does not exclude the possibility of MH susceptibility. Consequently, the definitive diagnosis of MH by clinical criteria is practically impossible. Events representing a true MH crisis can be estimated using the MH Clinical Grading Scale. This was initially developed by Larach et al[7], and in 2010 the European MH Group and the MH Association of the United States collaborated to produce the downloadable MH app featuring the clinical grading scale. The multi-factor scale ranks the qualitative

likelihood of an adverse event being MH from one (MH likelihood almost never) to six (MH likelihood almost certain)[8].

The classic clinical features, consequent to the hypermetabolic skeletal muscle response, include tachycardia, inappropriately elevated end-tidal carbon dioxide concentration, hyperthermia, muscle rigidity (particularly following administration of suxamethonium, in which case masseter muscle spasm can be an early sign), mixed respiratory/metabolic acidosis, hyperkalaemia and associated arrhythmias, hyperCKaemia and myoglobinuria. Additionally, there may be evidence of disseminated intravascular coagulopathy. Creatine kinase levels rise exponentially with levels above 10,000 IU not uncommon, plateauing according to the severity of the crisis and muscle mass. Typically, MH features appear within 30 minutes of commencement of anaesthesia, but can be delayed for several hours, even after the anaesthetic has stopped. With fulminant malignant hyperthermia, the hyper-metabolic syndrome culminates in multi-organ failure and potential death if left untreated[2,9].

Many of the clinical features are non-specific, so the differential is quite broad. These include inadequate anaesthesia, sepsis, thyrotoxicosis, phaeochromocytoma, neuroleptic malignant syndrome, anti-dopaminergics, and drug overdose (for example, amphetamines and related drugs).

Greater than 50 per cent of cases are reported from the paediatric population. Their clinical presentation exemplifies the non-specific nature of MH and characteristics vary according to age. A retrospective analysis of data of patients under the age of 18 from the North American Malignant Hyperthermia Registry showed that the most consistent findings across all age groups was sinus tachycardia (73.1 per cent), hypercarbia (68.6 per cent), and accelerated temperature rise (48.5 per cent), all of which were more common in the 12-18 years age group. The 0-24 months age group experienced a greater degree of metabolic acidosis and associated skin mottling, however, were less likely to develop muscle rigidity with lower peak creatine kinase. Higher peak temperatures, diaphoresis and greater peak serum potassium levels were found in the older age group. There was no difference in outcome across the age groups[10,11].

Genetics

Malignant hyperthermia is a heterogeneic disease, inherited in an autosomal dominant fashion and exhibiting variable penetrance. The proportion of individuals who are MH susceptible due to a de novo mutation is unknown. The genetic basis of MH has not yet been fully characterised and remains elusive, despite advances in DNA sequencing technology enabling the identification of many new variants. Currently known MH-associated mutations involve genes encoding two of the receptors responsible for skeletal muscle calcium homeostasis. These include the ryanodine receptor (RYR1) gene encoding the calcium release channel of sarcoplasmic reticulum, and the alpha-1 subunit of the dihydropyridine-sensitive L-type voltage dependent calcium channel receptor (CACNA1S) gene.

The primary gene responsible for 50-70 per cent of MH susceptibility is the RYR1 gene located on chromosome 19. More than 400 variants have been identified in this gene, however the clinical significance of some of these has yet to be determined. Mutations associated with malignant hyperthermia are miss-sense mutations and small in-frame deletions clustering in three hotspots. Thirty mutations have been classified by the EMHG as being definitively causative, however polymorphic variants which modulate the RYR1 function may result in genotype/phenotype discordance[9].

Less than one per cent of MH is associated with mutations in the CACNA1S gene, which was first characterised in a French family and reported by Monnier et al in 1997.

DNA sequencing and linkage studies have excluded RYR1 and CACNA1S mutations as the cause in 30 per cent of MH susceptible (MHS) patients and predictive genetic testing can only test for the known mutation that has been identified in an index case in MH susceptible families. Importantly, even in these cases MH susceptibility cannot be ruled out with a negative genetic test as evidence has shown a 5 per cent discordance between genetic and in-vitro contracture testing (IVCT)[10].

In a number of MHS cases, more than one mutation/variant has been identified. Mutations in a number of other genes have been shown to be associated with MH-like clinical reactions and abnormal IVCT results, but whether these are in fact real (i.e. potentially hypermetabolic) MH cases is not clear. The remainder of MH susceptible patients is presumed to have mutations as yet to be determined. Other potential putative Ca^{2+} modulators under investigation include calsequestrin, a major storage protein in the sacroplasmic reticulum, calmodulin and different subunits of the dihydropyridine (DHP) receptor.

Identifying the at-risk patient

Anaesthetic history, family history of adverse events including unexplained peri-operative death, a history of post-operative rhabdomyolysis or unexplained or exertional rhabdomyolysis and inappropriate heat stroke should raise the suspicion of potential MH susceptibility.

The following are considered at risk groups according to the European Malignant Hyperthermia Group[12] and therefore should have a trigger-free anaesthetic:

- Confirmed MH susceptible.
- MH equivocal.

- Family history of MH in individuals who have not yet been tested.
- Pregnant woman who is MHS or whose partner is MHS – fetus must be treated as MHS.
- RYR1 associated myopathies: central core disease (CCD), King Denborough Syndrome, Multiminicore myopathy (MmD) and Native American myopathy.
- Unexplained/ recurrent rhabdomyolysis including heat or exercise induced.

Central core disease is a rare non-progressive myopathy with autosomal dominant inheritance. Typically, it presents in infancy and is characterised by hypotonia and proximal muscle weakness. Causative mutations are clustered in similar hotspots to MH on the RYR1 gene. As a result, the single RYR1 mutation can cause: (a) MH only; (b) MH with variable CCD penetrance; (c) CCD only[2]. Affected individuals must therefore be treated as MHS.

Multiminicore disease is another rare myopathy characterised by muscle weakness. Recessive RYR1 mutations are a major cause of MmD, and some of these are also associated with MH. MH susceptibility may therefore be associated with MmD.

King Denborough syndrome is a rare myopathy characterised by dysmorphic facial features, some skeletal abnormalities, hypotonia, diffuse joint hyperextensibility and mild proximal muscle weakness. Such patients have MH susceptibility.

Mutations/variants of the RYR1 gene have been identified in patients with exertional myalgia and rhabdomyolysis which have previously been associated with MH[13]. Indeed, there is an increasing body of evidence to support an association between exercise induced rhabdomyolysis and malignant hyperthermia[14]. There is also a suggestion of a link between MH and heat stroke, in the presence of rhabdomyolysis.

Patients with the X-linked recessive muscular dystrophies, Duchenne and Becker although not at risk of developing the hypermetabolic syndrome may experience exacerbation of their disease with hyperkalaemia and muscle breakdown on exposure to MH triggering agents and thus should have a trigger-free anaesthetic[2]. Any individual at risk of myotonia should avoid depolarising agents to avoid the potential for hyperkalaemia.

Management of the peri-operative MHS (or potential MHS) patient[15]

Pre-operative

The pre-operative assessment provides the opportunity to identify those with risk factors for MH or associated conditions, while any patient with a diagnosis of MH should ideally be seen in the pre-assessment clinic to review the diagnosis and to discuss the anaesthetic options. Individuals with a diagnosis of MH, or at risk of MH should be scheduled for a trigger-free anaesthetic with an appropriately prepared anaesthetic workstation. It is worthwhile advising the patient that their risk of an MH crisis is essentially zero if they are not exposed to the triggering agents. Pretreatment with dantrolene is neither recommended nor required.

Peri-operative

Ideally the patient should be first on the list. The anaesthetic workstation is prepared in order to minimise the potential exposure to triggering agents. The aim is to achieve volatile agent concentrations of less than 5ppm. This is based on level five evidence and an arbitrary upper safe limit described by Hall et al in 1996 where the authors sought to investigate if halothane concentrations of 5ppm could induce an MH crisis in susceptible swine[16].

1. Flush and prepare anaesthesia workstation according to manufacturer's recommendations; this may take 10 to >90 minutes. Disconnect vaporisers and remove from the operating theatre; use a new, disposable breathing circuit; and replace the carbon dioxide absorbent. During the case, fresh gas flow should be kept at 10L/min to avoid "rebound phenomenon" which is the increased release of residual volatile anaesthetic agent when fresh gas flow is reduced.

Alternatively:

2. Use commercially available activated charcoal filters that have been shown to remove trace levels of volatile anaesthetic agents following a 90-second flush with high fresh gas flows. It is only necessary to place one on the inspiratory limb of the breathing circuit, but to avoid error, they are marketed in pairs with instructions to place one each on both the inspiratory and expiratory limbs. These filters have been demonstrated in one in-vitro study to be effective for 12 hours[17].

Alternatively:

3. If available, use a dedicated "vapour-free" machine for MH-susceptible patients.

Intra-operative

Core body temperature and end tidal CO_2 should always be monitored, as with all patients. All triggering agents should be avoided including the inhalational agents sevoflurane, desflurane, isoflurane, enflurane and halothane and the depolarising muscle relaxant, suxamethonium (succinylcholine). Safe anaesthetic agents include all local anaesthetics, all intravenous anaesthetic agents, all non depolarising neuromuscular agents, nitrous oxide, xenon and helium.

Treatment of MH[18]

Prompt recognition is the key to a safe outcome. Complications occur in 20 per cent of patients who survive a fulminant crisis, most commonly renal dysfunction. MH is a true operating emergency. A state of emergency should be declared. Task cards should be available on an MH trolley to help prompt treatment and delegate tasks. Treatment protocol focuses on:

- Discontinuation of triggering agents (commence iv anaesthesia).
- Maintenance of adequate oxygenation and ventilation (100 per cent O2 at >15lpm fresh gas flows and 3-4 x normal minute ventilation).
- Administration of dantrolene – initial loading dose of 2.5 mg/kg, repeated as needed; stabilisation of an MH episode may take some time and multiple doses of dantrolene.
- Treatment of hyperkalaemia – 8.4 per cent NaHCO3, 50 per cent dextrose, Actrapid insulin.
- Instituting aggressive cooling measures- stop heating, remove drapes or linen, ice packs, cold iv fluid, insert urinary catheter +/- cold bladder washout.
- Treatment of acidosis – for example, 8.4 per cent NaHCO3, THAM.
- Treatment of arrhythmias – lignocaine, amiodarone.
- Insertion of arterial and central line.

For more detailed information, including task cards, see here:
http://www.anaesthesia.mh.org.au/mh-resource-kit/w1/i1002692/

Arrange transfer to an Intensive Care Unit and then refer to an MH Investigation Unit for testing at a later stage.

Diagnosis

The diagnosis of MH is two-tiered, based on strong clinical suspicion and confirmed by in-vitro contracture testing (IVCT). The main criterion for referral to a MH centre is when MH cannot be excluded[12].

Initial assessment and review of past medical, anaesthetic and family history guide the next step. The gold standard with the highest sensitivity of greater than 99 per cent and a specificity of 94 per cent is the IVCT with a turnaround time of approximately five hours. Although genetic screening is less invasive, sensitivity remains at 60 per cent and its role is in the investigation of index cases and subsequent family screening.

In-vitro contracture testing in Australasian centres adheres to the European Malignant Hyperthermia Group protocol[12]. It is not performed in children under four years and is not advised in children under the age of 10 years or under 30 kg. It is a day-case procedure, a 4 x 3 x 1cm biopsy is taken from the quadriceps muscle – either the vastus lateralis or vastus medialis – under a non-triggering GA or regional anaesthesia. The live muscle is transported to the laboratory without delay and the result is available same day. Muscle viability is maintained by carboxygenation and demonstrated with repetitive electrical stimulation. Muscle tension is measured and recorded, as caffeine and halothane concentrations are incrementally increased. The potential laboratory results are: MHShc (formerly MHS), MHSh (formerly MHE), MHSc (formerly MHE) or MHN (normal), depending on the degree of contracture generated on exposure to caffeine and halothane. The previously used MHE (Equivocal), is now obsolete and been replaced by MHSh or MHSc; it referred to an abnormal response of uncertain clinical significance to either halothane or caffeine respectively. Caffeine is a pharmacological stimulant of calcium release from the sarcoplasmic reticulum, however, muscle exposed to caffeine from persons of MHS has a lower threshold for force generation than those who are not susceptible.

The laboratory diagnostic classification as per the EMHG is as follows:

- MHShc: a caffeine threshold at a caffeine concentration of 2.0 mmol/L or less, and a halothane threshold concentration at 0.44 mmol/L (2 per cent) or less.
- MHSh: a halothane threshold concentration at 0.44 mmol/L or less and a caffeine threshold at a caffeine concentration of 3 mmol/L or more.
- MHSc: a caffeine threshold at a caffeine concentration of 2.0mmol/L or less and a halothane threshold concentration above 0.44mmol/L.
- MHN: a caffeine threshold at a caffeine concentration of 3 mmol/L or more and halothane threshold concentration above 0.44 mmol/L.

The threshold is defined as the lowest concentration of either caffeine or halothane required which produces a sustained increase in tension of at least 2mN (0.2g) from baseline force.

FUTURE DEVELOPMENTS

Ryanodex

Ryanodex is a formulation of dantrolene sodium, manufactured by Eagle Pharmaceuticals, NJ, US. It is a lyophilised suspension and therefore more water-soluble than previous formulations (Dantrium in Australia and New Zealand), thus facilitating a more expedient preparation time and avoiding the large fluid load. It is reconstituted with 5mL of sterile water and with a pH of 11, it is advisable to infuse into a large peripheral vein to avoid extravasation and subsequent tissue necrosis. The dosage of Ryanodex is the same as other formulations of dantrolene. Vials contain 250 mg of dantrolene (compared to 20mg of dantrolene per vial of Dantrium) and the recommended initial dose remains 2.5 mg/kg. Therefore, one vial is adequate as an initial dose for a 100-kg patient. The median T_{max} is one minute post injection and its $T_{1/2}$ is 8.5-11.5 hours regardless of dose administered in the 1-2.5 mg/kg dose range. Dantrolene, unsurprisingly, can cause skeletal muscle weakness, dysphagia, reduced inspiratory capacity and drowsiness. Concomitant use with calcium channel blockers can lead to marked cardiovascular compromise in the setting of hyperkalaemia, and in the setting of neuromuscular blocking agents, dantrolene will potentiate their effects[15,19].

At the time of writing, Ryanodex has not been formally approved by the TGA (Therapeutic Goods Administration) in Australia or by Medsafe in New Zealand. However, following a recent shortage of Dantrium, Ryanodex has been imported and supplied to some hospitals in Australia and New Zealand under the relevant provisions allowing for supply of non-approved drugs in exceptional circumstances.

GENETIC ADVANCEMENTS

The advent of whole exome sequencing has certainly facilitated the routine analysis of the very large RYR1 and CACNA1S genes; however it has not yet resulted in the identification of any new "primary" MH genes – more families with multiple affected individuals across multiple generations are required to facilitate this. These next generation sequencing methods are, however, allowing the connection between MH and other diseases to be clarified.

CONCLUSION

Malignant hyperthermia is a rare entity and is potentially life threatening for the susceptible individual undergoing general anaesthesia, or, exposed to implicated environmental stressors. Despite advances in genetic screening, identifying the MH susceptible individual by routine DNA analysis alone remains elusive. Thus, the gold standard in diagnosing MH is the in-vitro contracture test (IVCT). Early identification, removal of the precipitant, supportive measures and dantrolene continue to be the mainstay of management.

REFERENCES

1. Rosenberg H, Pollack N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis. 2015;10:93.
2. Litman Ronald S. Malignant hyperthermia: Clinical diagnosis and management of acute crisis. [Internet]. 2016. From: https://www.uptodate.com/contents/malignant-hyperthermia-clinical-diagnosis-and-management-of-acute-crisis. Accessed 4 October 2017.
3. Denborough MA, Lovell RRH. Anæsthetic deaths in a family. Lancet.1960;276(7140):45
4. Hockey B, Gillies R. Malignant Hyperthermia. [Internet]. From: http://www.anaesthesia.mh.org.au/malignant-hyperthermia/w1/i1001286. Accessed April 2017.
5. Brady JE, Sun LS, Rosenberg H, Li G. Prevalence of malignant hyperthermia due to anaesthesia in New York State, 2001-2005. Anesth Analg. 2009;109:1162-1166.
6. Bjorksten AR, Gillies RL, Hockey BM, Du Sart D. Sequencing of genes involved in the movement of calcium across human skeletal muscle sarcoplasmic reticulum: continuing the search for genes associated with malignant hyperthermia. Anaesth Intensive Care. 2016;44(6):762-768.
7. Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology. 1994; 80(4):771-779.
8. Rosenberg H, Girard T. MHApp. [Internet]. 2010. From: iTunes Apps Store. Accessed February 2017.
9. Klinger W, Heidrich S, Girard T, Gravino E, Heffron J, Johannsen S, et al. Functional and genetic characterization of clinical malignant hyperthermia crises: a multi-centre study. Orphanet J Rare Dis. 2014,9:8
10. Larach MG, Allen GC, Brandon BW, Lehman EB. Temperature changes are not late signs of malignant hyperthermia: a NAMH registry of MHAUS study. Anesthesiology. 2008;109:A374.
11. Nelson P, Litman RS. Malignant hyperthermia in children: an analysis of the North American malignant hyperthermia registry. Anesth Analg. 2014;118(2):369-374.
12. Hopkins P, Ruffert H, Snoeck M, Girard T, Glahn P, Ellis F, et al. European Malignant Hyperthermia Group Guidelines for investigation of malignant hyperthermia susceptibility. Br J Anaesth. 2015;115(4):531-539.
13. Diamini N, Voermans NC, Lillis S, Stewart K, Kamsteeg EJ, Drost G, et al. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. Neuromuscul Disord 2013;23(7):540–548.
14. Capacchione JF, Muldoon SM. The relationship between exertion heat illness, exertion rhabdomyolysis, and malignant hyperthermia. Anesth Analg 2009;109:1065-1069.
15. Malignant Hyperthermia Association of the United States. MHAUS recommendations. [Internet]. 2013. From: http://www.mhaus.org/healthcare-professionals/mhaus-recommendations. Accessed April 2017

16. Maccani RM, Wedel DJ, Kor TM, Joyner MJ, Johnson ME, Hall BA. The effect of trace halothane exposure on triggering malignant hyperthermia in susceptible swine. Anesth Analg. 1996;82:S287.
17. Bilmen JG, Gillies RL. Clarifying the role of activated charcoal filters in preparing an anaesthetic workstation for malignant hyperthermia-susceptible patients. Anaesth Intensive Care. 2014;42(1):51-58.
18. Wardle K. Malignant hyperthermia (MH). [Internet]. 2015. From: www.anaesthesiawa.org/mh.html. Accessed August 2017.
19. Eagle Pharmaceuticals. Ryanodex. [Internet]. From: www.ryanodex.com. Accessed April 2017.

Paediatrics

Hypnosis and communication in paediatric peri-operative care

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INTRODUCTION

Hypnosis and hypnotic communication allow the anaesthetist to give suggestions to children that can enhance their peri-operative care, reframe negative expectations and teach new skills to manage symptoms such as pain, anxiety and nausea[1,2]. The language of hypnosis can be particularly effective in children as they live in a world full of imagination and fantasy.

WHAT IS HYPNOSIS?

Hypnosis is a state of mind that we have all experienced, but are often unaware of. It may arise and fall away spontaneously, particularly when people are affected emotionally, for example while watching an engaging movie. It can also be deliberately induced by hypnotherapists or by activities such as meditation, yoga, exercising and mindfulness. Children who are anxious or in pain frequently experience hypnosis or trance-like states spontaneously making them highly responsive to suggestion. Suggestions are verbal or non-verbal communications that can alter perceptions, mood and/or behavior[3].

Spontaneous hypnosis in the peri-operative setting results in increased suggestibility so there may be no need for formal hypnosis as suggestions combined with specific language and communication structures may be all that is necessary. The utilisation of communication techniques allows the anaesthetist to enhance rapport and facilitate the effective delivery of therapeutic suggestions to improve peri-operative care.

CASE HISTORIES

Case one illustrates how skilled communication enhances peri-operative care for children. Introducing specific language into our everyday practice can be helpful for patients and their families, as we produce positive change in a period where negative expectations and anxiety can become overwhelming. Case 2 shows how formal hypnosis may be used in the peri-operative period to manage anxiety and specific fears such as needles and mask induction. Hypnosis can enhance analgesia, reduce peri-operative adverse effects such as nausea and allow patients to envisage recovery, healing and return to normal function.

CASE ONE. LANGUAGE AND COMMUNICATION

An eight-year-old girl, Lily, is booked for a tonsillectomy for recurrent tonsillitis. She had a general anaesthetic two years previously for a fractured forearm. Both Lily and her parents appear anxious and they are concerned about pain, nausea and breathing problems following surgery. Negative expectations abound.

Lily and her family are reassured that you will be looking after Lily and ensuring she is as safe and comfortable as possible for when she wakes up in the recovery room. You check what name Lily prefers to be called, ask her permission to talk to her mum, and note her expression and demeanour. Matching vocal tone, body position and language to that of the family, listening to their concerns and confirming understanding and meaning enhances rapport. An acceptance of their reality (at least for that moment) opens up the possibility of a shift in mind set. Reframing and providing alternative perspectives as suggestions can shift negative thoughts to a focus on therapeutic goals.

On examining Lily, she is asked, "If you could go to your favourite place or do your favourite activity, sport, movie – what would that be?" This exploration allows the anaesthetist to take note of her likes and dislikes and the language she uses. As she (and her parents) begin to relax, you discuss the choice of anaesthetic induction. "And when you go to sleep for your operation, you can either breathe on the gas or we can put some cream on your hand to make it numb and then place a cannula into the vein and let you go to sleep that way". "And when you come to theatre, would it be OK if you take yourself back to your favourite place? Perhaps you could

stay there, in your special place, while we take care of you, and you can look forward to waking up comfortably having something nice to eat, with mum and dad there to look after you? Would that be OK?"

Turning to the parents, the remainder of the anaesthesia can be described in terms of providing medications to ensure Lily is comfortable and able to eat and drink after her surgery. "And when she is coming out of the anaesthetic she will be watched closely in recovery by experienced nurses and you can look forward to seeing her soon after the surgery finishes. In fact, you may be pleasantly surprised at how well she recovers after surgery." You offer Lily and her parents the opportunity to ask questions and you answer them. Although a sedative pre-medication is rarely required, it is available. However, the expectation is that she will be able to cooperate well.

When Lily comes to theatre she is asked several short questions designed to elicit a yes response such as "Is it OK to bring your toy in to theatre?" Then she is asked if she can climb onto the operating table or if she would like mum/or dad to help (double bind – a choice of comparable alternatives, as either way she will be on the bed). When lying comfortably, she is asked to "Take yourself to your favourite place" and given verbal cues to help relive the experience, "Notice the colours, the shapes, the sights, listen to the sounds, take a deep breath in and really step into it, really be there…". You begin a mask induction – "as you go to sleep with the mask, would you like to breathe quietly or would you prefer to take deep breaths and blow the balloon up?" As breaths are taken the sevoflurane is introduced and you provide a suggestion of a smell, colour, feeling or sound that relates to her favourite place.

Hypnotherapeutic communication is frequently used by many anaesthetists during induction of anaesthesia[4].

The specific language and persuasive techniques to be discussed are:

1. Establishing rapport.
2. Persuasive language techniques.
3. Social proof.
4. Lived-in imagination.
5. Direct suggestions.
6. Informed consent.

1. Establishing rapport
Many anaesthetists rapidly establish rapport with anxious patients. A useful framework for building rapport is the LAURS acronym which provides a structured approach of listening, accepting, utilising, reframing and suggestion[3].

Introduction: "Hi – I'm ……., I'm the doctor who is going to take care of you during your operation". Reframe to caring and personalisation.

Name: "Is it OK to call you Lily or do you prefer another name?" This acknowledges Lily as an individual.

Control and autonomy: Anaesthesia care frequently engenders feelings of loss of control and it is important to give some autonomy back to the patient and family. Asking "Is it OK if I talk to your parents?" may seem trite at first glance, but it acknowledges the child as an individual, gives them a feeling of control and builds rapport.

Surgery: "Do you know why you have come to hospital? Tonsillectomy – won't it be nice when you don't have tonsillitis anymore – are you looking forward to that?" A reframe focusing on the goal of surgery.

Mirroring
Rapport can be facilitated by adopting the patient's or parent's vocal tone, posture and language in a manner congruent to that of the family. You can ask Lily what she likes doing or comment on an item of clothing or a possession.

2. Persuasive language techniques
"Yes sets", "compliance sets" and "no sets" – by asking two or three simple questions early in the interaction, each question eliciting a "yes" answer increases the success of the compliance set that follows. For example:

Would you like to bring your toy into theatre with you? – yes

Are you looking forward to having something to eat after the operation? – yes

Would you like mum to hold your hand? – yes

Then move to a compliance set:

Can you lie comfortably on the operating table? – yes

Can you make sure you are in the middle of the bed? – yes

Can you hold the mask for me? – helpfully holds the mask

If the child is negative and disinterested you can substitute a "no set" and segue to a "yes set". The "no set" also acknowledges the child's feelings and builds rapport.

You don't want to be here today, do you? – no

You don't want to have an operation do you? – no

You don't want Mummy to be here either? – no

Now flip to a "yes set":

But you are here – yes

And your Mum is here – yes

And I'm here to help you – yes

And now a "compliance set":

So you can sit on mum's lap as you go to sleep.

Can you take some deep breaths and blow the balloon up?

That's great.

Double binds and presuppositions
"As you go to sleep, you can breathe on the mask or just blow it away". This sentence presupposes that Lily is going to sleep, and that she has a choice of comparable alternatives; either to breathe or blow. Another example of a double bind combined with presuppositions is:"When you are lying still on the bed, would you prefer to hold mummy's left hand or her right hand?"

Negatively valenced words, sabotage, and negative suggestion

Words with a negative connotation are best avoided unless the patient uses them first. They can act as negative suggestions and fuel potential negative emotional responses. These words include pain, vomit, sting and needle, which are commonly used in peri-operative settings.

Rather than ask post-operative patients how much pain they have on a one to 10 scale, they can be asked whether they are comfortable or how comfortable they are. When describing the anaesthetic process you can say "We will give a combination of medications to help you be comfortable after your operation, and you may be pleasantly surprised how well you feel".

Nausea and vomiting can be replaced by "We will give you medications which will help you to feel hungry so you can look forward to enjoying something to eat this afternoon". Asking a patient to imagine eating their favourite food acts as a distraction or a pattern break but also as a suggestion to be hungry on emergence.

Minimising words are unhelpful as they draw attention to the issue that you hope to minimise. So "Just a little sting" when inserting a cannula draws attention to the sting and acts as a negative suggestion. This has a nocebo effect, worsening the discomfort of cannulation. Negative suggestions can be replaced with a neutral or positive suggestion, such as "We'll use some local anaesthetic to numb the skin to make it more comfortable"[5].

Negating words can have the opposite effect. "Don't worry" or "Don't move" may have the unintended but opposite effect of causing worry or movement. Using "not" or "don't" in a phrase first requires that attention is drawn to the aspect that you hope to prevent. An alternative to "don't move" is "stay still".

Avoiding failure words. Asking someone to "try" to do something implies an acceptance of failure. "Just try to relax" often fails. If you want someone to relax, use either a direct suggestion "As you breathe out, you can blow away some tension and feel yourself relax"" or an indirect suggestion such as "Many children notice how slow breaths out allow them to feel relaxed".

3. Social proof can increase the likelihood of suggestions being accepted. "I am always amazed at how soon kids are able to eat after surgery these days" or "Most kids really enjoy an ice block a couple of hours after their tonsillectomy". These are indirect suggestions which imply Lily can do this too.

4. Lived-in imagination is a form of visual imagery that can be used to recall a previous experience and replace the current anxious state with the state of mind that was present in a favourite place or activity. The request for Lily to talk about her favourite place acted as a pattern break, a distraction and a means to access a more resourceful state from her past. Lived-in imagination may be enough to induce a hypnotic state that can allow suggestions to be given at the time of assessment and at induction in theatre. Hypnotic techniques such as lived-in imagination have been shown to be superior to midazolam premedication prior to inhalational induction[7].

5. Direct suggestions
Throughout the pre-anaesthetic and induction encounters Lily is in a suggestible state. This is due to anxiety, the use of persuasive language and lived-in imagination to access a hypnotic state. Suggestions are used

throughout this interaction. The general themes are of safety, caring and good recovery from surgery with the goal of reducing anxiety. There are also specific suggestions for pleasant smells, hunger and comfort. Prior to inhalational induction of anaesthesia, awake suggestions can be given to change the smell of the volatile anaesthetic agent from sevoflurane to a pleasant smell, ideally one that matches a child's likes, such as strawberries or chocolate. The possibilities are limitless and can be modified to suit the circumstances[6]. If the smell of strawberries is suggested and accepted, another suggestion of "looking forward to eating strawberries when you wake", can be given to enhance appetite and reduce the risk of nausea.

7. Informed consent
Instead of informed consent being a check list of possible complications and adverse effects which may act as negative suggestions[8], we endeavour to reframe informed consent as an opportunity to explain how we are going to help avoid complications. So instead of negative suggestions we give positive suggestions of comfort, appetite and caring. For example: "As part of Lily's anaesthesia care she will be given a number of medicines to make her feel comfortable as she awakens and returns to the ward. She can be given more medications in recovery or on the ward if needed to ensure she is comfortable". More serious but less common adverse effects can be put into a context of safety, for example – "One of my other concerns is ensuring Lily has a good airway both during the surgery and as she recovers. She will be watched carefully throughout the operation and as she wakes up". For a child we can also explain the anaesthetic in simple terms that emphasise therapeutic goals suggestive of rapid recovery. Suitable goals include eating and drinking when she feels like it or getting back to drawing or other favourite activity.

Approaching informed consent in this manner achieves the goals of providing truly informed consent without the nocebo effect produced by a list of negative outcomes. It is also likely that improved rapport leads to less risk of medical litigation.

CASE TWO. PERI-OPERATIVE HYPNOSIS FOR RUBY

A seven-year-old girl, Ruby, with a genetic predisposition to endocrine tumours was referred for hypnosis prior to prophylactic thyroidectomy. Ruby has developed anticipatory anxiety and distress with repeated venous access procedures. She was offered hypnosis to help manage her needle phobia[9-11] and to reduce pre-operative anxiety and post-operative pain.

The structure of a hypnotic session for perioperative care and needle phobia involves:

1. Assessment.
2. Rapport.
3. Suggestibility tests.
4. Induction and deepening of hypnosis.
5. Suggestions.

1. Assessment
Information was gathered during a phone interview with Ruby's mother. The paediatric hypnosis process was described and she was keen for her daughter to proceed. Dealing with these aspects during the phone call meant that the initial session could focus on solutions and positive outcomes.

2. Rapport
In a similar manner to Case 1, rapport was established using the LAURS approach[3].

3. Suggestibility tests
Ruby was offered a trial of formal hypnosis to check that she was comfortable with the technique. The "balloon and dictionary" suggestibility test was used to give a brief experience of hypnosis.

"Close your eyes, and place both arms out in front of you, one palm up and the other down. Great, now I am going to place the biggest book in your house (press gently on their palm) and I would like you to balance that large heavy book in your hand. While you keep holding that large heavy book, I would like you to notice me tying a large helium balloon to the other wrist, you can use your imagination to picture that balloon – It's colour, it's size, it's shape, you can feel the ribbon tied to your wrist and you can feel the balloon starting to pull your arm upwards…"

"Now open your eyes and see where your arms are." One arm will almost always be 10-20 cm higher and the other 10-20 cm lower than the starting position. "That's fantastic… You are good at using YOUR imagination!"

At this stage, we have achieved four essential elements for hypnosis – a belief that hypnosis is real, a realisation that they can use their imagination, a conviction that it will do something and an expectation that hypnosis will help.

4. Induction and deepening of hypnosis
After checking with Ruby, the balloon and dictionary suggestibility test was used as a hypnotic induction.

"And now begin to focus on the arm, effortlessly floating, suspended by three helium balloons, and imagine what will happen as I push your arm down, it just pops back up, pulled up by that balloon, it just pops back up each time I push it down, and as your mind relaxes it can be open to suggestions".

When you stop pushing the arm down, it usually remains suspended, which is a hypnotic phenomenon of a cataleptic limb and "arm levitation". The cataleptic limb can be used to further deepen hypnosis – "As that limb begins to slowly sink down, you can allow yourself, to become even more relaxed, and as it comfortably rests on your lap you can be even more deeply relaxed and begin to…" Adapted from video demonstration[12].

There are many ways to induce hypnosis in children including "lived-in imagination" as described in the first case study, or guided imagery, for instance: "imagine flying up to the sky and finding a very comfortable cloud to lie down on". The choice of technique will depend on the child's individual likes and dislikes, age, developmental stage and the hypnotherapist's preference. The actual induction technique is not important. The predictors of success are rapport, engagement and development of focused attention.

Deepening of hypnosis may be required in adolescents and is almost universal in adults, however with children the induction is often all that is needed to achieve an adequate depth of hypnosis. There are a variety of deepening techniques, with children these can be simply using a series of inductions such as lived-in imagination, visual imagery or muscle relaxation stacked upon each other. In adolescents and adults deepening may involve utilisation of catalepsy, fractionation – which involves partially awakening from hypnosis and then re-inducing hypnosis several times or the use of indirect techniques such as metaphor or story.

The depth of hypnosis may be tested by observing the response to suggestions and by observing hypnotic phenomena such as muscle relaxation, catalepsy, slowing of breathing, eye movement and posture.

Further reading[13-17].

5. Suggestions
Once hypnosis has been induced suggestions are given to achieve the goals of hypnotherapy. As with Case 1, specific language is important. Suggestions can be given directly – "As X happens then Y can follow", or indirectly with the use of a story, an illustrative example which relates to the child's interests and development stage, or citing the experience of others. Suggestions for peri-operative care for Ruby may include relaxation, pain management, symptom relief and prevention (nausea and itch), ego-strengthening, envisaging a time when they can return to their favourite activities and teaching self-hypnosis.

Relaxation
Suggestions to promote relaxation include muscle relaxation, breathing techniques such as awareness of breathing, slowing breathing and blowing away tension and anxiety, and the use of metaphor. For example, filling a basket with all of your cares and worries then floating this away.

Pain management
Strategies for using hypnosis and suggestion to manage pain include managing anxiety, altering perception of pain, dissociating from pain, substituting feelings that are antithetical to pain, distraction techniques and envisaging a time in the future when they have healed and are comfortable[17].

Hypnosis is used to suggest altered pain perception, such as suggesting numbness or presence of local anaesthesia, or loss of sensation. Common techniques are the magic glove or anaesthetic glove – "picture putting on a fantastic glove, of the most comfortable material that is soaked in local anaesthetic"[1].

Another suggestion utilises the analogy of the wiring to the lighting in a house, and using switches to turn off sensation to a limb or part of the body[20].

Dissociating suggestions include moving one's self away from the pain – "Take yourself away on your bike ride, leave all the discomfort as you go to that favourite place (lived in imagination from Case 1)…" utilised with self-hypnosis.

Suggestions for feelings antithetical to pain include replacing pain with comfort, laughter, relaxation, strength or confidence.

Distraction can be achieved by using lived-in imagination, or by techniques such as a "Trip around the body". This technique uses a metaphoric story of shrinking down and travelling around the body to check all the organs. Taking a repair kit but also noting the strong heart and lungs pumping blood and delivering oxygen.

Ego-strengthening
Drawing on the child's previous experiences and capacities, direct suggestions of their ability to overcome challenges and use their strengths can be given.

Forward progression
Re-focusing the patient on the goal of surgery and envisaging a time when they are fully healed moves them away from their negative expectations of surgery to a time when they have overcome obstacles and life is normal again.

Post hypnotic suggestions
While in hypnosis a suggestion can be given to allow the child to go rapidly into hypnosis at a later time. This can be anchored with an action such as gently pressing the shoulder along with a suggestion of going rapidly into hypnosis at a later time when they wish to go into hypnosis and the shoulder is pressed by the hypnotist. This can be utilised for subsequent sessions or on arrival in theatre.

Teaching self-hypnosis
Self-hypnosis can be taught within hypnosis and later practiced. While in self-hypnosis the child is taught to use the techniques that were part of the suggestions and metaphors used previously by the hypnotherapist.

"In a moment, I will ask you to focus on a spot on the ceiling. When your eyes go blurry or start to tire, I would like you to take a deep breath in, and then count backwards from five. As you breathe out, shut your eyes and drift down into hypnosis. Allow your whole body to relax with each breath out and feel strong with each breath in. As you relax take yourself to that safe place, see all the sights, the colours, the shapes…"

Then suggest that they use one of the techniques to manage anxiety or pain that they have learnt, such as lived-in imagination, the magic glove or floating up to a cloud full of comfort.

MANAGING NEEDLE PHOBIA WITH HYPNOSIS

As part of her peri-operative hypnosis Ruby was taught self-hypnosis and the use of lived-in imagination to dissociate from pain and anxiety. She also used suggestion of an anaesthetic towel to create numbness and comfort, and she rehearsed successful venepuncture using these techniques. She used these techniques in the first session and had her pre-operative bloods taken without distress or discomfort.

Other approaches to needle phobia include graded exposure to needles during hypnosis, modifying memories of previous distressing needle events and rehearsing success in the future[19].

SURGERY

Arriving in theatre Ruby appeared calm, and voluntarily climbed onto the operating table. She kissed her mother and as her shoulder was pressed she was asked to count backwards from five and take herself back into hypnosis. "Take yourself into that beautiful relaxing rainforest as we look after you". Breathing on the gas, she received suggestions to smell the damp leaves in the rainforest (as the sevoflurane was turned to 8 per cent) and look forward to something really nice to eat in the afternoon. Further reminders for self-hypnosis were given after she woke up. She had an uneventful recovery with minimal analgesic requirements[20].

CONCLUSION

Hypnotherapy can be useful to improve pain management, nausea and anxiety about surgery, anaesthesia and venipuncture. The goal is to allow patients to use their own capabilities to manage the challenges of the peri-operative journey and to enhance their care and recovery. Essential features of this process are establishing rapport and using the language of the subconscious. Paediatric anaesthetists are in the fortunate position of being able to practice hypnotic inductions for many routine patients. This equips us with very useful skills for managing problems which benefit from a hypnotic approach.

REFERENCES

1. Kuttner L. Pediatric hypnosis: pre-, peri-, and post-anesthesia. Paediatr Anaesth. 2012;22(6):573–577.
2. Sugarman L. Therapeutic hypnosis with children and adolescents. 2nd ed. London: Crown House Publishing, 2014.
3. Cyna AM. Handbook of communication in anaesthesia and critical care a practical guide to exploring the art. New York: Oxford University Press, 2011.
4. Carlyle AV, Ching PC, Cyna AM. Communication during induction of paediatric anaesthesia: an observational study. Anaesth Intensive Care. 2008;36(2):180–184.
5. Lang EV, Hatsiopoulou O, Koch T, Berbaum K, Lutgendorf S, Kettenmann E, et al. Can words hurt? Patient-provider interactions during invasive procedures. Pain. 2005;114(1–2):303–309.
6. Zoanetti DC, Cyna AM. Distorting the perception of smell during gaseous induction. Paediatr Anaesth. 2005;15(12):1148; author reply 1149.
7. Calipel S, Lucas-Polomeni MM, Wodey E, Ecoffey C. Premedication in children: hypnosis versus midazolam. Paediatr Anaesth. 2005;15(4):275–281.
8. Krauss BS. "This may hurt": predictions in procedural disclosure may do harm. BMJ. 2015;350:h649.
9. Uman LS, Chambers CT, McGrath PJ, Kisely S. A systematic review of randomized controlled trials examining psychological interventions for needle-related procedural pain and distress in children and adolescents: an abbreviated Cochrane review. J Pediatr Psychol. 2008;33(8):842–854.

10. Birnie KA, Noel M, Parker JA, Chambers CT, Uman LS, Kisely SR, et al. Systematic review and meta-analysis of distraction and hypnosis for needle-related pain and distress in children and adolescents. J Pediatr Psychol. 2014;39(8):783–808.
11. Uman LS, Birnie KA, Noel M, Parker JA, Chambers CT, McGrath PJ, et al. Psychological interventions for needle-related procedural pain and distress in children and adolescents. Cochrane Database Syst Rev. 2013;10:CD005179.
12. Wicks G. Hypnosis with children. Adelaide: SA Hypnosis Society, 2007.
13. Lyons L. Using hypnosis with children. New York: WW Norton & Company, 2015.
14. Hudson L. Scripts and strategies in hypnotherapy with children. Wales: Crown House Publishing, 2009.
15. Olness K, Kohen DP. Hypnosis and hypnotherapy with children. 4th ed. New York: Routledge, 2011.
16. Tiers M, Woods K. Integrative hypnosis for kids and teens. North Charleston: CreateSpace Independent Publishing Platform, 2016.
17. Thomson L. Harry the hypno-potamus metaphorical tales for the treatment of children. Wales: Crown House Publishing, 2005.
18. Cyna AM, Tomkins D, Maddock T, Barker D. Brief hypnosis for severe needle phobia using switch-wire imagery in a 5-year old. Paediatr Anaesth. 2007;17(8):800–804.
19. Weigold C. The use of hypnosis in the management of needle phobia. Aust J Clin Exp Hypnosis. 2011;39(2):189–195.
20. Lobe TE. Perioperative hypnosis reduces hospitalization in patients undergoing the nuss procedure for pectus excavatum. J Laparoendosc Adv Surg Tech A. 2006;16(6):639–642.

Postoperative behaviour change in children

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INTRODUCTION

Children who undergo surgery under general anaesthesia may subsequently develop changes in their behaviour. These changes can occur acutely during recovery from anaesthesia, or they can be delayed and occur in the days and weeks after surgery. Acute behaviour change is known as emergence delirium and is characterised by a dissociated conscious state where the child is unaware of his or her surroundings. Delayed behaviour change (known as post-hospitalisation behaviour change) is characterised by sleep and eating disorders, temper tantrums, nightmares and anxiety. It has been reported that Post-Hospitalisation Behaviour Change (PHBC) occurs in more than 50 per cent of children undergoing a general anaesthetic[1]. The effect is usually short-lived (two to four weeks), however in 5-10 per cent of children these behaviours can last up to 12 months[2]. The risk factors for developing PHBC include underlying anxiety in the child or parent, a previous bad hospital experience, emergence delirium and pre-school age. PHBC leads to increased general practitioner visits, parental time off work and reduced compliance with future episodes of health care[3]. PHBC after surgery and anaesthesia can be a significant problem for children and parents. The cause of negative behaviour change may be related to the psychological impact of the experience and there may be other pathophysiology directly related to brain changes from the anaesthesia, the stress response to surgery and pain associated with the procedure.

INCIDENCE OF POST HOSPITALISATION BEHAVIOUR CHANGE

The true incidence of PHBC is unknown with wide ranges reported in the literature varying from 24 to 80 per cent on days one to three and between nine and 28 per cent one month after surgery (table 1). The different incidences reported may be due to variations in the age of subjects and the type of surgery and the definition of PHBC used. One study followed up children for a year and found 20 per cent had behaviour change at six months and 7.3 per cent still had some negative changes at one year[2].

Table 1. The incidence of PHBC reported in various studies

Study	Year	Sample Size	Age (Years)	PHBC Incidence Day 1 to 3	PHBC Incidence Day 14	PHBC Incidence Day 28	PHBC Incidence 6 Months	PHBC Incidence 12 Months
Kain et al[2]	1996	163	2-10		54%		20%	7.3%
Kotinemi et al[4]	1997	551	0-13	46%		9%		
Kain et al[5]	1999	91	1-7		30%			
Keaney et al[6]	2004	120	0-14	58.3%		38.3%		
Stargatt et al[7]	2006	1250	3-12	24%		16%		
Fortier et al[1]	2010	260	2-12	80.4%	29.8%			
Power et al[8]	2012	131	2-12	73%		32%		

MEASUREMENT OF POST HOSPITALISATION BEHAVIOUR CHANGE

There are a number of reasons to explain the wide range of incidences reported in the literature. There may be cultural and institutional differences between the study populations and some of the studies only looked at one type of procedure or a subset of the general paediatric population. Another reason is that there are methodological differences in the selection, allocation and analysis of subjects. One major difference is how the Post Hospitalisation Behaviour Questionnaire (PHBQ) is used. The PHBQ is the most commonly used measurement tool for studies examining PHBC after surgery and anaesthesia. It has been used multiple times in the psychology and anaesthesia literature. The tool was developed in the 1960s and consists of 27 items of behaviour that are rated by parents. Vernon et al developed the tool based on six studies of children's behaviour after hospitalisation in the 1950s[9]. Symptoms that were mentioned in two or more of the studies were included in the questionnaire[9,10]. The items on the questionnaire can be grouped into six subscales: general anxiety, separation anxiety, sleep anxiety, eating disturbance, aggression towards authority and withdrawal/apathy. The original study by Vernon et al administered the PHBQ on 387 children aged six months to 16 years. The internal consistency (Cronbach's alpha) varied from 0.45 to 0.73 for the subscales and was 0.82 for the overall score. The construct validity was tested by comparing PHBQ scores with ratings of 20 children by a child psychiatrist one week after tonsillectomy (r=0.47)[9]. In addition it was found that there were no significant differences in the test result when the parents were interviewed, filled out the form without interview and filled out the form with interview[9,10]. Test-retest reliability was established in 37 children aged three to 11 (r=0.63). A more recent study by Karling et al found the PHBQ to have better internal consistency than the original study with Cronbach's alpha of 0.81-0.87 for the sub-scales and 0.92 overall. It also confirmed the face validity of the factors by consensus of a panel of child psychologists[10]. Another study by Karling et al examined the correlation between the PHBQ and the Child Behaviour Checklist (CBCL). The CBCL assesses 100 items for children aged two to four and 113 items for older children. It divides problem behaviours into internalising behaviours (withdrawn, somatic complaints, anxious-depressed) and externalising behaviours (delinquent behaviour, destructive behaviour and aggressive behaviour). The study found moderate correlation for children aged two to seven, but no correlation for children aged seven or above[11]. The authors suggest that perhaps the PHBQ reflects more subtle changes in behaviour after a stressful event whereas the CBCL may represent more general behavioural problems. However, it does suggest that the PHBQ is more suited to a younger age group and that perhaps school age children are not as affected by surgery and anaesthesia, or that the PHBQ may not reflect the behaviours of school age children[11].

One of the major limitations of the PHBQ is that no cut-off score was described in the original study. The definition of PHBC varies between studies with some defining PHBC as any deterioration in behaviour while others set a minimum number of negative behaviours that need to be observed for PHBC to be present. For example, the study by Stargatt et al that found a PHBC incidence of 24 per cent on day three post procedure, defined PHBC as seven or more negative behaviour changes. The mean number of negative behaviour changes on day three was 4.4[7]. Another difference is that some studies use the relative version of the PHBQ and others use the absolute version. The relative version asks parents to rate each of the 27 behaviour items relative to the child's behaviour preoperatively on a five-point Likert scale (much less than before, less than before, the same, more than before, much more than before). The absolute version uses a four-point scale (never to always) and is administered preoperatively to get a baseline score and then again at various time points postoperatively. It has been suggested that the relative version, as originally described by Vernon et al, is more sensitive but may be more subjective[11].

Jenkins et al have recently developed a revised PHBQ that reduces the number of items from 27 to 11. The Post Hospitalisation Behaviour Questionnaire for Ambulatory Surgery (PHBQ-AS) was developed by examining the California Irvine School of Medicine database of children who had been assessed using the PHBQ in 17 studies over 15 years (n=1064, mean age= 5.88)[12]. A factor analysis was performed which could not replicate the original six subscale structure of the PHBQ. A Principal Components Analysis then identified potential items on the questionnaire that were redundant and a panel of experts decided which items should be retained based on content validity. The reliability was found to be high for both the PHBQ and the PHBQ-AS (Cronbach's alpha 0.82 and 0.8 respectively) and concurrent validity was assessed by correlating both questionnaires with the Functional Disability Inventory (Pearson's r=0.48 and 0.49 respectively). The authors suggest that the revised, shortened questionnaire may be more relevant for day case procedures as well as being more efficient and more valid[12]. However, the authors also state that until further validation of the revised questionnaire occurs, it may not be suitable for use in postoperative behavioural research. The PHBQ-AS has not been validated against other child behaviour measurement tools such as the Strengths and Difficulties Questionnaire (SDQ) and the Child Behaviour Checklist (CBCL). The SDQ is well-validated in the child psychology literature and consists of 25 items in five domains. When compared to the CBCL, the SDQ was found to be significantly better at detecting inattention and hyperactivity and at least as good as detecting internalising and externalising problems. It was also preferred by parents[13]. A study underway at the Lady Cilento Children's Hospital in Brisbane is using the PHBQ-AS to assess behaviour change in preschool age children and concurrent validity will be measured against the SDQ. If further evidence for the validity of the instrument is established then we would recommend that researchers studying behaviour change in day-case surgery use this tool. To obtain a score on the PHBQ-AS each item is scored from 1 to 5 (much less than before, less than before, same as before, more than before, much more than before) then the total divided by 11 to obtain a continuous variable. Values above 3 indicate negative behaviour change, values below 3 indicate improvement in behaviour and a score of 3 indicates no change in behaviour.

Figure 1. Post hospitalisation behaviour questionnaire for ambulatory surgery

Does your child make a fuss about eating?

Does your child spend time just sitting lying and doing nothing?

Is your child uninterested in what goes on around him or her?

Does your child get upset when you leave him or her alone for a few minutes?

Does your child need a lot of help doing things?

Is it difficult to get your child interested in doing things (like playing games with toys)?

Does your child have temper tantrums?

Is it difficult to get your child to talk to you?

Does your child have bad dreams at night or wake up and cry?

Does your child have trouble getting to sleep at night?

Does your child have a poor appetite?

Each item scored:
Much less than before, less than before, same as before, more than before, much more than before.

RISK FACTORS FOR POST HOSPITALISATION BEHAVIOUR CHANGE

Many studies have explored risk factors associated with PHBC after surgery and anaesthesia. Younger age, anxiety of the child, anxiety of the parent, previous bad hospital experience and longer hospital stay have all been shown to be associated with PHBC[3,4,7,8]. Postoperative pain was found to be not significantly correlated with PHBC in studies by Stargatt et al and Fortier et al[7,14] but pain on the day of operation was found to be predictive of PHBC up to four weeks post-operatively by Kotiniemi et al (OR 4.44, 95 per cent CI 3.4-5.48, p=0.0005)[4]. According to most studies there is no association between the type of procedure and PHBC[4,8,14]. However, one study by Kain found that PHBC was less frequent with minor ENT procedures compared to other ENT and general surgical procedures[16]. There does not appear to be any association between the type of induction and the development of PHBC. This is supported by the results of multiple studies[6,7,15,17,18]. The use of premedication has conflicting results. Studies by Kain et al and McCluskey et al show significantly less PHBC with the use of premedication[5,19], however other studies show no difference or even increased PHBC when midazolam premedication is used[7,20]. Other risk factors that have been reported to increase the incidence of PHBC include two or more older siblings, a higher level of parental education and having a discussion with the anaesthetist preoperatively[7,8].

Figure 2. Risk factors for post hospitalisation behaviour change

GOOD EVIDENCE	MIXED OR CONFLICTING EVIDENCE	NO EVIDENCE
Pre-school age	Postoperative pain	Type of induction
Anxiety in child	Type of procedure	
Anxiety in parent	Midazolam premedication	
Previous negative hospital experience		

CONSEQUENCES OF POST HOSPITALISATION BEHAVIOUR CHANGE

Behaviour changes after hospitalisation can be distressing for both the child and the parents. It has also been shown to increase general practitioner visits and parental time off work[8]. This may have significant public health and economic implications considering the large number of paediatric anaesthesia episodes worldwide each year. Furthermore, when these behaviours do not resolve quickly, they can interfere with the child's education, social interactions and development[3]. It has also been shown that a child's compliance with future episodes of heath care is reduced following a distressing experience and that a negative medical experience as a child can result in an increase in pain and anxiety surrounding medical events as adults[1].

EMERGENCE DELIRIUM

Emergence delirium is a specific subtype of paediatric delirium that occurs during emergence from general anaesthesia. Current definitions of emergence delirium include features such as combative behaviours, motor agitation, inability to recognise familiar objects and people and an inability to be consoled[21]. A comprehensive review of emergence delirium by Costi featured in the previous edition of *Australasian Anaesthesia*[22].

The incidence of emergence delirium varies in the literature depending on the type of anaesthetic medication used, other medications administered before or during the anaesthetic, the age of the child and which measurement scale is used[23]. A propofol-based anaesthetic results in a lower incidence of emergence delirium compared to a sevoflurane anaesthetic according to a meta-analysis performed by Kanaya et al[24]. It has also been shown that the administration of fentanyl, alpha-2 agonists (clonidine or dexmedetomidine) or propofol during or at the end of anaesthesia reduces the incidence of emergence delirium[3,25,26]. Some of the risk factors that have been identified for emergence delirium are similar to those for PHBC. For example, preschool age children are at higher risk of both emergence delirium and PHBC[27]. Similarly, Kain et al found an association between the preoperative anxiety level of the child and the risk of developing emergence delirium and PHBC[28].

There are a variety of scales used for the detection and measurement of emergence delirium. Bajwa et al compared the Pediatric Anesthesia Emergence Delirium (PAED), Watcha and Cravero scales and found they all correlated well with each other but each scale had its own limitations[29]. One issue in diagnosing emergence delirium is distinguishing true delirium from other sources of distress, such as pain and separation anxiety. Furthermore, none of the currently used scales are able to detect hypoactive delirium, a type of delirium where the child is unaware of his or her surroundings but is quiet and withdrawn. These children are easier to care for in recovery than those with motor agitation, but they may still have similar long-term behaviour change issues and apprehension regarding future episodes of health care. There has been an increasing amount of work investigating hypoactive and mixed delirium in children in the intensive care unit. It is felt that younger children, like elderly people, are at a higher risk for delirium. The reason for this is that the developing brain is in some ways similar to the ageing brain. As people get older brain volume decreases with a loss of neurons and decreased levels of noradrenaline, acetylcholine, dopamine and gamma-aminobutyric acid. Children's developing brains are similar except that there are an increasing number of neurons and neurotransmitters and psychological maturity depends on activation of various synapses and pathways[30]. Patients at the extremes of age have less neurocognitive reserve and therefore are more susceptible to any central nervous system insult. In the hospital setting these insults include stress, inflammation, pain and medications. Further support for this theory comes from evidence that children with developmental delay or an abnormal brain are at greater risk of delirium, as are elderly people with dementia[31]. These groups of patients have even less neurocognitive reserve.

Currently, there is no evidence regarding whether or not hypoactive delirium exists in the recovery room setting in the context of emergence delirium. However, given that none of the emergence delirium scales in use are able to detect hypoactive delirium and the fact that staff are not trained to detect it, then it is possible that children are experiencing this form of delirium. The Cornell Assessment of Paediatric Delirium (CAP-D) was developed as an extension of the PAED scale and is a rapid screening tool for paediatric delirium (figure 2). It is able to detect both hyper- and hypoactive delirium and has been validated in the intensive care setting[32]. To date, it has not been used in children recovering from general anaesthesia, but it may be a valuable tool in this environment, particularly in identifying hypoactive delirium. A score of 9 or greater indicates delirium, however this has only been validated in intensive care patients. The Lady Cilento Children's Hospital in Brisbane is currently evaluating the CAP-D in its recovery and auditing the results.

Figure 3. Cornell Assessment of Paediatric Delirium (CAP-D)

	NEVER	RARELY	SOMETIMES	OFTEN	ALWAYS
Does the child make eye contact with the caregiver?	4	3	2	1	0
Are the child's actions purposeful?	4	3	2	1	0
Is the child aware of his/her surroundings?	4	3	2	1	0
Does the child communicate needs and wants?	4	3	2	1	0
Is the child restless?	0	1	2	3	4
Is the child inconsolable?	0	1	2	3	4
Is the child underactive – very little movement while awake?	0	1	2	3	4
Does it take a long time to respond to interactions?	0	1	2	3	4

INTERVENTIONS

A variety of interventions have been assessed to determine their effect on postoperative behaviour change. These include midazolam premedication, type of induction, type of anaesthetic agent, preparation packages, distraction at induction and parental presence at induction or in recovery. Other medications given either before or during surgery may be of benefit, the most promising of these are the alpha-2 agonists clonidine and dexmedetomidine.

Midazolam

The use of premedication has conflicting results. Some studies have shown a reduction in PHBC with the use of midazolam premedication[5,19] while others have shown no difference or even an increase in its incidence[7,20]. A study by Kain et al randomised 86 children to receive midazolam 0.5 mg.kg^{-1} orally or placebo preoperatively. They found less incidence of PHBC in the midazolam group in the first week but no difference after two weeks[4]. Conversely, McGraw and Kendrick randomised 70 children to receive midazolam 0.5 mg.kg^{-1} or placebo preoperatively and found that while the children who had midazolam were less likely to cry at induction, they had more than double the incidence of PHBC one week after surgery (54 per cent versus 23 per cent)[20].

Induction

Intravenous versus inhalation induction has been suggested as a possible factor in perioperative anxiety in children. Anaesthetists who are more familiar or comfortable with one technique will most likely be able to minimise the anxiety caused to children using that technique. However, there are some children who may have an exaggerated fear of needles or a fear of something being placed over their face. In these cases there will be an obvious advantage in using one technique over the other. In general, there does not appear to be any association between the type of induction and the development of PHBC. Many studies that have looked at PHBC as an outcome have reported no association with the method of induction[6,7,15,17,18].

Anaesthetic agent

The choice of inhalational agent has been studied with respect to PHBC. Kain et al randomised 102 children to receive either sevoflurane or halothane maintenance and then measured the incidence of PHBC in the week following surgery. There was no difference between groups[33]. Similarly, Keaney et al examined the difference between sevoflurane and halothane in a randomised, controlled trial and found more emergence delirium in the sevoflurane group but no difference in PHBC in the month following surgery[6]. In contrast, a retrospective study by Foesel and Reisch found that 25.7 per cent of children who received sevoflurane developed behaviour changes that lasted longer than a week compared to 16.1 per cent in children who received halothane[15].

Preparation packages

The effect of preoperative preparation on behaviour change has been investigated. One study randomised children and their families to receive limited preoperative information or extensive information consisting of videos, operating theatre tours and coping strategies. It found that the children and parents who received extensive preparation were less anxious on the day of surgery in the holding area, but this did not translate to any difference in PHBC at two weeks[34].

Distraction and parental presence

Many studies have evaluated distraction techniques in terms of reducing anxiety at induction of anaesthesia, however few studies have looked at its effect on PHBC. A study by Kim et al randomised children to have a video playing during induction or parents present at induction or both. There were no differences in the incidence of PHBC at day one and day 14 post surgery[35]. While there is no clear evidence that parental presence at induction reduces PHBC, there may be a role for parental presence in recovery. Lardner et al randomised 300 children to have a parent present or absent upon eye opening in recovery and found that at two weeks after surgery there was a 29.3 per cent incidence of PHBC in the parent present group compared to 45.8 per cent

in the parent absent group[36].

Dexmedetomidine

Dexmedetomidine is a highly-selective alpha-2 agonist that produces drowsiness, anxiolysis, and analgesia. It causes minimal respiratory depression and it has a shorter duration of action than clonidine. It has poor bioavailability when given orally (around 15 per cent) but is effective and well tolerated when administered intranasally or bucally. A recent meta-analysis by Pickard et al showed that an intraoperative dose of dexmedetomidine reduced the incidence of emergence delirium in children (OR 0.22, 95 per cent CI 0.14-0.33, P<0.001). Clonidine was also effective, although the size of the effect was lower (OR 0.50, 95 per cent CI 0.26-0.95, P=0.04)[3]. There were no differences in time spent in recovery or time to discharge. There was also a reduced need for rescue analgesia and this finding has been replicated by another meta-analysis by Schnabel et al which found decreased post-operative pain in children following an intra-operative dose of dexmedetomidine[37]. A meta-analysis by Pasin et al comparing dexmedetomidine and midazolam as a premedication in children found the incidence of emergence agitation in children given dexmedetomidine was 10 per cent and in those given midazolam group was 40 per cent (RR=0.31, 95 per cent CI 0.13-0.73, p=0.008). Furthermore, the need for rescue analgesia in the dexmedetomidine group was 20 per cent compared to 39 per cent in the midazolam group (RR=0.52, 95 per cent CI 0.39-0.70, p<0.001)[38]. There is also growing evidence that dexmedetomidine is neuroprotective in both animal and human models. A meta-analysis by Man et al found adults who had an intraoperative dose of dexmedetomidine had better neurocognitive outcomes compared to placebo and midazolam[39]. Another meta-analysis by Pasin et al examined critically ill patients in an intensive care setting and found dexmedetomidine reduced the incidence of agitation, confusion and delirium compared to control[40]. Other interesting findings from recent meta-analyses have shown decreased levels of interleukin-6, interleukin-8, tumour necrosis factor-alpha, serum catecholamine levels and serum cortisol levels in patients who received perioperative dexmedetomidine[41,42]. In summary, dexmedetomidine reduces anxiety and pain in the perioperative period which may have an influence in reducing negative behaviour change post-operatively. It also has neuroprotective effects, anti-inflammatory effects and an ability to modulate the stress response. All of these effects may also contribute to longer term benefits.

SUMMARY

Children may experience early and delayed behaviour change after general anaesthesia. Development of these behaviours may have long term detrimental effects on future episodes of healthcare. Children, especially preschool age children, are particularly susceptible to central nervous system insults due to psychological immaturity and a developing brain. A variety of insults to the central nervous system occur during the perioperative period, including stress, inflammation, pain and anaesthetic medications. Attempts should be made to reduce perioperative anxiety in children using both pharmacological and non-pharmacological methods. Dexmedetomidine may be a useful adjunct to general anaesthesia for its anxiolytic, analgesic, anti-inflammatory and neuroprotective effects. It has been shown to be effective at reducing emergence delirium but longer term outcomes such as PHBC are yet to be assessed. The results of current studies should provide some evidence for the role of dexmedetomidine in the prevention of PHBC.

REFERENCES

1. Fortier MA, Kain ZN. Treating perioperative anxiety and pain in children: a tailored and innovative approach. Paediatr Anaesth. 2015;25(1):27–35.
2. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children: predictors and outcomes. Arch Pediatr Adolesc Med. 1996; 150(12):1238–1245.
3. Pickard A, Davies P, Birnie K, Beringer R. Systematic review and meta-analysis of the effect of intraoperative alpha(2)-adrenergic agonists on postoperative behaviour in children. Br J Anaesth. 2014;112(6):982–990.
4. Kotiniemi LH, Ryhänen PT, Moilanen IK. Behavioural changes in children following day-case surgery: a 4-week follow-up of 551 children. Anaesthesia. 1997;52(10):970–976.
5. Kain ZN, Mayes LC, Wang SM, Hofstadter MB. Postoperative behavioral outcomes in children: effects of sedative premedication. Anesthesiology. 1999;90(3):758–765.
6. Keaney A, Diviney D, Harte S et al. Postoperative behavioural changes following anesthesia with sevoflurane. Pediatr Anesth. 2004;14(10):866–870.
7. Stargatt R, Davidson AJ, Huang GH, Czarnecki C, Gibson MA, Stewart SA, et al. A cohort study of the incidence and risk factors for negative behavior changes in children after general anesthesia. Paediatr Anaesth. 2006;16(8):846–859.
8. Power NM, Howard RF, Wade AM, Franck LS. Pain and behaviour changes in children following surgery. Arch Dis Child. 2012;97(10):879–884.
9. Vernon DT, Schulman JL, Foley JM. Changes in children's behavior after hospitalization: some dimensions of response and their correlates. Am J Dis Child. 1966;111(6):581–593.
10. Karling M, Stenlund H, Hagglof B. Behavioural changes after anaesthesia: validity and liability of the Post-Hospitalization Behavior Questionnaire in a Swedish paediatric population. Acta Pædiatrica. 2006;95(3):340–346.

11. Karling M, Hagglof B. Child behaviour after anaesthesia: association of socioeconomic factors and child behaviour checklist to the Post-Hospital Behaviour Questionnaire. Acta Paediatr. 2007;96(3):418–423.
12. Jenkins BN, Fortier MA, Kaplan SH, Mayes LC, Kain ZN. Development of a short version of the modified Yale Preoperative Anxiety Scale. Anesth Analg. 2014;119(3):643–650.
13. Goodman R, Scott S. Comparing the Strengths and Difficulties Questionnaire and the Child Behavior Checklist: Is small beautiful?. J Abnorm Child Psychol. 1999;27(1):17–24.
14. Fortier MA, Del Rosario AM, Rosenbaum A, Kain ZN. Beyond pain: predictors of postoperative maladaptive behavior change in children. Paediatr Anaesth. 2010;20(5):445–453.
15. Foesel T, Reisch HJ. Postoperative behavioural changes in children: comparison between halothane and sevoflurane. Paediatr Anaesth. 2001;11(6):719–723.
16. Kain ZN, Wang SM, Mayes LC, Caramico LA, Hofstadter MB.. Distress during the induction of anesthesia and postoperative behavioral outcomes. Anesth Analg. 1999;88(5):1042–1047.
17. Kotiniemi LH, Ryhänen PT. Behavioural changes and children's memories after intravenous, inhalation and rectal induction of anaesthesia. Paediatr Anaesth. 1996;6(3):201–207.
18. Aguilera IM, Patel D, Meakin GH, Masterson J. Perioperative anxiety and postoperative behavioural disturbances in children undergoing intravenous or inhalation induction of anaesthesia. Paediatr Anaesth. 2003;13(6):501–507.
19. McCluskey A, Meakin GH. Oral administration of midazolam as a premedicant for paediatric day-case anaesthesia. Anaesthesia. 1994;49(9):782–785.
20. McGraw T, Kendrick A. Oral midazolam premedication and postoperative behaviour in children. Paediatr Anaesth. 1998;8(2):117–121.
21. Olympio MA. Postanesthetic delirium: historical perspectives. J Clin Anesth. 1991;3(1):60–63.
22. Costi D. Strategies to reduce emergence agitation in children. In: Riley R, editor. Australasian Anaesthesia. Melbourne: Australian and New Zealand College of Anaesthetists, 2015. pp. 115–122.
23. Dahmani S, Delivet H, Hilly J. Emergence delirium in children: an update. Curr Opin Anaesthesiol. 2014;27(3):309–315.
24. Kanaya A, Kuratani N, Satoh D, Kurosawa S. Lower incidence of emergence agitation in children after propofol anesthesia compared with sevoflurane: a meta-analysis of randomized controlled trials. J Anesth. 2013;28(1):4–11.
25. Cravero JP, Beach M, Thyr B, Whalen K. The effect of small dose fentanyl on the emergence characteristics of pediatric patients after sevoflurane anesthesia without surgery. Anesth Analg. 2003;97(2):364–367.
26. Aouad MT, Yazbeck-Karam VG, Nasr VG, El-Khatib MF, Kanazi GE, Bleik JH. A single dose of propofol at the end of surgery for the prevention of emergence agitation in children undergoing strabismus surgery during sevoflurane anesthesia. Anesthesiology. 2007;107(5):733–738.
27. Aono J, Ueda W, Mamiya K, et al. Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. Anesthesiology. 1997;87(6):1298–1300.
28. Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg. 2004;99(6):1648–1654.
29. Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. Paediatr Anaesth. 2010;20(8):704–711.
30. Martini DR. Commentary: the diagnosis of delirium in pediatric patients. J Am Acad Child Adolesc Psychiatry. 2005;44(4):395–398.
31. Silver G, Traube C, Gerber LM, Sun X, Kearney J, Patel A, et al. Pediatric delirium and associated risk factors: a single-center prospective observational study. Pediatr Crit Care Med. 2015;16(4):303–309.
32. Traube C, Silver G, Kearney J, Patel A, Atkinson TM, Yoon MJ, et al. Cornell assessment of pediatric delirium: a valid, rapid, observational tool for screening delirium in the PICU. Crit Care Med. 2014;42:656–663.
33. Kain ZN, Caldwell-Andrews AA, Weinberg ME, Mayes LC, Wang SM, Gaal D, et al. Sevoflurane versus halothane: postoperative maladaptive behavioral changes: a randomized, controlled trial. Anesthesiology. 2005;102(4):720–726.
34. Kain Z, Caramico L, Mayes L, Genevro J, Bornstein M, Hofstadter M. Preoperative preparation programs in children: a comparative examination. Anesth Analg. 1998;87(6):1249–1255.
35. Kim H, Jung S, Yu H, Park S. Video distraction and parental presence for the management of preoperative anxiety and postoperative behavioral disturbance in children: a randomized controlled trial. Anesth Analg. 2015;121(3):778–784.
36. Lardner D, Dick B, Crawford S. The effects of parental presence in the postanesthetic care unit on children's postoperative behavior: a prospective, randomized, controlled study. Anesth Analg. 2010;110(4):1102–1108.
37. Schnabel A, Reichl SU, Poepping DM, Kranke P, Pogatzki-Zahn EM, Zahn PK. Efficacy and safety of intraoperative dexmedetomidine for acute postoperative pain in children: a meta-analysis of randomized controlled trials. Paediatr Anaesth. 2013;23(2):170–179.
38. Pasin L, Febres D, Testa V, Frati E, Borghi G, Landoni G, Zangrillo A. Dexmedetomidine vs midazolam as preanesthetic medication in children: a meta-analysis of randomized controlled trials. Paediatric Anesthesia. 2015;25(5):468–476.
39. Man Y, Guo Z, Cao J, Mi W. Efficacy of perioperative dexmedetomidine in postoperative neurocognitive function: a meta-analysis. Clin Exp Pharmacol Physiol. 2015; 42(8):837–842.
40. Pasin L, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, et al. Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically Ill patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2014;28(6):1459–1466.
41. Li B, Li Y, Tian S, Wang H, Wu H, Zhang A, Gao C. Anti-inflammatory effects of perioperative dexmedetomidine administered as an adjunct to general anesthesia: a meta-analysis. Sci Rep. 2015;21(5):123–142.
42. Wang XW, Cao JB, Lv BS, Mi WD, Wang ZQ, Zhang C, et al. Effect of perioperative dexmedetomidine on the endocrine modulators of stress response: a meta-analysis. Clin Exp Pharmacol Physiol. 2015;42(8):828–836.

Assessment

Epigenetics and anaesthesia

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Epigenetics and anaesthesia

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INTRODUCTION

The human genome consists of approximately 25,000 genes. However, not all of these genes are active at the same time. The genetic material in a cell is found mostly in the nucleus as multiple long deoxyribonucleic acid (DNA) molecules that are packaged up with proteins, such as histones, to form chromosomes. The genes within these chromosomes are the cell's "nuclear genome" that promote cell function including gene expression and protein translation. Therefore, the nucleus is said to be the control centre of the cell. Human cells contain of 23 pairs of chromosomes (22 autosomal pairs and the sex chromosomes) that is essentially an enormous fixed sequence of three billion DNA base pairs (Adenine, Thymine, Guanine, Cytosine) called the genetic code. Genetics is the science that investigates how the inherited DNA sequence itself contributes to different phenotypes or traits. In anaesthesia, important phenotypes are clinical events such as pain, postoperative cognitive dysfunction or adverse drug reactions. Perhaps the most well known, but rare, example in anaesthesia is malignant hyperthermia (MH)[1], in which inherited variants (or mutations) within the DNA sequence change the structure and function the ryanodine receptor causing MH[2].

Another important example of anaesthesia related pharmacogenetics relates to genetic variants that alter drug metabolism. The cytochrome P450 enzyme, CYP2D6, metabolises codeine, oxycodone, tramadol, and other commonly prescribed opioid analgesics. One form of variation duplicates the CYP2D6 gene increasing the level of activity of the enzyme. This so called "gain of function variant" results in high levels CYP2D6 activity and ultra-rapid drug metabolism (UM). It has been associated with increased conversion of codeine (pro-drug) to morphine. UMs are at increased risk of opioid side effects (respiratory depression, nausea and sedation) and, in the of case of codeine specifically, high (potentially fatal) levels of morphine are transferred to neonates during breastfeeding[3,4]. While this variant is uncommon (2 per cent in Caucasians) the impact of altered drug metabolism may be significant in specific clinical settings[5,6] and The Clinical Pharmacogenetics Implementation Consortium Guidelines[7,8] provides further guidance for a wide range of CYP450 variants on pharmacotherapy.

In contrast to genetics, epigenetics refers to different marks "over DNA" that impact on the function of DNA. These marks are a form of non-genetic variation that fundamentally determines whether the molecular machinery that drives gene expression (transcription: creation of messenger ribonucleic acid (RNA)) and therefore protein production (translation) can proceed. Unlike the genome, the epigenome of any cell is highly dynamic, differing between cell types, and continually changing throughout development and life as a result of environmental exposures. The epigenome of a cell is the status of specific epigenetic mechanisms known as chromatin modifications/remodelling, DNA methylation and non-coding RNA (e.g. shRNA/siRNA/miRNA) (figure 1).

These mechanisms often determine cellular development and function and may effectively regulate the response of the brain and central nervous system to anaesthesia. Specific epigenetic patterns are required in hippocampal neurons for synaptic plasticity, learning and memory formation[9], and aberrant changes can be associated with age related cognitive decline and impairment[10,11]. Distinct similarities in the cellular processes regulating hippocampal gene expression during memory formation (known as long term potentiation (LTP)) and spinal central sensitisation[12] would point towards epigenetic mechanisms as prime research targets to further understand the biological processes contributing to phenotypes like postoperative cognitive dysfunction and chronic pain. This review aims to inform the reader of recent research involving a range of epigenetic mechanisms that may contribute to further understanding important, but complex, clinical phenotypes associated with anaesthesia.

EPIGENETIC MECHANISMS

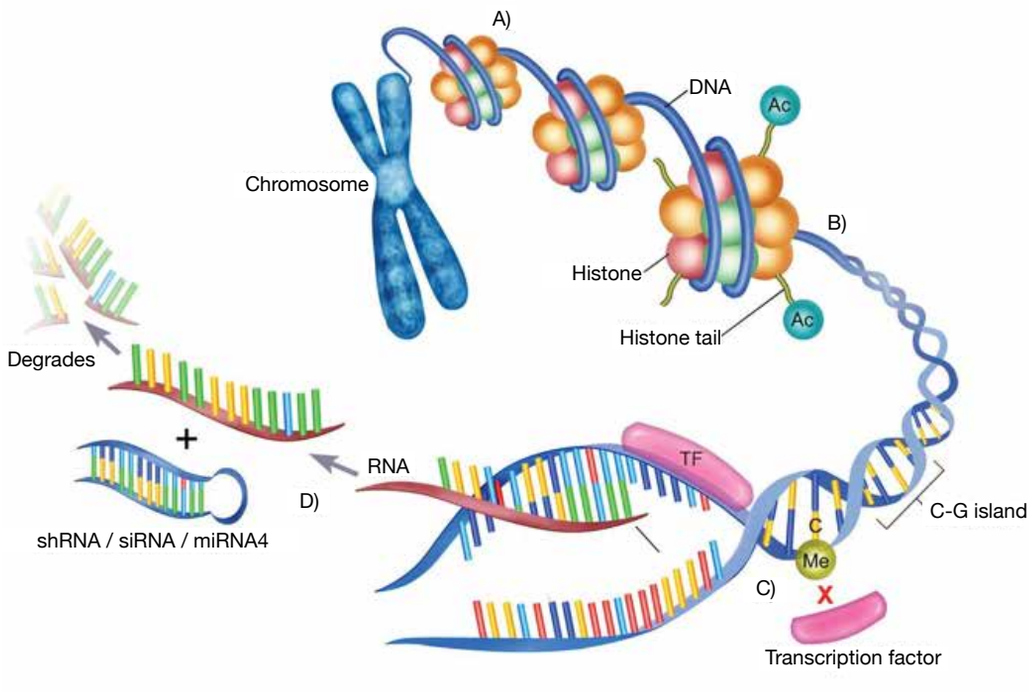
DNA exists within the chromosome as a tightly folded structure known as chromatin. Chromatin is made up of nucleosomes, packets of DNA wrapped around octamers of packing proteins called histones (figure 1-A). Histones are categorised into five major families, H1/H5, H2A, H2B, H3 and H4. The N-terminal of the histone protein forms a tail that protrudes from the nucleosome where it is accessible to chemical modification (e.g. acetylation (Ac), methylation (Me) (figure 1-B)). Histone modification remodels the three dimensional structure

of chromatin resulting in changed gene expression. Histone acetylation occurs by the addition of an acetyl group from acetyl coenzyme A and is tightly involved in the regulation of many cellular processes including transcription, gene silencing, cell differentiation, DNA replication and apoptosis. The enzymes involved in histone acetylation are called histone acetyltransferase (HAT) which play an essential role in controlling histone H3 and H4 acetylation. Histone deacetylase (HDAC) catalyse the removal of the acetyl groups from the histone lysine residues. Acetylation relaxes chromatin allowing for increased gene expression whereas deacetylation compacts chromatin silencing gene activity.

DNA methylation is another form of epigenetic modification that dramatically impacts gene expression. Mediated by DNA methyltransferase (DNMT), a methyl group can be added to cytosine residues that are adjacent to guanine residues. These are known as a CpG sites. There are regions within DNA with high concentrations of CpG, known as CpG islands (G-G Island), that are located near the start of genes (figure 1-C). Methylation physically interferes with gene expression by preventing the binding of transcription factors (TF) that are required to activate transcription. Methylated DNA also serves as a docking site for methy-CpG-binding domain (MBD) proteins that may bind methylated CpGs in promoter areas near genes, acting either as an attractant for other co-repressor proteins or transcription activator proteins.

Recent studies have uncovered a further complexity to the classical epigenetic mechanisms as described above. While the vast majority of the human genome is transcribed, only ~2 per cent of these transcripts are translated into protein. The remaining 98 per cent of transcripts, termed non-coding RNA (ncRNA), do not code for proteins and were thought of as experimental artefacts. However, more recently it has come to light that these ncRNAs can be functional and play a critical regulatory role. Further, ncRNA consists of small (10-200 nucleotide) lengths of microRNA (miRNA) and more complex molecules of long ncRNA (lnRNA). Gene expression can be regulated post transcriptionally by binding directly to mRNA, inducing degradation and silencing gene expression (figure1-D)[13,15].

Figure 1. Epigenetic mechanisms



A) The nucleosome: DNA wrapped around an octamer of histone proteins.

B) Histone/chromatin modification by acetylation of histone tails resulting in relaxation of chromatin and increased gene expression.

C) DNA methylation of cytosine residues in the promoter region of a gene preventing transcription factor binding suppressing gene expression.

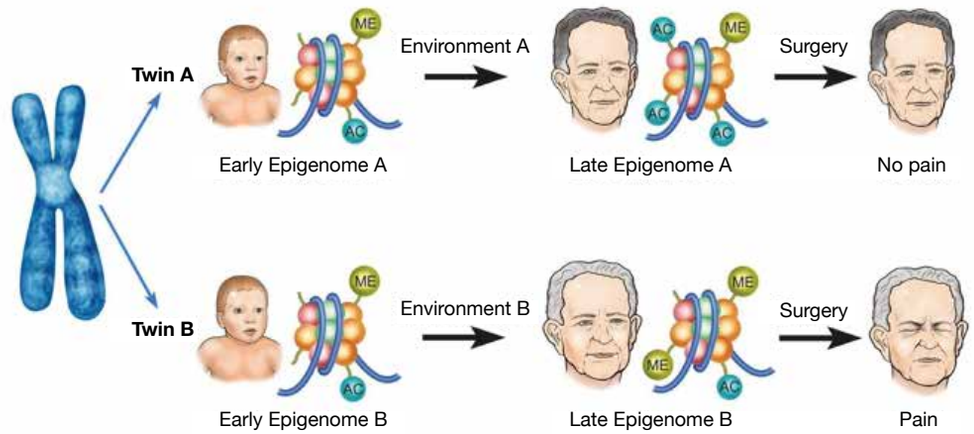
D) Short non-coding RNAs such as short hairpin (shRNA), silencing (siRNA) and microRNA (miRNA) bind to mRNA causing degradation[16].

(Source: US government)

PAIN AND ANALGESIA

Pain sensitivity is an extremely complex phenotype with contributory underlying biological, psychosocial and emotional factors. Indeed accurately quantifying pain sensitivity[17] is critical to understanding the significance of genetic, environmental and other distinct factors that affect the efficacy of analgesic therapy or the process of transition from acute to chronic pain. Analyses of discordant identical twins for different pain phenotypes has highlighted that genetic contributions alone are at most modest[18,19]. This fundamentally implies that, in most cases, chronic pain is not related to the underlying DNA sequence, and is therefore a dynamic process at the genomic level, and will be occurring in different tissues. This reflects the inherent plasticity of epigenetic mechanisms to regulate and modify gene expression, in a tissue-specific manner, in response to specific environmental stressors effectively resulting in an acquired phenotype (figure 2).

Figure 2. Epigenome and chronic pain



Twin A and B have an identical DNA sequence and similar patterns of histone methylation (ME) and acetylation (AC) at birth. Exposure to different environmental factors (social interaction, medication, trauma) throughout development and life drives dynamic changes the pattern of histone acetylation and methylation, remodelling chromatin structure and the transcriptional response to surgery. For twin B the response results in increased risk of central sensitisation and pain[16].

(Source: US government)

One experimental method to investigate the association between the status of the epigenome and chronic pain is to conduct an epigenome wide association study (EWAS). By utilising powerful DNA sequencing technology (Next Generation Sequencing (NGS)), it is possible to examine the status of chromatin modifications or DNA methylation across the entire genome in a specific cell type (usually whole blood), at a specific point in time, in specific cohorts of affected individuals. Bell and colleagues[20] conducted an EWAS of DNA methylation for heat pain sensitivity in a cohort of 50 discordant identical twins and 50 unrelated individuals. This identified specific areas within the epigenome termed pain Differential Methylation Regions (pain DMRs) that were associated with heat pain sensitivity. They discovered a strong signal for increased CpG island methylation near the promoter region of the ion channel gene TRPA1 in individuals with lower pain thresholds. They also observed nominally increased levels of TRPA1 gene expression in the skin of individuals with high pain thresholds indicating a link between TRPA1 promoter methylation, suppressed gene expression and thermal sensitivity.

EWAS are an extremely powerful method to investigate epigenetic contributions to complex traits and may highlight either important links in known pain genes[21] and pathways or provide for the discovery of novel biomarkers of pain sensitivity. While TRPA1 is not a known mammalian thermosensor, it is possible that its activity is linked to other ion channel pain genes that are differentially expressed in skin (e.g. TRPV1)[22]. Epigenetic mechanisms are increasingly recognised as important therapeutic targets to modify pain responses. Research now examines the impact of reversing epigenetic changes on known neurobiological processes that underlie peripheral and central sensitisation and chronic pain[23].

Animal-based evidence in rats and mice, indicate that inflammatory pain may be related to the level of activity of specific HDAC enzymes in the spinal dorsal horn and brain, and treatment with HDAC inhibitors (e.g. Suberoylanilide hydroxamic acid, SAHA) can reverse the effect. In a model of Complete Freunds Adjuvent (CFA) induced peripheral inflammatory pain, intrathecal SAHA prevented spinal HDAC changes and attenuated thermal hyperalgesia[24]. Zhang and colleagues then demonstrated that CFA induced inflammatory pain was related to the level of H3 acetylation in the promoter region of GAD2 in critical central pain modulating neurons in the

nucleus raphe magnus. They were able show that increasing H3 acetylation with SAHA restored GAD2 expression and relieved sensitised pain behaviour[25]. Increased histone acetylation is also involved in the development of opioid tolerance and opioid induced hyperalgesia (OIH). In a model of morphine OIH, it appears that the effect is determined by the balance of HAT versus HDAC activity in mice. Co-administration of a HAT inhibitor (Curcumin) reduces the effect whereas SAHA increases OIH[26]. Furthermore it appears that OIH is related to changes in H3 acetylation in the promoter regions of the genes for Brain-derived neurotrophic factor (BDNF) and Prodynorphin (PYDN)[27]. It now appears that the same mechanisms are associated with enhanced postoperative pain and analgesic tolerance (in mice), and this can be reduced by HAT inhibition (anacardic acid) or drugs that block the receptors of BDNF (ANA-12) and PYDN (nor-binaltorphimine)[28].

MEMORY AND COGNITION

Early childhood exposure to anaesthesia is associated with transient postoperative cognitive impairment[29] and, while much debate surrounds the issue, may increase the risk of long term neurocognitive dysfunction[30,31-34]. Animal studies have highlighted the developmental neurotoxicity and cognitive deficits resulting from exposure to anaesthetic agents acting at γ-aminobutyric acid type A and N-methyl-D-aspartate glutamate receptors[35]. There is now evidence to suggest that epigenetically mediated changes in the balance of the expression of BDNF may underlie this process.

The BDNF gene (BDNF) is a memory and neuronal plasticity related gene with increased expression being associated with enhanced memory formation[10]. BDNF plays a critical role in stimulating developmental pathways involved in synapse formation and brain maturation. Isoflurane anaesthesia, administered at the time of peak brain development (e.g. Rat postnatal day 7 (P7)) induces neuroapoptosis via a BDNF modulated apoptotic cascade[36]. Sen and colleagues have recently demonstrated that isoflurane (1.4 per cent for two hours) induces transcriptional inactivation of cyclic AMP response element-binding (CREB) by increasing the activity of HDAC4 in the rat P7 brain, resulting in reduced BDNF expression and loss of dendritic growth[37]. Wu and colleagues[38] investigated specific epigenetic modifications that alter hippocampal BDNF signalling following isoflurane (1.5 per cent for six hours) anaesthesia, again at rat P7. They demonstrated that isoflurane increased the interaction between specific transcriptional repressors (MeCP2, HDAC2), condensed chromatin structure and reduced hippocampal BDNF expression. Cognitive deficiency was associated with significantly reduced histone (H3) acetylation and methylation in the promoter region of BDNF.

Decreased BDNF activity may therefore underlie cognitive dysfunction associated with anaesthesia. Anaesthesia induced changes in HDAC activity mediate chromatin remodelling silencing BDNF. This makes inhibitors of specific HDAC enzymes attractive targets for future translational research. However strategies to protect the developing brain by preventing epigenetically mediated changes need not necessarily rely on new pharmacotherapy. Wu and colleagues further examined the therapeutic potential of exposing rats to highly social (6 pups/cage) and novel (toys and running wheels) environments, termed environmental enrichment (EE). Impressively they demonstrated that EE mitigated the epigenetic changes and corrected the cognitive impairment induced by neonatal anaesthesia.

Neurodevelopmental interventions in human infants to optimise the sensory experience and reduce stress, is a commonly practiced clinical application of EE. Infant massage is widely used in neonatal intensive care units to provide a higher level of tactile stimulation to counter the stress of environmental lights and noise. Indeed, there is evidence that massage in pre-term infants approaching term favours maturation of EEG activity that is consistent with increased synaptic density and connectivity[39].

ANAESTHETIC PRECONDITIONING

Volatile anaesthetic agents are known to protect the myocardium from reversible and irreversible ischaemic injury. This was first described when halothane was shown to attenuate ST-segment elevation after coronary occlusion in dogs[40]. The concept of preconditioning arose with the observation that pre-administration of isoflurane before myocardial ischaemia reduced infarct size in rabbits[41]. There has since been a large body of research into the potential benefits of anaesthetic preconditioning in animals and humans, particularly in the setting of coronary artery bypass graft (CABG) surgery. Numerous clinical trials and meta-analyses indicate that volatile anaesthetics most likely reduce the severity of myocardial necrosis associated with CABG when compared with intravenous (propofol) anaesthesia[42-44].

The mechanism for anaesthesia induced preconditioning is an area of continued investigation. Initial studies highlighted the activation of adenosine A1 receptors and the opening of mitochondrial adenosine triphosphate sensitive potassium channels (K_{ATP}). This process triggers multiple signal transduction pathways involving protein kinase C (PKC), mitogen-activated protein kinases (MAPK), extracellular-regulated kinase (ERK) and phosphatidyl-3-kinase/AKT. Ultimately there is increased expression of preconditioning mediators such as inducible nitric oxide synthase (iNOS) and heat shock protein resulting in decreased reactive oxygen species and increasing cellular viability[45-48].

However, more recent investigations suggest that microRNA plays a critical regulatory role in this pathway. An analysis of cardiac myocytes during myocardial infarction in rats revealed one particular microRNA (miR-21) was significantly down regulated in infarcted areas and up-regulated in the border zone areas[49]. It was then demonstrated that ischaemic preconditioning specifically inhibited down regulation of miR-21 suggesting its involvement in the preconditioning pathway. Investigators confirmed the protective effect of miR-21, by demonstrating reduced cell apoptosis in the border zone, after treatment with an adenovirus expressing miR-2149. Olsen and colleagues then investigated the effect of isoflurane on miR-21 mediated cardiac myocyte protection in rats and observed that, isoflurane induced up-regulation of miR-21 protected cardiac myocytes from oxidative stress (using Peroxide in vitro) and ischaemia reperfusion injury (coronary artery occlusion in vivo)[50]. To further characterise the impact of loss of miR-21 on anaesthetic preconditioning, Qiao and colleagues utilised a miR-21 knockout mouse model (genetically engineered mice with no miR-21 expression). They found that the absence of miR-21 ablated the ability of isoflurane to protect the heart from ischaemia reperfusion with the activity of known downstream mediators (AKT/NOS) being specifically affected[51].

This work, although preliminary, is an example of a new and enticing area of investigation into the impact of anaesthetic induced changes in miRNA on organ function and dysfunction. There is increasing understanding of the central role miRNA has in essentially every aspect of cellular and organ function in health and disease that may interact with anaesthesia[52]. Therefore, the clinical importance of therapeutically targeting miRNA, either by inhibition or as mimics, is an emerging concept that future studies will undoubtedly focus on.

CONCLUSION

Epigenetic mechanisms fundamentally determine cellular activity and the response of cells to changed environmental conditions. Much of the work described in this review is preliminary and pre-clinical with the primary aim of informing the reader of the methods being utilised to discover and understand how different epigenetic mechanism may interact with anaesthesia to affect outcomes. Importantly, clinical phenotypes related to anaesthesia are extremely complex, difficult to define and represent a dynamic interaction between the environment and thousands of cellular processes and pathways. Therefore, understanding the contribution of epigenetic mechanisms to acquired phenotypes offers an opportunity to further understand the biological response to anaesthesia and surgery, always with the hope of creating new interventions to improve outcomes.

REFERENCES

1. Denborough MA. Malignant hyperthermia. 1962. Anesthesiology. 2008;108(10):156-157.
2. Galli L, Orrico A, Lorenzini S, Censini S, Censini S, Falciani M, et al. Frequency and localization of mutations in the 106 exons of the RYR1 gene in 50 individuals with malignant hyperthermia. Hum Mutat. 2006;27(8):830.
3. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med. 2004;351(27):2827-2831.
4. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet. 2006;368(9536):704.
5. Landau R, Smiley R. Pharmacogenetics in obstetric anesthesia. Best Pract Res Clin Anaesthesiol. 2017;31(1):23-34.
6. Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: a prospective pilot randomized controlled trial. PLoS ONE. 2017;12(2):1-16.
7. Crews KR, Gaedigk A, Dunnenberger HM, Klein TE, Shen DD, Callaghan JT, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) Genotype. Clin Pharmacol Ther. 2011;91(2):321-326.
8. Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376-382.
9. Day JJ, Sweatt JD. Epigenetic mechanisms in cognition. Neuron. 2011;70(5):813-829.
10. Day JJ, Sweatt JD. Epigenetic treatments for cognitive impairments. Neuropsychopharmacology. 2012;37(1):247-260.
11. Kosik KS, Rapp PR, Raz N, Small SA, Sweatt JD, Tsai L-H. Mechanisms of age-related cognitive change and targets for intervention: epigenetics. J Gerontol A Biol Sci Med Sci. 2012;67(7):741-746.
12. Ji R-R, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci. 2003;26(12):696-705.
13. Buchheit T, Van de Ven T, Shaw A. Epigenetics and the transition from acute to chronic pain. Pain Med. 2012;13(11):1474-1490.
14. Lutz BM, Bekker A, Tao Y-X. Noncoding RNAs: new players in chronic pain. Anesthesiology. 2014;121(2):409-417.
15. Doehring A, Geisslinger G, Lötsch J. Epigenetics in pain and analgesia: an imminent research field. Eur J Pain. 2011;15(1):11-16.
16. Bain CR, Shaw AD. Genetics and epigenetics in perioperative medicine. Curr Opin Critical Care. 2012;18(5):548-554.
17. Edwards RR, Dworkin RH, Turk DC, Angst MS, Dionne R, Freeman R, et al. Patient phenotyping in clinical trials of chronic pain treatments. Pain. 2016;157(9):1851-1871.
18. Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. Pain. 2008;136(1-2):21-29.

19. Norbury TA, MacGregor AJ, Urwin J, Spector TD, McMahon SB. Heritability of responses to painful stimuli in women: a classical twin study. Brain. 2007;130(11):3041-3049.
20. Bell JT, Loomis AK, Butcher LM, Gao F, Zhang B, Hyde CL, et al. Differential methylation of the TRPA1 promoter in pain sensitivity. Nat Commun. 2014;5:2978.
21. Foulkes T, Wood JN. Pain Genes. PLoS Genet. 2008;4(7):e1000086.
22. Fernandes ES, Fernandes MA, Keeble JE. The functions of TRPA1 and TRPV1: moving away from sensory nerves. Br J Pharmacol. 2012;166(2):510-521.
23. Denk F, McMahon SB. Chronic pain: emerging evidence for the involvement of epigenetics. Neuron. 2012;73(3):435-444.
24. Bai G, Wei D, Zou S, Ren K, Dubner R. Inhibition of class II histone deacetylases in the spinal cord attenuates inflammatory hyperalgesia. Mol Pain. 2010;6:51.
25. Zhang Z, Cai Y-Q, Zou F, Bie B, Pan ZZ. Epigenetic suppression of GAD65 expression mediates persistent pain. Nat Med. 2011;17(11):1448-1455.
26. Liang D-Y, Li X, Clark JD. Epigenetic regulation of opioid-induced hyperalgesia, dependence, and tolerance in mice. J Pain. 2013;14(1):36-47.
27. Liang D-Y, Sun Y, Shi X-Y, Sahbaie P, Clark JD. Epigenetic regulation of spinal cord gene expression controls opioid-induced hyperalgesia. Mol Pain. 2014;10(1):59.
28. Sahbaie P, Liang D-Y, Shi X-Y, Sun Y, Clark JD. Epigenetic regulation of spinal cord gene expression contributes to enhanced postoperative pain and analgesic tolerance subsequent to continuous opioid exposure. Mol Pain. 2016;12(0).
29. Millar K, Bowman AW, Burns D, McLaughlin P, Moores T, Morton NS, et al. Children's cognitive recovery after day-case general anesthesia: a randomized trial of propofol or isoflurane for dental procedures. Paediatr Anaesth. 2014;24(2): 201-207.
30. Ing CH, DiMaggio CJ, Whitehouse AJO, Hegarty MK, Sun M, Ungern-Sternberg von BS, et al. Neurodevelopmental outcomes after initial childhood anesthetic exposure between ages 3 and 10 years. J Neurosurg Anesthesiol. 2014;26(4):377-386.
31. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology. 2009;110(4):796-804.
32. Loepke AW, Soriano SG. An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. Anesth Analg. 2008;106(6):1681-1707.
33. Sanders RD, Hassell J, Davidson AJ, Robertson NJ, Ma D. Impact of anaesthetics and surgery on neurodevelopment: an update. Br J Anaesth. 2013;110(suppl 1):i53-i72.
34. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet. 2016;387(10015):239-250.
35. Mellon RD, Simone AF, Rappaport BA. Use of anesthetic agents in neonates and young children. Anesth Analg. 2007;104(3):509-520.
36. Lu LX, Yon J-H, Carter LB, Jevtovic-Todorovic V. General anesthesia activates BDNF-dependent neuroapoptosis in the developing rat brain. Apoptosis. 2006;11(9):1603-1615.
37. Sen T, Sen N. Isoflurane-induced inactivation of CREB through histone deacetylase 4 is responsible for cognitive impairment in developing brain. Neurobiol Dis. 2016;96:12-21.
38. Wu J, Bie B, Naguib M. Epigenetic manipulation of brain-derived neurotrophic factor improves memory deficiency induced by neonatal anesthesia in rats. Anesthesiology. 2016;124(3):624-640.
39. Cioni G, D'Acunto G, Guzzetta A. Perinatal brain damage in children: neuroplasticity, early intervention, and molecular mechanisms of recovery. Prog Brain Res. 2011;189:139-154.
40. Bland J, Lowenstein E. Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology. 1976;45(3):287-293.
41. Cason BA, Gamperl AK, Slocum RE, Hickey RF. Anesthetic-induced preconditioning: previous administration of isoflurane decreases myocardial infarct size in rabbits. Anesthesiology. 1997;87(5):1182-1190.
42. De Hert SG, Broecke ten PW, Mertens E, Van Sommeren EW, De Blier IG, Stockman BA, et al. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. Anesthesiology. 2002;97(1):42-49.
43. Symons JA, Myles PS. Myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery: a meta-analysis. Br J Anaesth. 2006;97(2):127-136.
44. Pagel PS. Myocardial protection by volatile anesthetics in patients undergoing cardiac surgery: a critical review of the laboratory and clinical evidence. J Cardiothor Vasc Anesth. 2013;27(5):972-982.
45. Weber NC, Schlack W. Inhalational anaesthetics and cardioprotection. Handb Exp Pharmacol. 2008;(182): 187-207.
46. Raphael J, Rivo J, Gozal Y. Isoflurane-induced myocardial preconditioning is dependent on phosphatidylinositol-3-kinase/ Akt signalling. Br J Anaesth. 2005;95(6):756-763.
47. Weber NC, Schlack W, Preckel B. Molecular biology in cardiovascular anaesthesia. Curr Opin Anaesthesiol. 2008;21(1): 71-77.
48. Amour J, Brzezinska AK, Weihrauch D, Billstrom AR, Zielonka J, Krolikowski JG, et al. Role of heat shock protein 90 and endothelial nitric oxide synthase during early anesthetic and ischemic preconditioning. Anesthesiology. 2009;110(2): 317-325.
49. Dong S, Cheng Y, Yang J, Li J, Liu X, Wang X, et al. MicroRNA expression signature and the role of microRNA-21 in the early phase of acute myocardial infarction. J Biol Chem. 2009;284(43):29514-29525.
50. Olson JM, Yan Y, Bai X, Ge Z-D, Liang M, Kriegel AJ, et al. Up-regulation of microRNA-21 mediates isoflurane-induced protection of cardiomyocytes. Anesthesiology. 2015;122(4):795-805.

51. Qiao S, Olson JM, Paterson M, Yan Y, Zaja I, Liu Y, et al. MicroRNA-21 mediates isoflurane-induced cardioprotection against ischemia-reperfusion injury via Akt/nitric oxide synthase/mitochondrial permeability transition pore pathway. Anesthesiology. 2015 7:1.
52. Huang Y, Shen XJ, Zou Q, Wang SP, Tang SM, Zhang GZ. Biological functions of microRNAs: a review. J Physiol Biochem. 2011;67(1):129-139.

Education

Preparing candidates for the ANZCA primary examination vivas

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INTRODUCTION

The ANZCA primary examination viva ("viva voce", an oral examination) is a constant source of anxiety, both to the candidates who are desperate for practice vivas prior to their examination, and to consultants and more senior registrars who are asked to provide these practice vivas.

Giving practice viva examinations offers several rewards to those who prepare them and undertake them; firstly giving Fellows the opportunity to refresh and update their knowledge of the physiology and pharmacology of their every day practice, secondly attaining continuing professional development points in the knowledge and skills category, and if the information gained is then applied to clinical protocols, potentially in the practice evaluation category, and thirdly the appreciation of junior colleagues who are sitting the examination, who hopefully on passing will follow this example and provide practice vivas to the next cohort of trainees who will follow them to the examination.

For many primary candidates, the examination will be their first experience of a viva examination, as opposed to the more structured OSCE (objective structured clinical examination) examinations they have previously experienced.

Being exposed to practice vivas allows candidates to:

- Experience a simulated examination situation.
- Perform under pressure.
- Determine if they are able to verbally explain their understanding and the clinical relevance of the basic sciences.
- Allow reflection on the application of strategies that allow for improved performance[1].

Fellows' memories of the primary examination are not always pleasant, which may cause some reluctance to providing practice vivas. However, the examination continues to evolve, and it is hoped that this chapter will provide appropriate guidelines to allow even the most reticent to engage in the process.

THE PURPOSE OF VIVA EXAMINATIONS

Oral examinations or vivas have been a traditional part of undergraduate and postgraduate medical assessment. Compared to written forms of assessment, they are not easy to organise, relatively expensive to facilitate, and in the past may have been relatively unstructured leading to what may have been well-deserved criticism of examiners and this form of assessment. As a result they have been well reviewed, processes improved, and been demonstrated to allow examiners to assess areas that are not particularly well assessed in other forms of assessment. In particular, vivas:

- Mirror the form of communication that dominates professional practice.
- Test the limits of a candidate's knowledge and understanding, applying especially to the candidate whose weaknesses may not otherwise be clearly exposed.
- Are thought to be effective in assessing the cognitive processes which constitute professional thinking[2].

Having stood the test of time, vivas are likely to remain for the foreseeable future as an assessment technique.

THE ANZCA PRIMARY VIVA

ANZCA defines the primary examination as a test of knowledge and understanding of the scientific foundations of clinical anaesthesia, and advises that candidates are expected to demonstrate an understanding of the subject matter and show their ability to integrate the relevant information so that it is applicable to the practice of clinical anaesthesia. The scientific foundations are divided into applied physiology, pharmacology, anatomy, measurement, equipment, and quality and safety[3]. It is not necessary to incorporate all the foundations into

any single viva, but there will be many occasions when an integrated approach will result in a more searching viva that enables the candidate to show how various ideas can be brought together.

Within the current examination format, each viva topic (the opening question and follow up questions) lasts for approximately five minutes. Examiners take great care in viva design such that their question list should be able to be completed within the allocated five minute time slot. When undertaking viva practice however, strict adherence to such a time frame is generally unnecessary, except if more formal mock vivas are to be undertaken.

Each group of questions should where possible allow a candidate to demonstrate knowledge of a basic science concept, an understanding of that concept, and how this relates to clinical practice.

TYPES OF VIVAS

Although no two vivas are exactly the same in their structure, there tend to be three general viva structures that progress in different ways. If you can decide at the outset on your viva structure, you can tailor the questions accordingly. The actual examination vivas tend to be a balance of these three different viva structures.

The first viva structure may be described as the "oil well" type viva. This has a narrow opening but it drills deep! This style of viva is used to examine a single topic, but in depth. It should be kept for examination of key concepts where a high level of understanding is expected, such as volatile agent pharmacokinetics or neuromuscular blockade monitoring. Some examples of this style of viva are shown in figure 1.

Figure 1. Examples of "oil well" type vivas

EXAMPLE A	EXAMPLE B
• Draw a wash-in curve for sevoflurane. • Why is the curve shaped as it is? • Superimpose desflurane on this graph. • Why is it drawn above sevoflurane? • How is solubility measured? • Why do less soluble agents reach equilibrium faster?	• What is the formula for nitrous oxide? • How is it manufactured? • Why is that important to us? • How is it supplied? • Why do we use it in anaesthesia? • There are concerns about toxicity, can you tell me about those?

The second viva structure is the "funnel" type viva – a wide opening but a narrow spout. These vivas commence with a broad area concept. It may be a brief list (be wary of lists that are too long) or a definition. From there questions are gradually refined down to a specific end point that can be examined in more depth. One of the great advantages of this style of viva is that you can have just one "mouth" to a funnel, but prepare many "spouts". Thus by branching off at an early stage in the viva, a single introductory question can lead to multiple end points. Examples of this style of viva are shown in figure 2.

Figure 2. Examples of "funnel" type vivas

EXAMPLE A	EXAMPLE B
Can you give me some examples of beta adrenergic blocking drugs? • How can we classify them? • Why is cardioselectivity important? • Is the distinction between cardioselective and non-cardioselective agents absolute? From here, a number of directions can be taken such as: a. Why does esmolol have a short half life? • What other cholinesterases do you know of apart from red cell esterase? • The metabolism of remifentanil by non specific esterases contributes to its favourable "context sensitive half life". What does that mean?	Write down the blood gases for both an arterial and mixed venous blood gas breathing room air. From here, a number of directions can be taken such as: a. How would these numbers change if the patient had an FiO_2 of 1.0? • Using the oxygen content equation to assist you, can you explain why there is a large difference in the arterial oxygen but not the mixed venous? • What are the factors that determine mixed venous oxygen? • What therapeutic manouevres can you use to increase mixed venous oxygenation?
or b. What are the clinical indications for using selective beta blockers? • In myocardial ischaemia, why is it useful to lower heart rate? • What are the other determinants of myocardial oxygen consumption?	or b. How would these numbers change in a pregnant woman at term? • What are the major cardiovascular and respiratory changes that contribute to this? • What underlies these changes? • How do these affect oxygen delivery to the foetus?

The third viva structure is the "paint the wall" type viva – only one coat, but you cover a lot of area. This is a common viva style, and very much suited to the modern concept of examining knowledge in an integrated fashion. You are able to cover a large amount of material, sometimes half a dozen or more learning objectives, but because of time constraints, in a somewhat more superficial fashion that the preceding two approaches. You can see from the examples in figure 3 that in just a few questions quite complex interrelationships between physiology, pharmacology, equipment and anatomy may be explored.

Figure 3. Examples of "paint the wall" type vivas

EXAMPLE A	EXAMPLE B
What is the "normal" pH of arterial blood? (Shown an ABG of metabolic acidosis with an increased anion gap.) • Here is a blood gas. Can you point out any abnormalities? • What conditions might cause these abnormalities? • What is meant by anion gap? • This is due to diabetic ketoacidosis. How does the kidney normally handle glucose? • How do we assess renal function in a patient? • Can you draw a graph relating GFR and serum creatinine?	You are in the process of undertaking a spinal anaesthetic. At which level will you insert the needle and why? • As you insert the needle what structures will you pass through? • You successfully enter the intrathecal space, and CSF drips from the needle. Why does that happen? • What is the definition of "pressure"? • What is normal CSF pressure? • Why is it pressurised? • What are the determinants of CSF pressure?

WRITING A VIVA

The basic key to those seemingly effortless vivas that you see performed by experienced examiners is segue. The dictionary definition of this term is either to proceed without pause from one musical number or theme to another; or to make a transition without interruption from one activity, topic, scene, or part to another. Your viva should have a series of questions where one builds on the information gained earlier. You know you have a good viva when you can see the candidate using knowledge from a previous question to answer the next question. Your viva should not be just a series of questions blasted out machine gun style!

Choosing a topic

It is a common misconception that primary examiners know everything about every learning outcome. Primary examiners are everyday practising anaesthetists who all have areas of expertise in their clinical practice in which they have extra knowledge and feel comfortable about examining, and it is from these areas that they tend to write their viva questions. Those who take practice vivas are no different. One strategy is to choose a topic with which you are extremely familiar or interested (e.g. an anaesthetist who specialises in regional techniques may wish to discuss local anaesthetic toxicity, nerve blockade, or the effects of a sympathetic block), or a topic in which you wish to revise or update your knowledge (e.g. the interactions between the newer anti-depressant medications and anti-emetics and analgesics, or the anaesthetic interactions of herbal medications and illicit drugs). Most importantly, there should be some clinical relevance to the basic sciences examined.

ANZCA publishes a list of all the learning outcomes that are assessed in the primary examination on the College website, http://www.anzca.edu.au/documents/curriculum-appendix-two.pdf, and this is regularly updated[4]. In addition to the published learning outcomes, ANZCA also publishes a reading list, and indicates that the majority of information is found in the texts on this list[5]. These texts are freely available online to all College Fellows and trainees. It is critical that when writing vivas, the first port of call should be the ANZCA learning outcomes. This is especially so if a viva is designed to assess anatomy, or equipment topics. It is somewhat disheartening to write a “brilliant” viva on upper limb blocks, only to find that unfortunately this topic is not part of the primary exam syllabus!

No subject is too simple to be examined in a viva. Examiners’ reports continue to mention that candidates failed to perform well on some of the most basic and simple concepts in physiology and pharmacology. A viva examining simple concepts is often the most discerning viva. Do not think that all concepts examined need to be difficult.

Opening question

The opening question should clearly identify the topic, and should be one that should enable the candidate to start gaining marks. Examples of these are:

- Define hypoxaemia, and classify the physiological causes.
- List the various classes of drugs that may be used in the treatment of hypertension.
- Draw and label a lead II ECG for one cardiac cycle.

It is important that the opening question be unambiguous – it must have a clear correct answer, and allow for a quick transition to the next question. If you wish to discuss the drugs that may be used in the treatment of intraoperative hypertension rather than those used in the management of chronic hypertension, then this should be clearly stated. The opening question generally assesses knowledge rather than understanding or clinical relevance. A “list”, “classify” or “draw” opening question often puts both the novice candidate and the novice practice examiner at ease.

Follow up questions

The concept of segue should apply to all follow up questions. It is important that in the eyes and ears of the person receiving the viva, there should be some logical connection and transition between the opening question and the follow up questions.

Some general guidelines for follow up questions are:

- Questions should move from simple to more complex, so that candidates are given the maximal opportunity to score marks before they are asked extremely difficult concepts (and which may not need be known for a pass) which may throw them.
- In the case of physiology-related questions, questions should commence with normal physiology before moving on to altered physiology or pathophysiology (for example normal respiratory mechanics should be considered before moving on to one-lung ventilation). This does not apply to basic concepts such as commenting on an arterial blood gas.
- Placing questions in a clinical concept may assist in gaining the appropriate answers (for example, using Virchow’s triad, can you explain the principles of how we prevent venothromboembolism under anaesthesia?).
- In discussing monitoring or equipment it may be worth giving candidates a choice (for example, in discussing processed EEG monitoring, ask the candidate which form of monitoring they are most familiar with and wish to discuss. The major principles can be discussed with any of the proprietary systems available).

DELIVERING THE VIVA

Trainees often fail to understand that it is often as stressful, if not more stressful, to deliver a viva than it is to have to receive one! A viva can go in many directions, be on a topic that a trainee may have limited knowledge, be quickly exhausted by an exceptional trainee, and at the same time there is an expectation that feedback will be given after the viva.

Survival suggestions include having:

- Clear unambiguous questions.
- Rescue questions – questions that revert back to the basic concepts of the viva, to enable the poorly performing candidate the chance to re-engage with the subject matter.
- More difficult questions for the candidate who is excelling.
- Pre-prepared material. For example, it takes time to draw and label an oxygen-haemoglobin dissociation curve. Depending on the area you which to examine it might be more appropriate to give the candidate a pre-drawn curve and ask them to either label the axes and/or point out salient points on the graph.
- Examiners are not out to trick candidates in the vivas. As a general rule of thumb, an examiner will not ask “Are you sure?” with respect to a correct answer given. If a candidate provides an answer about which you may have your doubts as to whether it was a guess or not, it is much more appropriate to ask the candidate the reasoning that supports this answer. “Are you sure?” in this situation may only lead a nervous candidate to change their answer to the complete opposite, and then be thrown for the following questions. If the candidate has said something that is completely unreasonable, or you suspect it has been a slip, then it may be appropriate to ask “Are you sure?”.

FEEDBACK

Trainees will nearly always request feedback after a practice viva. In the actual examination, the examiners have the luxury of examining in pairs, allowing a second person to assist in determining the standard that been achieved by the candidate. It is very difficult for the novice practice examiner to be able to ask questions, listen to the answers, direct the flow of the viva, and mark the candidate simultaneously. When starting off it is probably best to have a mark sheet for your viva, where you can give marks for each question within the viva. This is useful as you can clearly state to the candidate what parts were done well, or not so well.

Trainees will continue to gain knowledge as they prepare for the examination. Feedback regarding technique may be just as welcomed and as valuable as the actual standard achieved by the trainee as they continue to prepare for the examination.

The information in figure 4 may serve as a useful guide to the areas in which feedback may be given.

Figure 4. Proforma for providing viva feedback

PRACTICE VIVA FEEDBACK	
KNOWLEDGE	
Basic sciences	Adequate / Inadequate
Understanding	Adequate / Inadequate
Clinical application	Adequate / Inadequate
Overall Impression	Fail / Pass / Good Pass
TECHNIQUE	
Engagement with examiner (e.g. eye contact, interaction, posture)	Adequate / Inadequate
Responses (e.g. answers questions appropriately, avoids, does not answer the questions asked)	Adequate / Inadequate
Avoiding distracting habits (e.g. fidgeting, covering mouth when speaking)	Adequate / Inadequate
Communication (e.g. speech delivery, clarity of thought)	Adequate / Inadequate
Written (e.g. drawing and labelling of graphs)	Adequate / Inadequate

CONCLUSION

No means of assessment is ever perfect, but ANZCA remains committed to ensuring that its assessment processes are fair. Assisting trainees with practice vivas may enable them to perform in the actual viva to their highest potential, allowing those who have the appropriate knowledge and who should pass the examination, to do so. As the old adage goes, practice makes perfect, for both the practice examiners and the candidates.

Start off with a bank of six or seven vivas and keep working on them to improve their structure. After you have given the same viva a few times, you will soon work out its strength and weaknesses and can make adjustments accordingly. If things do not go well initially, persevere – every examiner has struggled with their vivas – and as you become more comfortable in delivering your vivas, seeing improvement in both candidates' performances and yours may be very rewarding!

REFERENCES

1. Selzer R, Ellen S, Rotstein L, Roseby R. Twelve tips for performing well in vivas. Med Teach. 2014;37(5):428–432.
2. Memon M, Joughin G, Memon B. Oral assessment and postgraduate medical examinations: establishing conditions for validity, reliability and fairness. Adv Health Sci Educ. 2010;15(2):277–289.
3. Australian and New Zealand College of Anaesthetists. Primary examination. n.d. From: http://www.anzca.edu.au/training/examinations/primary-exam. Accessed 29 August 2017.
4. Australian and New Zealand College of Anaesthetists. Learning outcomes mapped to the primary examination. 2017. From: http://www.anzca.edu.au/documents/curriculum-appendix-two.pdf. Accessed 29 August 2017.
5. Australian and New Zealand College of Anaesthetists. Library guides primary examination: overview. n.d. From: http://libguides.anzca.edu.au/primary. Accessed 29 August 2017.

Trainee monitoring – Tips to setting up a program and issues encountered along the way

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INTRODUCTION

There are currently more than 107,000 medical practitioners in Australia, of which more than 5200 are anaesthetists. In 2013 there were 1484 registered anaesthesia trainees[1,2]. These are big numbers, and big numbers occasionally lead to individuals not receiving the care and mentoring that the College, the community and the trainee expects. Recent headlines in our local papers point out a number of suicides among junior doctors and highlight the increasing stress our trainee doctors are under[3,4]. It is important, given the large number of junior doctors in anaesthesia, that appropriate care and support is given to these people.

Mentoring has been shown to be an effective tool in the support, both emotionally and professionally of junior doctors. In 1997 the Anaesthetists Association of Great Britain and Ireland (AAGBI) published a document titled *Stress in anaesthetists* that outlined mentoring as part of the "stress support system"[5]. Since then there has been an increasing number of mentor programs introduced into anaesthetic departments in Australia. Unfortunately, however, we still lag behind the US and Canada in the provision of such important programs for the support of our trainees.

This article will outline a system of mentoring that we have established at The Women's hospital, Melbourne, a tertiary referral hospital and a major training hospital of anaesthetic registrars in Victoria and national and international anaesthesia Fellows. It will also explore some of the major issues that have presented themselves in the five years the program has been running.

MENTORING

Mentorship can be described as "a relationship in which a person with useful experience, knowledge, skills, and/or wisdom offers advice, information, guidance, support, or opportunity to another for that individual's professional development"[6]. It is based on the relationship in Greek mythology that Mentor – an older, wiser friend of Odysseus – had with Telemachus, who was Odysseus' son. Telemachus developed a strong relationship with Mentor based on his guidance and support. The term mentor is now used to encompass terms such as counsellor, coach, motivator and friend and in medical world a "safe space" or like in childhood games, "barley."

The business world in the US was the first to set up mentoring systems in the 1970s and the benefits of improved productivity, personal development leadership skills and job satisfaction were quickly identified by forward-thinking companies[7]. Medical mentoring was much slower to emerge in the literature with mentoring in the anaesthetic literature lagging behind many of the other medical specialties.

I began my anaesthetic training in the late 1980s when mentoring was only considered for those that were in difficulty professionally. I watched and learnt from those that I admired for their style or skill. The medical world was not an empathic environment and poor outcomes, personal issues and life stresses were generally not openly addressed within the workplace environment. Trainees often felt vulnerable and occasionally alienated when there was little official support in the system. The development of trainee welfare and mentoring within anaesthetic departments has greatly improved the workplace for anaesthetic trainees.

In 1998 the Subcommittee of Post Graduate Medical Education in the UK stated "there should be local analysis of the need for support for doctors, and local decisions made about the provision of such support" and so formal medical mentoring began to emerge.

Although it is difficult to quantify the exact emergence of mentoring in anaesthetic departments it appears the US is best represented with 88 per cent[8] of anaesthetic departments having a mentoring/welfare program compared with Canada 68 per cent[9] and Australia 37 per cent[10].

SETTING UP A MENTORING PROGRAM

Mentees

The decision as to who should be the mentees at an institution is important, as the robustness of a mentor program, is determined by the success of the program as measured by the feedback of the trainees and the degree of satisfaction of the mentors. If a program involves all junior and senior trainees, medical students, and allied health professionals, it may be too cumbersome and not sustainable.

It has been shown that mentoring programs in institutions particularly benefit mentees who are new to the institution, mentees encountering personal or professional difficulties, mentees unsure of their career opportunities and those mentees going on to leadership roles[11]. Mentees need to be at an institution at least three months minimum to benefit from a mentor program.

Mentors

The inclusion of the right mentors in a mentoring program is fundamental to the success of the program. Determining who should be involved in the mentoring program can be a difficult and controversial question. At one level it could be argued that all staff can be mentors as the qualities you need to be a mentor are good interpersonal skills, time, non-judgmental listening and a passion to be a mentor. Many people may have these qualities and thus a voluntary mentor program is an ideal way for these people to nominate themselves. While being involved in a mentoring program may have benefits for the mentor such as increasing the chance of promotion in the business world or achieving required continuing professional development points, these should not the be driving forces behind wanting to enter a mentoring program.

Important benefits for the mentor include engaging with trainees who may be of a different generation and therefore having a different world view, feeling more relevant, reconsidering established ways and increasing communication skills. These advantages should not be sought after but arrive as a surprising side effect of being part of a mentor program.

The issue of whether mentors should have formal training in mentoring is an interesting and controversial topic. In 1998, the Standing Committee on Postgraduate Medical and Dental Education (UK) (SCOPME) recommended that medical mentors should have formal training in mentorship[12]. Most mentoring programs do not require all mentors be formally trained, however, it is advantageous for the coordinator of the mentoring program to have formal training. There may be a time when formal mentoring training becomes mandatory, but at this stage, it is a long way off.

Finally there are certain members of a department who should not be involved in the mentoring program due to a conflict of interest. The supervisor of training (SOT), director of department and others with official training roles may have the interests of the mentee at heart but need to report to department, College or the hospital and so may have significant conflicts of interest.

Formal versus informal mentoring

Mentoring is often described as being “informal and invisible”[13]. It is true that the best form of mentoring is voluntary and takes place without a structured program. However, not all trainees establish a mentoring relationship and some can miss out on the benefits and possible safe environment mentoring has to offer. It is better to be mentored than not and informal mentoring is associated with a higher rating by the trainee, however, it comes at a cost that some trainees may miss out on mentoring completely. Formal mentoring leads to a more likely development of a mentor relationship (82 per cent versus 17 per cent)[14].

Allocated versus choice of mentor

The decision as to whether a mentee should have a choice of mentor as opposed to being allocated a mentor also remains a controversial area. Higher satisfaction levels are reported from the mentee when a mentee has a choice of a mentor. This however does have its own problems for the organisation in that one mentor may be the “favourite mentor” and have too many mentees to work with or that particular mentor may be the “favourite” as a person but not necessarily the best mentor.

There are a number of factors to consider when determining whether an organisation allocates or allows voluntary selection of mentors.

The first is the time that trainees spend at an institution. The shorter the stay the more important it is to allocate a mentor to the trainee early in the rotation as it is important not to waste weeks trying to determine the mentee’s favourite mentor.

The number of suitable mentors in the department is the second factor to consider in the decision to allocate a mentor or not. A small department cannot have the majority of mentees selecting one mentor and monopolising their time, so allocated mentoring may be best for a small department.

A third factor that is mentioned in mentoring literature (especially from the US) is whether mentors and mentees should be gender matched. There is little information on this in the Australian context. It is interesting that in the University of California, San Francisco (UCSF) Anesthesiology Department where they had assigned mentors for the first six months of their program, just over 70 per cent changed their mentor when allowed[15].

One alternative solution to the issue of formal allocation of mentors is to provide a form of “speed-mentoring”, similar to “speed-dating”, in the first week at an institution allowing all the trainees to meet the consultants briefly. This could be a solution to the mentor finding a mentor quickly, however, it may also mean that there is unequal distribution of trainees to mentors.

Communication

A hospital and departmental positive approach to a mentoring program is instrumental in the success of a program. Open and inclusive communication without feeling obligated to become involved is important. A program of Respectful Workplace Behaviours is in place at The Women’s. This is a hospital-wide program that every staff member is required to undertake on a yearly basis. Respectful behaviours are therefore a fundamental part of day-to day life at the hospital. It is within this respectful workplace that the mentoring program takes place.

Mentoring is a skill that is both innate and learnt and one of the most important components of mentoring is communication. Medical practitioners spend years learning to diagnose and treat illnesses in patients. Communication with our patients and relatives uses the “medical model” where medical practitioners are the experts and patients are given the answers or what medical practitioners believe are the answers.

Mentoring requires another type of communication that involves “active listening” or “empathic listening”. This is where practitioners treat their mentee with an unconditional positive regard and engage in listening to them without trying to solve their issues. It may involve summarising and paraphrasing, and allowing the full story to evolve. Early interrupting and claiming to know the answer are often counter- productive in a mentoring role and being real and genuine are important positive characteristics of being a mentor. One fundamental component of mentoring is respect with a strong mentor-mentee relationship developing through mutual respect.

THE WOMEN’S HOSPITAL EXPERIENCE

The Women’s hospital can present trainees with certain challenging situations and experiences. Most trainees are in their third year of anaesthetic training, which means they are beginning to move towards consultant level and so are given more responsibility and more afterhours work by themselves. They can sometimes also be exposed to traumatic situations such as maternal haemorrhage, neonatal and even maternal deaths and the other many emotional situations that arise in a women’s hospital.

The effects of increased responsibility and exposure to some traumatic events can have a deleterious effect on some of our trainees, and so in 2012 a mentoring program was established to help with trainees who were struggling with work or other issues.

The program

The Women’s trainees comprise of six third-year trainees that stay for both four or eight months, and five Fellows that stay for six to 12 months each. A formal system has been most appropriate for the trainees that stay for four month rotation. The mentors are volunteers with no pressure placed on anyone to be in the mentor program. The Director of Anaesthesia, Supervisor of Training and College representatives are not involved in the program.

The mentor is allocated to the mentee in the first week of the trainee’s rotation according to no specific criteria. The trainee and mentor both know whom they have been allocated.

There is no specific plan given to each mentor or mentee but both are encouraged to catch up within the first week and have a relaxed meeting outside the theatre complex. Meetings should be regular without seeming overly onerous for mentor or mentee. The format of the meetings is not dictated and is at the mentor’s discretion. A more regulated format of mentor-mentee meetings is used at other hospitals such as The Royal Children’s Hospital in Melbourne where the Bolton Box is used[16]. This encourages conversation along three certain headings namely “Skills/attributes”, “Your job” and “Life away from work”. There are many templates to aid in the discussion between mentor and mentees and it is up to each institution to decide whether to formalise the process or not.

The mentors are encouraged to report anything they are concerned about to the coordinator of the program first, and depending what the issue is, may be escalated to the coordinator seeing the trainee personally. The follow up after this would depend on the issue encountered.

Confidentiality is crucial and should be explained to the trainee in the first meeting. The mentor and the coordinator have a duty to the trainee and not the hospital, college or the department unless the issue is subject to mandatory reporting.

There must be a mechanism for an alternative mentor if the relationship between the allocated mentor and the mentee breaks down. Our program has not experienced this however it remains a possibility.

The feedback to the trainee should be balanced and presented in a non-threatening way, with negative feedback discussed with the coordinator, or others, before being presented to the trainee.

The assessment of our mentoring system is difficult as the end points are often intangible and can be difficult to quantify. Monitoring the effectiveness of mentoring systems is an area for all hospitals to work on in the future as medical workforce welfare will come under increased scrutiny in the future by the media, the government and the public.

Common issues discussed at mentor-mentee meetings

Future employment

One of the major issues that came up in trainee discussions was the concern about the possibility of finding a consultant position in the public system or finding enough work in the private system. A recent survey of trainees who had gone through The Women's training scheme from 2008-2013 and were three years post-fellowship was conducted. Out of the 60 trainees 76 per cent were working in Victoria, 19 per cent interstate and five per cent overseas. Sixty-six per cent were working in the public system and 34 per cent in the private system. None of the anaesthetists surveyed were working only in the private system. The mean number of hours worked per week was 38 hours which provides encouraging information for future trainees. The mean level of job satisfaction was 8.5/10; suggesting a positive future for those trainees about to gain fellowship.

Stress in the workplace

Stress at work and how individual trainees deal with it seems to be a very common discussion point at mentor-mentee meetings and between mentors and their supervisors. It is a complicated area with many factors that need to be examined to try to assist the trainee in dealing with the various stresses that they confront and have to deal with at work.

It is interesting that medical practitioners are over represented in the general population in the abuse of alcohol, incidence of depression and the number of psychiatric admissions. Anaesthetists are over represented in the abuse of drugs and level of suicide relative to the medical practitioner population.

Some of these issues relate to the selection process at medical school where students are selected that have a voracious appetite for succeeding regardless of personal cost. This can lead to some of these students having a lack of personal and professional support systems and leaving them prone to personal anxiety, feelings of inadequacy and self-doubt and often not being able to share their feelings with their peers or even mentors[17].

Medical training further fosters an excessive work ethic with long unsocial hours, particularly once the training enters registrar years. The "physician culture" denigrates and ignores the adverse effect of sleep deprivation and fatigue and relegates social and recreational activities needed for successful stress management to a lesser worth. This can lead to unbalanced and unhealthy lifestyles in those that may be susceptible. Self-regard is not respected leading to impaired resilience and emotional blunting[17].

It is interesting to note that a medical practitioner is generally thought of as a caregiver where the patient and the doctor are on the same level of mutual appreciation. Should the doctor become a caretaker and feel the responsibility of necessity to look after a patient completely this can lead to problems of workplace stress and eventually burnout if this happens regularly[18].

Anaesthetic training has its own specific stresses. Anaesthesia provision involves continuous intense vigilance with ongoing physiological arousal. This sounds very like the definition of the word stress. The traits of an anaesthetist include perfectionism, self-sacrifice, a heightened sense of responsibility and being prone to guilt. These traits can all be exacerbated with even minor harm to a patient.

The anaesthetic trainee faces issues such as a high level of responsibility early in their career, sleep deprivation and physical fatigue, a possible culture of negativism where there is a focus on mistakes and a period of uncertainty in their own ability, especially when learning new techniques and skills[17].

Female trainees face a further level of stress relative to their male counterparts. They face the added stress of balancing a career with possible family commitment. Nineteen per cent of female trainees interrupt their training for parenting compared with less than one percent for male trainees[19]. Female medical practitioners have a 40 per cent higher divorce rate than male counterparts and the suicide rate of female trainees is four times that of women in the general population[17].

Tips to help manage stress in the workplace

Seeking support

Trainees in their training should seek out a number of "support crew" to help them now and into the future. It is important to try to seek out and establish four levels of assistance during training.

1. A senior member of an anaesthetic department which they work in. This person can be used for professional anaesthetic advice and to discuss/deal with difficulties that occur in our profession such as mishaps, errors and even patient death.
2. Establishing or joining a journal club or a group of likeminded anaesthetists who meet regularly to discuss cases and incidents. This provides a non-threatening, safe environment to discuss any anaesthetic issues without the fear of department/hospital management overseeing proceedings. It is also a rich source of experience to call on about difficult cases and scenarios, which helps to provide a sense of relief that you are not alone in anaesthesia!

3. It is critical to develop a mentor during training, or shortly after, to be there for the individual when things get tough. The mentor can be of similar age or older and will have the role of guiding, advising, and more importantly being with the individual when difficulties arise both professionally or outside medicine. This is the person who will be there when an anaesthetic mishap occurs, and will look after the individual, and perhaps their family, during this tough time. This is the person who advises them not to continue the list after a disaster, and to look after themselves, even when they feel guilty and want to keep working.
4. Anaesthetic colleagues also provide a gentle support system and can be used almost daily when we see them in a tearoom, corridor or socially.

Time management

Anaesthetists are highly skilled at time management within an operating theatre setting and generally are the ones that control the daily throughput of those theatres. Unfortunately this skill is not reflected in the time management of many anaesthetists' lives and the life balance often weighs heavily on the work side of the work/life balance. This is particularly true in the first few years of being an anaesthetic consultant when there is huge pressure to establish your practice which may be to the detriment of the rest of your life and family.

The ability to say no is a critical skill and a skill that is not well developed in an anaesthetist who has come through the "physician culture" of rewarding a strong work ethic and denigrating "time off ". There are two good reasons for saying no.

Firstly, at some stage early in a new consultant's career it is best to work out where the work/life balance is going to sit best. This will enable the person to work out how much they wish to work and when to say no to the extra work should it become available. Secondly, saying no to an individual case or a list, in an unfamiliar hospital with an unknown surgeon, doing unfamiliar surgery is OK. Saying no enables stress control and helps determine when situations are beyond one's command. The skill of saying no is an important one to help to avoid burnout, a common end point from working in a stressful environment for a prolonged period.

Nurturing a sense of humour

Humour is another very useful tool to counter stress as it not only can change the direction of a serious discussion or situation but is associated with the release of endorphins critical to protection against prolonged stress. We must learn to take our work and responsibilities seriously while taking ourselves lightly. It is important not to become afflicted with AADS – "Acquired Amusement Deficiency Syndrome". Don't forget a baby smiles 400 times a day compared with an adult smiling only 15!

Physical and mental well being

It is important that trainees look after themselves physically and mentally so that they are at their best to face the challenging anaesthetic workplace. Exercising three times a week or playing team sports are both associated with stress reduction with team sports having the further advantage of a commitment and communication with fellow team mates. A healthy diet and allowing time for meals, especially breakfast, is all part of trying to maximise wellbeing and longevity in anaesthesia. Writing your thoughts in a diary and mindfulness activities such as meditating or focusing on the immediate surroundings in an appreciative way may also assist with relaxation and are useful tools in fighting stress.

Substance use and suicide

Unfortunately, as anaesthetists we have a 1.5 relative risk of suicide and a 2.2 relative risk of drug-related suicide relative to other physicians. The increasing representation of propofol in substance use and suicide in Australian and New Zealand anaesthesia needs highlighting. The over representation of trainees and particularly female trainees in both substance use and drug related suicide is highly concerning and needs addressing at a national level[10]. This is an area that may come up in mentor mentee discussions and requires great tact and consultation with the mentor coordinator or even external counselling assistance. A full discussion of these two areas are beyond the realm of this chapter but are areas that do come up in discussion at mentor-mentee meetings so a few points do need to be made. Both of these issues may present as medical emergencies or there is grave concern for the person's life. In conjunction with the person, obtaining help is a key priority. The Welfare of Anaesthetists Special Interest Group Website has a range of important resources available: www.anzca.edu.au/fellows/special-interest-groups/welfare-of-anaesthetists#resources. The Doctors' Health Advisory Service, which has regional helplines in all Australian states and territories, and New Zealand (http://dhas.org.au/contact/contact-dhas-in-other-states-territories-and-new-zealand.html) is an excellent contact point for anaesthetists and trainees who you may think need assistance in these two areas.

Other discussion areas

1. Anaesthetic complications: Anaesthetic complications are rare and in contemporary practice the patient often expects a perfect anaesthetic. This means that a complication is often very heartfelt by the anaesthetist and particularly a trainee having a complication for the first time. A tooth knocked out at intubation or a dural tap experienced for the first time needs to be discussed gently in a supportive environment as the trainee may not have had any serious complications until now and will be feeling particularly guilt ridden.

2. Death during anaesthesia or resuscitation: Nothing can prepare a trainee or anaesthetist for such a catastrophic event. Everyone involved obviously needs support and if the trainee was the main anaesthetist involved then that person needs full counselling not only from their mentor but from the department and possibly external counselling. The incident needs to be discussed in a very supportive way with no blame attached and gentle positive feedback. The trainee needs full support both internally and also outside the hospital and it is important to make sure there are people outside the hospital to help the trainee – friends, family and colleagues. The trainee should never have to deal with this situation by themselves.
3. Other areas of discussion: Trainees competence and resilience are other difficult areas of discussion, as are conflict with others and coping with life events, but if the foundations of a mentor are adhered to and a strong mentor-mentee relationship is allowed to grow then these areas can be discussed fully and with great benefit to the trainee.

CONCLUSION

A mentoring program within an anaesthetic department is an invaluable asset not only for the mentee with proven benefits around research, continuity and professional development but also for the mentor with improved communication skills and being exposed to new techniques and being challenged about old ways. There are many combinations of setting up a mentoring program such as formal versus informal mentoring, allocated versus chosen mentors and the decision as to who will be the mentees and the mentors in your institution.

The Women's hospital has set up a formal, allocated mentoring program for junior and senior trainees based on the time the trainees are there but this may not be the best set up for other hospitals with less staff or shorter trainee rotations.

Finally the act of mentoring should not be feared, as everyone has the ability to listen, be non-judgemental and care about someone else. The real ability is to sit back and listen and not always have the answer.

REFERENCES

1. Australian Health Practitioner Regulation Agency (AHPRA) 2017. The AHPRA Annual Report 2015/16. From: http://www.ahpra.gov.au/annualreport/2016/. Accessed 17 July 2017.
2. Australian and New Zealand College of Anaesthetists (ANZCA) 2017. ANZCA Annual Report 2014. From: http://www.anzca.edu.au/documents/anzca-annual-report-2014-final.pdf. Accessed 17 July 2017.
3. Three of my colleagues have killed themselves. Medicines dark secret can't go on. The Sydney Morning Herald. 2017 Feb 10.
4. Swanson SP, Roberts LJ, Chapman MD. Are anaesthetists prone to suicide? A review of rates and risk factors. Anaesth Intensive Care. 2003;31(4):434-445
5. The Association of Anaesthetists of Great Britain and Ireland (AAGBI) 2017. Stress in Anaesthetists 1997. From: https://www.aagbi.org/sites/default/files/stress97.pdf. Accessed 17 July 2017.
6. Berk RA, Berg J, Mortimer R, Walton-Moss B, Yeo TP. Measuring the effectiveness of faculty mentoring relationships. Acad Med. 2005;17:66-71
7. Roche GR. Much ado about mentors. Harv Bus Rev. 1979;1:14-31
8. Gonzalez LS, Donnelly MJ. A survey of residency program directors in anesthesiology regarding mentorship of residents. J Clin Anesth. 2016;333:254-265
9. Ergun S, Busse JW, Wong A. Mentorship in anesthesia: a survey of perspectives among Canadian anesthesia residents. Can J Anaesth. 2017;64:402-410
10. Fry RA, Fry LE, Castanelli DJ. A retrospective survey of substance abuse in anaesthetists in Australia and New Zealand from 2004 to 2013. Anaesth Intensive Care. 2015;43:111-117.
11. Feldman MD, Arean PA, Marshall SJ, Lovett M, O'Sullivan P. Does mentoring matter: results from a survey of faculty mentees at a large health sciences university. Med Educ Online. 2010;15:5063.
12. Standing Committee on Postgraduate Medical and Dental Education. Supporting doctors and dentists at work: an enquiry into mentoring. London, United Kingdom: SCOPME, 1998.
13. Bligh J. Mentoring: an invisible support network. Med Educ. 1999;33:2-3.
14. Zakus P, Gelb AW, Flaxman AM. A survey of mentorship among Canadian anaesthesiology residents. Can J Anaesth. 2015;62:972-978.
15. Flaxman AM, Gelb AW. Mentorship in anesthesia. Curr Opin Anesthesiol. 2011;24:676-681.
16. Howe P. The mentor case: a proposed model for mentoring in anaesthesia departments. Australasian Anaesthesia. 2007; 103-110.
17. Jackson SH. The role of stress in anaesthetists' health and wellbeing. Acta Anaesthesiol Scand. 1999;43:583-602.
18. Corke C. The courage to act on burnout. Medical Journal of Australia: Insight. 2017; 27 February. From: https://www.doctorportal.com.au/mjainsight/2017/7/have-the-courage-to-act-on-burnout/ Accessed 17 July 2017.
19. Australian and New Zealand College of Anaesthetists (ANZCA). 25 years of ANZCA Leadership 1992-2017. 2017:44. From: http://v3au.zone-secure.net/drive/5022/271542/. Accessed 17 July 2017.

Free open access online education in anaesthesia

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INTRODUCTION

To say that the internet has had a dramatic impact on society is an understatement. Estimates from 2015 suggest that 85-90 per cent of Australian and New Zealanders report making use of the internet regularly[1]. The information age is showing no denouement, but continuing to shape the ways we communicate, learn, relate, trade, and live.

The digital revolution has also disrupted the norms of medical education[2-6]. Medical educators have harnessed the internet to produce and broadcast their own educational material, subverting the established control of published print. The internet has allowed the "flipped-classroom" to become a mainstream pedagogy; where the core elements of the traditional education model are reversed with the digestion of educational material occurring outside of the learning environment, and subsequent discussion and application of concepts with the guidance of a mentor at the workplace or university. The ability for asynchronous learning is also facilitated, where information can be shared outside the constraints of time and place among a network of educators and learners[4,7,8].

The wealth of online material has also allowed the novice learner to venture outside of prescribed educational material for independent co-curricular or extra-curricular learning and the qualified physician to pursue authentic lifelong education[4,7,8]. In the earliest days various online forums and journal clubs emerged, with subsequent proliferation of amateur altruistic educational resources and collaborative wikis, organisational resources, and paid (and at a later point) free formal online courses[9]. Most recently the widespread adoption of social media has been a potent catalyst for online education through blogs, podcasts, YouTube videos, Twitter feeds and Facebook groups continuing to grow globally[10]. In addition to the frank translation of knowledge, social media has become a useful medium in which to discuss, scrutinise, and ruminate over current medical practice and research[7]. Greater than 90 per cent of Canadian emergency medicine trainees were found to utilise online educational resources, and both trainees and program directors reported that this use increased the amount of peer-reviewed literature they consumed[4]. The widespread and popular use of online resources by physicians at all career levels suggests that this phenomenon is not simply a passing novelty[11]. Formal recognition of online educational resources as scholarly work is increasing; establishments such as The Mayo Clinic now recognise FOAM content in their criteria for academic advancement[12,13]. The distinction between traditional journals and online publishing is predicted to lessen[14].

FREE OPEN ACCESS MEDICAL EDUCATION (FOAM)

In 2012 the handle Free Open Access Medical education (FOAM, #FOAMed) was created by Australian critical care practitioners attending the International Conference on Emergency Medicine in Dublin[7]. As these physicians describe it, "FOAM should not be seen as a teaching philosophy or strategy, but rather as a globally accessible crowd-sourced educational adjunct providing inline (contextual) and offline (asynchronous) content to augment traditional educational principles"[15]. The acronym is a moniker describing the array of free resources, social fora and online users that focus on delivering free medical education, and in doing so bypass entrenched barriers to knowledge acquisition and dialogue in medical education[7,9,]. FOAM has no official leader; it is a medium, a community, and an ethos. Content is crowdsourced worldwide from a heterogeneous mix of individuals, the standard of which is evaluated by end-users. The FOAM educational model supports lifelong education, and realises the command for free education given by the Hippocratic Oath itself:

> "To teach them this art – if they desire to learn it – without fee and covenant; to give a share of precepts and oral instruction and all the other learning"[7].

As the definition of FOAM is somewhat nebulous there can be difficulty in deciding whether a resource is strictly a FOAM resource. Most visibly there are resources, often with a strong social media presence, that adopt the label FOAM explicitly. However there are also a multitude of online resources that are free and open access, for example publications of renowned medical organisations such as WHO, UNICEF, and prominent teaching institutions, that don't explicitly use the FOAM label. Research journals have recently begun to embrace an open-access model to varied degrees, and some have also recently begun to develop the capacity for end-user interaction and discussion through the use of online forums or social media. Although somewhat arbitrary the distinction between open-access research and open-access education has been made in defining the boundaries of FOAM.

Strengths of FOAM

With the adoption of a new and disruptive educational paradigm it is fundamentally important to understand its strengths and limitations. As for any educational system, demonstrating benefit is onerous. Current research has documented the rapid global uptake of FOAM resources via surveys and internet traffic data, and its utility in passing examinations clinical problem-solving and continuing medical education has been asserted by personal testimony[16]. Similar to proponents of simulation-based training, enthusiasts see the benefits as obvious however there has been limited high-grade research reporting its outcomes.

One of the central benefits of FOAM is the low barrier to entry. Access to FOAM resources is almost universal in all healthcare settings, given the high rate of internet access achieved with personal devices and institutional computers. The ease of access to FOAM is of great utility to trainees who are in isolated or remote locations of high income countries (HIC), and those in low and middle income countries (LMIC), where access to medical education through contact with specialist peers may be less at hand. FOAM is platform independent and cloud-based, executable across all browsers, all smart devices, and social media subscriptions. Given the widespread familiarity with use of the internet and social media, FOAM is easy to navigate and use for the contemporary doctor. There is little financial barrier to FOAM; the cost of smart devices and computers is at its lowest in history, social media accounts are free, and entry-level web-hosting costs for wikis or blogs are generally low or absent.

FOAM promotes asynchronous learning and supports the "flipped classroom" model[16]. Asynchronous learning materials facilitate information sharing outside the constraints of time and place among a network of people. In the flipped classroom model, learning resources are studied by learners prior to a clinical session, allowing the high-value clinical time to be dedicated to more educationally rich peer discussion and practical experience in contrast to didactic teaching sessions. In this model clinically-based guidance by experts facilitates the correct interpretation and application of asynchronous FOAM material, with the teacher correcting and guiding the inexperienced learner in their understanding of the nuances of the material. Asynchronous material is easily adaptable to local needs and training curricula, and supports self-directed lifelong learning. The flipped classroom meets the needs of adult learners; providing authentic and personalised material in a convenient and efficient manner. This style of learning is suited to the healthcare setting, where shift-work is common, learners frequently have differing depths of knowledge for a given topic, and one-on-one time with clinical experts is scant and invaluable[7].

FOAM employs a collaborative approach by exploiting digital connectivity. Through the power of crowdsourcing, an ever-changing user base, and with a route of direct and open commentary, a level of refinement of FOAM material is achieved[7,17]. An exhaustive critique of resources and thorough peer review of new research is possible through the insights and perspectives of a global community of specialist practitioners. New research and knowledge can be identified and discussed efficiently through the large networking capability of online discussion groups. Thus inaccuracies in FOAM content as a result of error, new knowledge, or a shift in real-world practice are able to be identified with great sensitivity. Post-publication review is both continual and rapid. Corrections to material and the dissemination of new knowledge can be achieved almost instantaneously without the need for a new publication cycle, in comparison with traditional educational resources. The power of a collaborative approach and a digital platform leads to the generation of material that is up-to-date, accurate, distilled, comprehensive, and reflective of a global consensus.

FOAM has a greater capacity for the sharing of tacit knowledge[7,18]. Knowledge that is difficult to communicate in text or lectures can be transferred. Solutions to clinical problems that research has not yet answered, or that texts have no space to discuss, can be shared.

The collaborative nature of FOAM promotes interaction between clinicians of differing specialties, institutions, and nations, fostering improvement in relations for collaboration in research and clinical practice[7,19,20]. The vibrant interaction and commentary on emerging knowledge engages scientists and promotes clinical research[10].

In comparison with traditional resources, FOAM more commonly exploits the wide variety of effective educational tools available; interactive written content, infographics, video, podcasts and forum based discussion. FOAM education is thus more dynamic, engaging and more likely to be effective. As FOAM material is universally accessible and broadcast to a wide audience, an economy of scale is attained offsetting any investment cost[19].

Weaknesses of FOAM

The major criticism of FOAM education concerns the lack of formal quality control governing FOAM-produced resources[10,11,21-23]. This is a direct consequence of the free dissemination of information through FOAM-capable media, with no requisite qualifications for authors or approval process for content produced. Some FOAM producers have attempted to incorporate adaptations of editorial management or formal peer-review to raise the credibility of their content, however in general there is minimal or no such process evident for the majority of material currently available[23]. Post-publication feedback can allow the corrections of errors and misunderstanding, but these corrections are often not as visible as the original publication. History has demonstrated that "disruptive", innovative, user-oriented products and solutions are at the outset often economical and of low-quality[20]. After establishing popularity and destabilising the status quo they then begin to improve in quality. The popularity and utility of FOAM is already evident, however to earn acceptance within the medical establishment it needs to now reach a level of credibility that meets that of traditional educational media. A systematic review published in 2015 by Paterson et al showed that there are currently no standardised methods to measure the quality of medical education resources online; learners are consuming online medical education resources with fervour despite a current inability to critically appraise these secondary literary resources[24]. The authors highlighted that the lack of quality metrics has negative implications for all stakeholders who share an interest in producing and consuming quality material: learners, educators, academic leaders, and content producers. At this time various methods of critiquing content quality have been proposed (checklists, modified Delphi method, METRIQ-5, METRIQ-8, ALiEM AIR), but none so far has reached widespread acceptance or use[10,20-22]. Experimental systems of peer-review have arisen to improve the quality of online resources, such as "coached peer review"[23].

Ideally clinicians should develop a working knowledge of clinically relevant primary literature, critically appraising the evidence base and integrating knowledge into practice. FOAM has the potential to allow learners to circumvent this process leaving them without the skills to critically appraise research and only able to make reference to blogs, podcasts and other secondary literature. This increases the risk of clinical practice that is not evidence-based. Importantly FOAM should help to distil a broad evidence base with the assistance of one's peers, and that FOAM resources should ideally include a discussion and critique of the current evidence base, adequate references to source material, and updated in the light of new evidence. FOAM augments learning but should not replace development of skills in appraising research.

A further criticism of FOAM education is the potential for oversimplification of medical knowledge. Medical concepts can be at times nuanced and difficult to conceive, however a thorough understanding assists in clinical decision-making, particularly in scenarios where patients deviate from the norm and practice guidelines are not appropriate. The FOAM platform may tend toward reductionism, limiting explanations in length and complexity to suit the audience and the limitations of the delivery medium[24]. This has the potential to be of detriment to a training clinician.

One of the strengths of FOAM is the rapid dissemination and uptake of new knowledge in the light of emerging evidence. Paradoxically this strength is also a potential weakness. Concerns have been raised over the risk of new research being incorporated clinically prior to confirmation of validity, safety and efficacy[10]. Conversely, a delay in the clinical uptake of new research findings can lead to patient harm.

A cornerstone of internet search algorithms and social media is that the most popular resources become more visible. In this way the most potentially useful information is provided to the consumer. However, the assumption that the most popular resources are the most useful may lead to unwanted consequences in medical education. Firstly, a note about populism and subject matter. Concerns have been voiced about the observable imbalance of resources dedicated to topics of current and popular interest, such as research with only positive findings, novel clinical techniques without proven efficacy or safety, and the most popular medical conditions[9,27]. This imbalance is at the expense of a broad education covering all essential knowledge for the true scope of clinical practice. Learners motivated by formal assessment combat this by utilising FOAM as extra- or co-curricular support; however this does not negate the long-term impact of this issue. The second issue is populism in authorship. The emergence of particularly popular resources results in the associated promotion of particular authors. Accompanying this is the risk of certain authors possessing an undue influence on learners, and hence clinical practice[9]. This has the potential for harm through unintentional or intentional bias.

The monetisation of FOAM resources through advertising is a potential source of income for authors, whether to cover the costs associated with maintaining resources or specifically for the financial benefit of authors. Concerns have been raised about the inappropriate courting of medical advertising with medical education, where there is a risk of influencing medical practice through the promotion of particular drugs, equipment or services[26]. A conflict of interest in this context does not legally need to be made explicit.

FOAM by nature often involves the reproduction of existing content, albeit distilled, integrated with other knowledge, or directly promoted. Authors need to by weary of the plagiarism of content from other sources. This may be a greater problem with FOAM resources due to the lack of oversight in the publication process. International copyright code should be followed and sources referenced. The copyright code set by peer-reviewed medical journals may restrain authors; publishing original content on FOAM sites can jeopardise an author's ability to submit content for publication. The rise of open-access medical journals may mitigate this issue. The provision of medical education resources must not be confused with medical advice; if not made explicit this has the potential to engender medico-legal liability. Patient confidentiality and consent must be respected as set out by our professional code of conduct.

FOAM in non-anaesthesia specialties

The proliferation of FOAM has been dramatic. In February 2016, 356 FOAM providers relating to emergency medicine and critical care were counted[26]. Within critical care medicine, 30 blogs of higher standing have been formally recommended as quality FOAM resources in a peer-reviewed journal[7]. The global aggregate of FOAM content focuses mainly on the practice of emergency medicine and critical care, however its uptake across the full gamut of specialty groups is evident with high-quality resources serving the disciplines of radiology[28], paediatrics[29], ophthalmology[30], general practice[31], haematology[32], oncology[33], orthopaedic surgery[34], cardiology[35],

and dermatology[36] among others. There also exists a diverse array of online resources that meet the criteria of a FOAM initiative but that do not overtly adopt the label, for example in public health and internal medicine.

FOAM in anaesthesia

In the quest for specialist education anaesthesia trainees can certainly profess to be "drowning in data, starving for knowledge". And yet any embrace of the FOAM education specifically serving the specialty of anaesthesia is still in its infancy.

The most widely known and embraced resources are produced by formal anaesthesia bodies, with various education initiatives forming part of their online publication;

1. The British Journal of Anaesthesia Education (previously Continuing Education in Anaesthesia, Critical Care & Pain)[37]
2. The New York School of Regional Anaesthesia (NYSORA) [38]
3. The Difficult Airway Society[39]
4. The World Federation of Societies of Anaesthesiologists[40]
5. The Association of Anaesthetists of Great Britain and Ireland[41]
6. The American Society of Anesthesiologists[42]

Educational resources produced by these bodies are generally of exceptionally good standard, however they are mostly non-user oriented, targeted institutional publications that are reproduced online according to the agenda of the institution, and are associated with minimal platform discussion. They do not reflect much of the mantra of FOAM.

The most active online forum for the discussion of anaesthesia-related knowledge is seemingly the anaesthesia-specific sub-forum on the site doctors.net.uk[43]. However this site requires General Medical Council registration in the UK for access and is therefore not open access. The site does not produce educational material.

In anaesthesia the internet was embraced early as a medium for dedicated sharing of specific examination preparation resources, and as expected this has been wildly popular among anaesthesia trainees. The most prominent, the Black Bank Wiki[44], however, is not open access (a token login required), and oriented specifically to aid candidates in the passing of exams as opposed to assisting the learner in the pursuit of an education in clinical anaesthesia.

The remaining compendium of online endeavours considered to be somewhat reflective of FOAM principles are severely lacking in quality content, have stalled with infrequent updates, or have been abandoned altogether[45-52]. There is a paucity of anaesthesia-specific education podcasts with ongoing production. A search on the social media platforms of Twitter, Facebook and Reddit, with the terms "FOAMed" or "FOAM" and "anaesthesia" or "anesthesia" unearths sporadic results generated by a handful of enthusiasts.

In Australia and New Zealand ANZCA has generated an online education community through its portal ANZCA Networks[53], however it is not open access, requiring College membership for a means of entry, restricting its ability to generate an assembly of learners, a fundamental principle of FOAM. Despite being in its infancy the anaesthesia community is particularly well positioned to take advantage of the benefits of FOAM. As a specialty anaesthetists are generally tech-savvy and embrace new technological advancements.

Anaesthetists have a high level of smartphone and computer-based internet access and are frequent consumers of social media. Shift-work patterns are well served by asynchronous learning, and the existence of easily accessed, distilled, up-to-date resources would be advantageous. Anaesthesia is a large specialty group, with the potential for cost-effective and rich online discussion due to a significant crowd size[54]. There is a large requisite bank of both theoretical and tacit knowledge in our day-to-day work.

THE DEVELOPMENT OF AN ANAESTHESIA FOAM RESOURCE

The present time is fitting for the expansion of our global anaesthesia FOAM community, which will only occur with the personal embrace of FOAM by teachers, students and researchers in anaesthesia. This growth would be catalysed by the development of a successful and authentic anaesthesia-centric FOAM venture. An ideal FOAM initiative would truly embrace the aforementioned principles of FOAM; a free, online, globally-accessible, crowdsourced educational adjunct, providing a platform for the dissemination of quality educational content as well as instantaneous peer review, feedback, and sharing.

Free and open access means by definition without charge, globally accessible, and without restricted login. The provision of a gratuitous resource can be problematic as an important impediment to the proliferation of FOAM is the "cost of free" to authors[7]. FOAM resources are mostly generated by philanthropic, enthusiastic individuals, at their own financial and temporal expense. However costs can be significant, including the cost of web hosting and development. Various solutions have been adopted, all of which carry some form of compromise to the integrity or function of the resource; these include charging for continuing professional development (CPD) points, allowing advertising, permitting donations, or institutional funding. Of these, funding

by relevant institutions such as affiliated universities, professional colleges or professional societies is likely to be most appropriate to avoid conflicts of interest.

An ideal FOAM resource for anaesthesia should also address and mitigate the criticisms that have been held against FOAM education model, not only to improve its intrinsic scholarship value but also to improve the perception of FOAM education by employers, academic institutions and specialty colleges.

An ideal resource would cover core anaesthesia knowledge, based on published College curricula. A wiki system has much to offer in this type of large-scale content management. A vulnerability of the wiki system is the open access to submissions and editing, which without a strong moderating team can lead to problems with quality control. A closed-author wiki mitigates this problem. A small, team-based, core author group not only allows control of quality, but also spreads the cost of time and effort in knowledge translation and communication which competes with clinical practice and other commitments. Restricted authorship also mitigates the accusation of populism or self-promotion in authorship. An open access comment and discussion capability would still be essential to capture the benefits of larger scale crowdsourced peer-level review. Specific requests to review material by specialists in each field of knowledge would serve as additional peer-review. A structured, associated teaching program for trainees would also facilitate review and revision of core material at a trainee level with each calendar year.

The standard of material published through this FOAM resource should be of exceptional quality. It should be sourced from peer-reviewed publications and recommended textbooks, and referenced. Content should be free from plagiarism, up to date when published and under continual review.

The incorporation of a blog-like capability would be of use to address novel and emerging literature in an authentic context, and to highlight recent practice-changing advancements. This would enhance the appraisal and translation of research into practice, however there should be little commentary on novel practices not likely to be widely translated to clinical practice.

EMBRACING FOAM

The development of an anaesthesia FOAM community is more importantly catalysed by the personal embrace of FOAM by clinicians, teachers, and researchers in anaesthesia. The individual embrace of FOAM by end-users is of utmost importance, creating a vibrant and productive community through online participation and interaction.

Chan et al have called for the engagement and participation of three types of modern scholar[10]. Firstly "translational teachers"; educators who work to translate new knowledge, dedicated to the task of engaging the community in education through traditional and modern platforms are required. Secondly, there should be "critical clinicians"; a digitally-active base of clinicians who provide meaningful critique of material in an open forum of debate. Thirdly, "interactive investigators"; researchers who do not only produce new knowledge, but also engage with the community to ensure that findings are relevant, and work with translational teachers to ensure findings are adapted to clinical practice. The individual embrace of FOAM by end-users is vital, creating a vibrant and productive community through online participation and interaction.

CONCLUSION

FOAM is a conglomeration of enterprising free educational resources that are globally accessible, crowd-sourced, and a philosophy that embraces freely accessible high quality education material. FOAM complements the traditional teaching model, has a low cost to entry, and can be integrated into an asynchronous "flipped" classroom model of education. It complements traditional teaching models and does not replace the value of an experienced clinical mentor. It is an adjunct in the aid of knowledge translation. FOAM resources allow rapid and purposeful interaction among peers via an online community. FOAM has the challenges of maintaining high-quality medical education, expected by end-users, and concurrently achieving sustainable financial support. With appropriate structures in place these challenges can be mitigated.

All healthcare providers need to collaborate, whether they be online or in real life so that we can progressively educate the next generation of healthcare providers. The internet has revolutionised much in our everyday life; now is the time to embrace online medical education for anaesthetists through FOAM as a complementary and progressive form of adult learning.

REFERENCES

1. International Telecommunication Union. Statistics: percentage of Individuals using the Internet [Internet]. From: http://www.itu.int/en/ITU-D/Statistics/Documents/statistics/2016/Individuals_Internet_2000-2015.xls. Accessed 17 June 2017.
2. Thoma B, Mohindra R, Artz JD, Chan TM. CJEM and the changing landscape of medical education and knowledge translation. CJEM 2015;17(2):184-187.
3. Cadogan M, Thoma B, Chan TM, Lin M. Free Open Access Meducation (FOAM): the rise of emergency medicine and critical care blogs and podcasts (2002–2013). Emerg Med J. 2014;31(1):76-77.
4. Purdy E, Thoma B, Bednarczyk J, Migneault D, Sherbino J. The use of free online educational resources by Canadian emergency medicine residents and program directors. CJEM. 2015;1717:101–106.

5. Mallin M, Schlein S, Doctor S, Stroud S, Dawson M, Fix M. A survey of the current utilization of asynchronous education among emergency medicine residents in the United States. Acad Med. 2014;89(4):598-601.
6. Christensen C, Raynor ME. The innovator's solution: creating and sustaining successful growth. Boston: Harvard Business School Press; 2003.
7. Nickson CP, Cadogan MD. Free Open Access Medical education (FOAM) for the emergency physician. Emerg Med Australas. 2014;26(1):76-83.
8. Pearson D, Bond M, Kegg J, Pillow T, Hopson L, Cooney R, et al. Evaluation of social media use by emergency medicine residents and faculty. West J Emerg Med. 2015;16:715-720.
9. Carroll CL, Bruno K, vonTschudi M. Social media and free open access medical education: the future of medical and nursing education? Am J Crit Care. 2016;25(1):93-96.
10. Chan T, Trueger S, Roland D, Thoma B. Evidence-based medicine in the era of social media: scholarly engagement through participation and online interaction. CJEM. 2017:1-6.
11. Krishnan K, Thoma B, Trueger S, Lin M, Chan T. Gestalt assessment of online educational resources may not be sufficiently reliable and consistent. Perspect Med Educ. 2017;6:91-98.
12. Sherbino J, Arora VM, Van Melle E, Rogers R, Frank JR, Holmboe ES. Criteria for social media-based scholarship in health professions education. Postgrad Med J. 2015;91:551-555.
13. Cabrera D. Mayo Clinic includes social media scholarship activities in academic advancement [Internet]. From:https://socialmedia.mayoclinic.org/discussion/mayo-clinic-includes-social-media-scholarship-activities-in-academic-advancement. Accessed 20 July 2017.
14. Smith R. What will the post journal world look like? [Internet]. BMJ blogs. 2016. From: http://blogs.bmj.com/bmj/2016/06/15/richard-smith-what-will-the-post-journal-world-look-like. Accessed 20 July 2017.
15. Nickson C. FOAM [Internet]. From: https://lifeinthefastlane.com/foam/. Accessed 19 July 2017.
16. Prober CG, Khan S. Medical education reimagined: a call to action. Acad Med. 2013;88(10):1407-1410.
17. Thoma B. Crowdsourced instantaneous review: the peer review of FOAM? Canadiem [Internet]. 2013 From: https://canadiem.org/dissenting-opinions-the-peer-review-of-foam/. Accessed 17 June 2017.
18. Weingart SD. Tacit knowledge and medical podcasting. EMCrit.org [Internet]. 2013 Feb. From: http://emcrit.org/wee/tacit-knowledge-podcasting/. Accessed 13 August 2017.
19. Chan T, Joshi N, Lin M, Mehta N. Using Google Hangouts on Air for medical education: a disruptive way to leverage and facilitate remote communication and collaboration. J Grad Med Educ. 2015;7:171-173.
20. Cabrera D, Cooney R. Wikis: using collaborative platforms in graduate medical education. J Grad Med Educ. 2016;8(1)99-100.
21. Colmers IN, Paterson QS, Lin M, Thoma B, Chan TM. The quality checklists for health professions blogs and podcasts. The Winnower [Internet]. From: https://thewinnower.com/papers/2641-the-quality-checklists-for-medical-education-blogs-and-podcasts. Accessed 20 July 2017.
22. Lin M, Thoma B, Trueger NS, Ankel F, Sherbino J, Chan T. Quality indicators for blogs and podcasts used in medical education: modified Delphi consensus recommendations by an international cohort of health professions educators. Postgrad Med J. 2015;91:546-550.
23. Sidalak D, Purdy E, Luckett-Gatopoulos S, Murray H, Thoma B, Chan TM. Coached peer review: developing the next generation of authors. Acad Med 2017;92:201-204.
24. Brabazon T. The Google Effect: googling, blogging, wikis and the flattening of expertise. Libri. 2006;56:157-67.
25. Paterson Q, Thoma B, Kenneth Milne W, Lin M, Chan T. A systematic review and qualitative analysis to determine quality indicators for health professions education blogs and podcasts. J Grad Med Educ. 2015;7(4):549-554.
26. Grock A, Paolo W. Free open access medical education: a critical appraisal of techniques for quality assessment and content discovery. Clin Exp Emerg Med. 2016;3(3):183-185.
27. Stuntz R, Clontz R. An evaluation of emergency medicine core content covered by free open access medical education resources. Ann Emerg Med. 2016;67(5):649-653.
28. Radiopaedia [Internet]. 2017. From: https://radiopaedia.org. Accessed 17 June 2017.
29. PaediatricFOAM [Internet]. 2017. From: https://www.paediatricfoam.com. Accessed 17 June 2017.
30. EyeWiki [Internet]. 2017. From: http://eyewiki.aao.org/Main_Page. Accessed 17 June 2017.
31. FOAM4GP [Internet]. 2017. From: http://foam4gp.com. Accessed 17 June 2017.
32. Hemonc.org [Internet]. 2017. From: http://hemonc.org. Accessed 17 June 2017.
33. OzRadOnc [Internet]. 2017. From: http://ozradonc.wikidot.com. Accessed 17 June 2017.
34. The Bone Surgeon [Internet]. 2017. From: http://www.thebonesurgeon.com/orthopaedic-notes. Accessed 17 June 2017.
35. Textbook of Cardiology [Internet]. 2017. From: http://www.textbookofcardiology.org/wiki/Main_Page. Accessed 17 June 2017.
36. DermNetNZ [Internet]. 2017. From: http://www.dermnetnz.org. Accessed 17 June 2017.
37. The British Journal of Anaesthesia Education (previously Continuing Education in Anaesthesia, Critical Care & Pain) [Internet]. 2017. From: https://academic.oup.com/bjaed. Accessed 17 June 2017.
38. The New York School of Regional Anaesthesia (NYSORA) [Internet]. 2017. From: http://www.nysora.com. Accessed 17 June 2017.
39. The Difficult Airway Society [Internet]. 2017. From: https://www.das.uk.com. Accessed 17 June 2017.
40. The World Federation of Societies of Anaesthesiologists [Internet]. 2017. From: http://www.wfsahq.org/resources/anaesthesia-tutorial-of-the-week. Accessed 17 June 2017.
41. The Association of Anaesthetists of Great Britain and Ireland [Internet]. 2017. From: http://www.aagbi.org/publications. Accessed 17 June 2017.

42. The American Society of Anesthesiologists [Internet]. 2017. From: https://www.asahq.org. Accessed 17 June 2017.
43. Doctors.net.uk [Internet]. 2017. From: https://www.doctors.net.uk. Accessed 17 June 2017.
44. BlackBankWiki [Internet]. 2017. From: http://www.anaesthesiamcq.com. Accessed 17 June 2017.
45. The University of Sydney Nuffield Department of Anaesthetics Lectures and Study Notes Listing [Internet]. 2017. From: http://sydney.edu.au/medicine/anaesthesia/resources/lectures/. Accessed 17 June 2017.
46. OpenAnesthesia [Internet]. 2017. From: https://www.openanesthesia.org. Accessed 17 June 2017.
47. OpenAirway [Internet]. 2017. From: http://openairway.org/anaesthesia-foam/. Accessed 17 June 2017.
48. GasExchange [Internet]. 2017. From: http://gasexchange.com. Accessed 17 June 2017.
49. GasDoc [Internet]. 2017. From: https://gasdoc2857.wordpress.com. Accessed 17 June 2017.
50. Propofology [Internet]. 2017. From: http://www.propofology.com. Accessed 17 June 2017.
51. Virtual Anaesthesia Textbook [Internet]. 2017. From: http://www.virtual-anesthesia-textbook.com. Accessed 17 June 2017.
52. PedsAnesthesia [Internet]. 2017. From: http://www.pedsanesthesia.net/wiki/index.php?title=Main_Page. Accessed 17 June 2017.
53. ANZCA Networks [Internet]. 2017. From: https://members.anzca.edu.au/networks/. Accessed 17 June 2017.
54. The Department of Health. Australia's Future Health Workforce - anaesthesia report [Internet]. 2016. From: http://www.health.gov.au/internet/main/publishing.nsf/Content/B10EC836A6CBDB91CA257FFC001897A1/$File/Anaesthesia%20Report%20Updated.pdf. Accessed 17 June 2017.

It's more complicated than that: Complexity and anaesthesia

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"That science can be overwhelmed by nature's 'messiness' seems like an admission of vulnerability to us – and a bridge to our own" – *Rhonda Roland Shearer*[1].

INTRODUCTION: A COMPLEX TALE

As a group of clinicians we became slightly obsessed, that despite increasing innovation, technology and educational opportunities, outcomes in health are driven by the interactions of the agents within. From the early 1960s, studies have continued to demonstrate the contribution of medical error to human morbidity and mortality[2-10].

Much like Arthur Dent, our paranoia that something was happening in the universe we didn't really understand, proved correct. The fact we are never fully in control, perceive little of our reality and serendipity helped more frequently than we would care to admit, was not paranoia. Descartes' dualism theory, in its simplest form, suggests there are two worlds; the actual world and the one we perceive in our mind. No human being can perceive everything in their reality and be aware of all the influences, on or of, their decisions and actions.

Marylin Bogner stated "There is no evidence in the empirical literature to support the premise that to err is an inherent human trait, rather, that statement is literary[11]". If humans aren't inherently fallible then is it complexity that provides the excuse?

Our journey into philosophy, safety science, cognitive, social, educational and organisational psychology began. We are not experts in this field, or any domain, nor will we ever be. So please indulge us in our mischief, as we briefly describe complexity theory and our first play using one model of complexity in our clinical practice.

SCIENTIFIC THEORY AND NEWTONIAN-CARTESIAN REDUCTIONISM

The philosophical and practical debate of this area is well beyond the scope of this document. However, it is important to introduce this as concept when using complexity in practice.

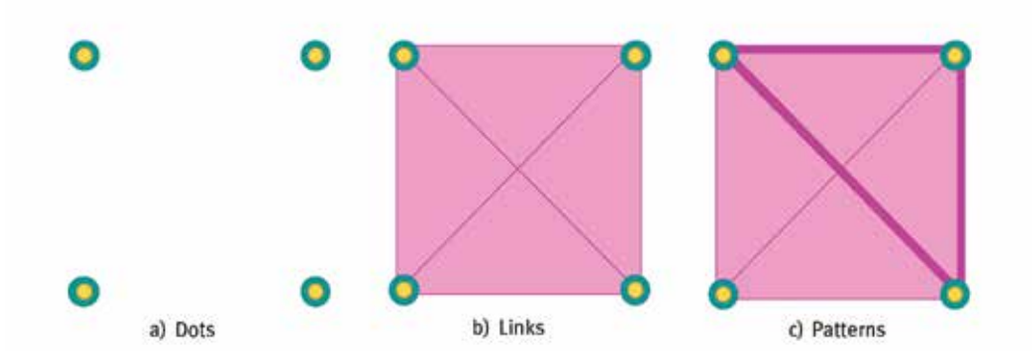
Human beings have always sought to categorise and promote order while reducing chaos. Many mythological, creationist, contemporary, fictional and non-fictional stories are concerned with restoring order from chaos. Agents of disorder are perceived as evil or mischievous, needing to be controlled, cast out or even destroyed. Individuals, cultures and societies find "chaos" so abhorrent that they will accept conditions that are almost universally unacceptable in an attempt to avoid it[12]. Poor decisions are made in attempts to reduce the risk of chaos.

Two titans of the scientific revolution, Isaac Newton and Rene Descartes, developed models of scientific analysis. These models, that are still held by the scientific community and society in general, are to analyse, understand and solve. Attempts to understand the laws of nature, describe them mathematically and predict future events were motivated by the effects of a chaotic and cruel natural world on the human race, when natural events such as weather, plague and famine had massive impacts on human lives. By understanding the laws of nature, we would predict, model and control[13].

In Newtonian-Cartesian thinking there is a perception that given enough time and resources we will eventually understand all the relationships in a complex system. Max Boisot, elegantly and arithmetically showed why this is not the case with his "link the dots" demonstration (figure 1) which has been used to defend those criticised by reductionist models such as the US intelligence community following 9/11[14].

Figure 1. Max Boisot "Dots, links and patterns"[14]

NUMBER OF DOTS	NUMBER OF POSSIBLE LINKS L= N(N-1)/2	NUMBER OF POSSIBLE PATTERNS $P=2^L$
N = 4	L = 6	P = 64
N = 10	L = 45	P = 3.5 Trillion



Dekker eloquently describes the issues with this form of rationality in approaching problems and failure in an increasing complex world[13]. Look for the broken component within a system. If the broken part cannot be found or the parts are too complicated, then further dismantling will reveal the issue. If still not apparent reduce the components further or get more data. Repeat as necessary until the broken part is discovered and fixed. This is Newtonian-Cartesian reductionism.

However, even if we do discover "a broken part", we cease to look further in the understanding of the processes that lead to the broken part. This reductionist model is used across many domains including aviation, NASA, construction, industry and medicine. It is seen in morbidity and mortality meetings, case-based discussions, clinical reviews, root cause analyses and coroner's reports.

The search for a broken part gives us closure on both an individual and societal level. As Dekker states, it has become a demand of society that we find the cause; be it a person, object or abstraction. We seek justice, revenge and change. Furthermore, we struggle when no component is identified as the culprit[13]. Fixing a broken part gives us comfort, but also risks false reassurance. The complexity of the situation that leads to failure is likely to never happen again and may ignore other factors that played a role. Solutions themselves will inevitably change a system through effects that may result in other failures – the law of unintended consequences.

We describe these issues as we have found them to be the biggest barrier in bringing complexity theory into clinical practice. We have conducted cognitive airway teaching in simulation and "hands off" mental modelling in the operating theatre and are repeatedly asked "What should I have done differently?" We have found, to a clinician, a complexity-driven approach is not perceived as helpful in improving aspects of skills or decision-making. The biggest challenge with complexity in clinical practice is to identify and challenge this 300-year-old model of rational thinking.

THE SYSTEMS

Anecdotally and colloquially we describe the systems in which we practice; "today was nice and simple", "no complications today" or "it was chaos". We use them indiscriminately. A system is a network which is coherent and governed by constraints; the constraints create the coherence. System taxonomy itself can be seen as complicated, but in terms of complexity it is possible to characterise them into three different systems:

1. Ordered: fully constrained behaviours with predictable and repeatable patterns. Aggregation is clear (the whole is the sum of the parts). Interventions such as checklists will work.
2. Chaotic: examples include accidents and crises. In chaotic systems, there are no effective links within the system. Chaotic systems can be can be good for innovation, they are not easy to create and the system rarely contains enough energy to sustain itself.
3. Complex: Variable links, influences from external, whole is not the sum of the parts, real-time feedback, can be modulated.

A component, or agent, in a system does not need to be a physical construct (person, group, equipment) but can be abstract such as perceived ideal, values or motivations (culture).

Complicated versus complex

"Complicated" and "complex" are terms used ubiquitously in anaesthetic practice. "Complex" is defined by the Oxford English Dictionary as "not easy to analyse; complicated or intricate" whereas "complicated" is defined as "consisting on many interconnecting parts or elements; intricate". We use these terms interchangeably while not appreciating the differences. Complicated systems are ultimately knowable closed systems. There is a clear boundary where a complicated system begins and ends, for example a continuous flow anaesthetic machine is a complicated system, as is an aircraft[15]. We also use words synonymously, such that "complicated" is used to describe medical "mishaps", for example "the laparoscopic cholecystectomy was complicated by bowel perforations".

Complex systems

Complexity science originated in the study of emergent natural patterns that are self-forming and self-organising and found in many ecological phenomena; snowflakes, termite mounds, bird-flocking.

Complex systems evolve from interactions between their components (agents) and the environment. There are a number of issues with humans acting as agents within systems beyond the scope of this article. They include humans having multiple identities within a system, not being limited by predetermined rules and are not limited by acting on local patterns[12].

However, complex systems have a number common features, that have been described[15,16,17]. They include:

- Open systems: in which it is hard to discern the boundaries of the system and environment. The environment influences the system and the system reciprocates.
- Components: the components of the system interact but are independently ignorant of the system as a whole, and possibly of other components. The behaviour of the system cannot be described by the behaviour of individual components and arises from the changing relationships and interactions of, known and unknown, components.
- Dynamic: the system is greater than the sum of its components.
- Emergence is the phenomena of solutions created by circumstance rather than a solution imposed on the system.
- History: the past influences and is integrated with the present behaviour of the system. It evolves with the system and is irreversible.
- Dysequilibrium: Inputs are needed to maintain the system. Inputs are required to ensure the survival of the system in response to changes in environment and its components
- Non-linear: input and outputs are not equal. Small events can produce large results. Feedback loops can result in multipliers leading to amplification and cascade effects (butterfly effect).

These features explain why more than one description of a complex system is possible and often necessary. Luhman states complex systems contain more possibilities than can be actualised as such they are not fully understandable[18]. This is echoed in David Snowden's Cynefin Framework which states that the inherent uncertainty in complex situations means that there are a number of possible realities. Complex systems may evolve while attempting to understand or describe the situation[15]. It is important to emphasis complexity is a feature of the system not the components.

Dekker describes elements of the features of the complex system that have the ability to result in failure[13]. These features make decision-making in all complex dynamic situations, including healthcare and anaesthesia, challenging. Practitioners in complex systems are vulnerable to the negative aspects of all decision-making frameworks.

CYNEFIN – A CONCEPTUAL MODEL

Cynefin was first developed by David Snowden in 1999, the then European Director of Knowledge Management at IBM, as part of a project to manage intellectual capital[12]. Through a narrative-based action research approach, the project assessed organisational knowledge exchange, decision-making strategies and policies. Cynefin is described as a conceptual challenge to the universal applicability to three basic assumptions that pervade practice, decision making and organisational policy, these being:

1. The assumption of order: past experience and evaluation produces causal links which allows us to predict and model. It results in a sense of "best practice" and that there is a correct or ideal answer.
2. The assumption of rational choice: humans will make rational decisions based on minimising gain and avoiding loss. Individuals or collective behaviour can be managed through education and manipulation of these outcomes.
3. The assumption of intentional capability: the acquisition of a capability indicates an intention to use that capability. The actions of any collective identity thus are a result of intentional behaviour; "we accept we do things by accident, but assume others do things deliberately"[12].

Snowden and Kurtz admitted that while these assumptions may be true in some contexts, they are not universally correct but are the most common tools and techniques used to manage situations.

Cynefin in practice

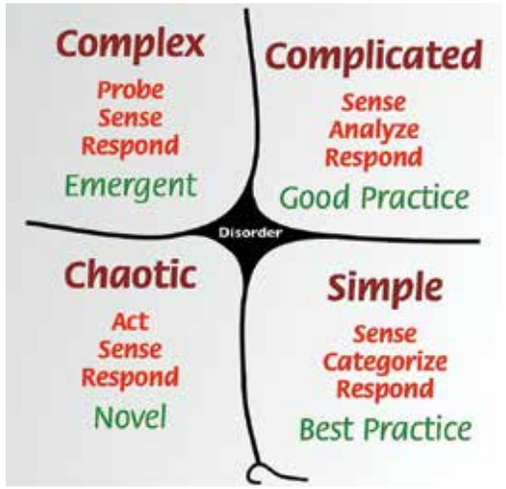
David Snowden, as a passionate Welshman, says that the literal English translation of cynefin being "habitat" or "place" does not embody the Welsh sentiment. He states "a place of our multiple affiliations" is a more appropriate descriptor. Cynefin embodies the idea that we have many roots, many of which we may be unaware of, but still affected by. Human interactions are influenced and determined by patterns of multiple experiences; direct personal and collectively expressed through stories.

Cynefin is not a categorisation tool but phenomenological sense-making framework which supports the decision-making capabilities of those using it. It does not provide logical or empirical solutions and unlike a categorisation system there is not an optimal, preferred or valued domain in which to exist or attempt to achieve.

The framework is used to consider the components, decisions, conflicts and changes in situations of uncertainty. Indeed, one of its advantages is promoting collective sense-making by facilitating shared understanding.

Cynefin has been used in a variety of domains to encourage novel ways of thinking including organisational knowledge management and policy strategy in healthcare, government infrastructure and homeland security as well as immediate operational strategies in situations of urgency including police and special forces teams.

Figure 2. Domains of the Cynefin framework[19]



The Cynefin framework (figure 2) consists of five domains which can divided in to two ordered (obvious/simple and complicated) and two unordered (complex and chaotic) with a fifth central domain – disorder. Within the Cynefin framework knowns and unknowns refer to the societal, organisational or a collective, not the knowledge of the individual. Clearly when using this framework clinically we use it in the context of both the individual and the collective decision-making. We describe the Cynefin framework based on two of the most cited papers[12,17].

Simple/obvious domain

This domain represents the known-known of the ordered side of the framework. Situations are stable with clear causality between components; linear cause-effect. Repeatability allows for prediction and the development of structured and objective best practice models in the form of effective standard operating procedures, policy and protocols. Cynefin suggest that the appropriate response in this situation is to sense (establish facts), categorise and respond by applying best practice (figure 2).

A "boundary of compliancy" exists between the obvious/simple and chaotic domains. Inappropriate assumptions in the simple domain may lead to decreased situational awareness and the evolution of a simple to a chaotic scenario.

Complicated domain

This is the known-unknowns or knowable ordered side of the framework. Causality is not clear, but is present and stable. It requires analysis or intervention, which may be time or resource dependent, to move these to known-knowns. The decision model in the complicated domain is to sense, analyse and respond as guided by experimentation, fact-finding, scenario planning, expert opinion and artificial intelligence. Entrained behaviours are hazardous in this domain; a simple assumption can lead to a false conclusion and error.

Complex domain

The complex domain represents the unknown-unknowns of the unordered side of the framework. The cause-effect relationships are present but the number of agents and connections between them are too great to understand, as demonstrated by the "link the dots" figure shown previously. Patterns may be recognised but are unpredictable, as such more than one "correct" solution may exist.

Retrospectively, patterns may appear logical once the system has stabilised. These patterns may appear to repeat over time, but they cannot be guaranteed as interventions, actions or observations may change the system in unpredictable ways. Cynefin suggests an appropriate probe (scrutiny of the situation), sense (identify facts) followed by safe to fail responses. Probes make patterns more visible which assists in stabilising the situation and aiding with their identification; desirable and undesirable. Multiple perspectives are required to assist in identifying patterns. Techniques associated with the ordered domain including relying on experience based, expert opinion do not work in this arena.

Chaotic domain

This is the domain of the unknowable-unknowns; cause and effect are unclear where no patterns can be recognised. The search for the "answer" is pointless. The aetiology of chaos includes the inappropriate application of best practice models. The system is too unstable to allow analysis and the immediate response is act (to establish order), sense (stabilise) and respond by moving chaos into complexity. Kurtz and Snowden discuss this in terms of an uncanny domain (order is possible but few see or act) and canny operators who can use the system to their advantage (shrewd but safe). Interventions can take different forms – creating constraints that reduce turbulence or using multiple options to create and enhance patterns which moves chaos into complexity. Some disciplines use chaos to create innovative environments.

Disordered domain

Disorder occurs when there is no clarity as to which domain the situation is in. However, it is important to avoid situational categorisation. It is the domain of conflict among decision makers where people will tend to prefer a course of action aligned with their personal preferences; rule-based, research-orientated, data-driven, or networking. It is the arena where individuals submit to avoid chaos. However, collaboration, consensus and negotiation can reduce the size of the disordered domain.

Domain dynamics, boundaries and movement in clinical practice

We do not have the capacity to include descriptions of the dynamics, boundaries and movements with the Cynefin framework. In the following we aim to provide the reader with a sense of our current experience of using this in our clinical practice. We work every day in the complex domain and fall to traditional fail-safe interventions for assumed knowns. Simulation-based and crisis resource management (CRM) training heavily weight toward a complicated environment with fail safe protocols. In contrast Cynefin framework advocate for safe-to-fail interventions in managing complex situations.

The following are examples we have encountered, with a discussion around the dynamics involved.

> **Example 1. Chaotic to complex: peri-arrest patient**
> Patient is in a peri-arrest situation. No obvious cause. Multiple competing priorities; haemodynamic instability, respiratory distress and need for intubation. Patient arrests during initial management.

A chaotic system requires a large amount of energy to maintain. Chaos is usually short-lived unless external influences maintain input. This scenario underlies the clinical situation which is unknowable – there are too many agents and connections in a time-restrained environment. While it appears a full cardiac arrest shows a deteriorating clinical state; a level of control is gained by the cardiac arrest (a recognisable pattern with a known response). We enter a situation which is familiar, through training and experience, to use algorithms, aids and tools.

A "sense of relief" occurs when patient goes from the peri-arrest situation to full cardiac arrest as we unconsciously recognise the movement from the chaotic to the complex situation. We have noted interesting use of language and behaviour skills in both clinical and simulated scenarios when moving between these two domains. Further probes and intervention may guide the clinician further around to the ordered side of framework.

> **Example 2. Order to chaos: airway management**
> A frail elderly lady undergoes an open reduction and fixation of a fractured neck of femur. She has significant gastro-oesophageal reflux disease and is on anti-coagulation for mixed mitral and aortic valve disease. Following intubation her systolic blood pressure falls to 75 mmg and the oxygen saturation falls to 83 per cent. She only partially responds to boluses of vasopressors, maintaining a systolic blood pressure of 80-90 mmHg. Increasing FiO_2 to 1.0 and manually ventilating with normal airway pressures and adequate volumes increases the saturations to 88 per cent.
>
> Help is called for. Right heart failure is considered, presumably due to unappreciated pulmonary hypertension. Multiple possible treatment options are considered. After approximately five to seven minutes in the same clinical situation, a repeated head-to-toe review of the patient reveals a left sided endobronchial intubation. The endotracheal tube is withdrawn and the blood pressure and ventilation parameters return to baseline with no perceived long-term harm to the patient.

This example illustrates the loss of control associated with the boundary between the simple/obvious and chaotic domains; the boundary of compliancy. It illustrates that the situation evolved from the chaotic towards a complex but more stable scenario, though there was still no understanding of the situation. Patterns appear to have multiple possible causes. In this situation, the repeat head-to-toe examination was the probe to sense (unequal air entry) and gave the team the appropriate action.

Retrospective sense-making makes it difficult to understand how such an error could occur with a specialist anaesthetist. All the features of a complex system must be appreciated before condemning. Some agents and interactions may not be easily perceived, or may never be able to be. Components, such as non-technical, emotional and cognitive skills have been, and still are considered by many, to be irrelevant to clinical decision making.

> **Example 3. Anecdotes and stories in formal and informal education – the power of narrative and intention**
> During a teaching session, examples of spinal cord injury from lumbar puncture are given. Anatomy and issues relating to spinal cord termination are discussed. The issues relating to lower insertions sites are also discussed. Following the session there are a number of failures associated with insertion: the opposite of the intention of the teaching session.

During post-failure discussions about location of site of insertion, trainees emphasised concerns about the insertion of spinal needles at or higher than the level of spinal cord termination. While they could recall discussions about low insertion sites they placed higher utility on information related to high insertion site risks. However, the failure to successfully perform and feelings of inadequacy and incompetence became the issue.

"Hangar talk" has been shown to be a useful naturalistic method of teaching, however, its effects on priming and framing must be considered in complex systems where they can cause a trophic cascade of unintended consequences[19]. As such the power of anecdotes and stories in medical education and later decision making should not be underestimated as a feature of complex systems

> **Example 4. Complicated with safe-to-fail: airway management**
> A trainee conducts an intubation for a BMI 41 kg/m^2 patient under ANZCA Level 3 supervision. On the consultant's return to the operating theatre after intubation the trainee states that oxygen levels had decreased to 93 per cent despite an FiO2 of 0.8, and that peak airway pressures are 29 cmH_2O with a tidal volume of 560 mL. On enquiry from the specialist, the trainee lists a number of appropriate causes of desaturation immediately post-induction. The trainee states they feel the most likely aetiology is that the period of apnoea during intubation, patient position and patient habitus have resulted in a degree of atelectasis. The trainee has already increased the positive end expiratory pressure. The specialist prepares to leave the trainee after a discussion of the plan if the patient does not improve.
>
> A copy of the Cynefin framework is on theatre wall. The specialist notices this and takes the framework from the wall. The anaesthetic team proceeds to work through the framework, knowns and unknowns, to aid decision-making, specifically the boundary of compliancy. Endobronchial intubation is considered and the tube length examined: 22 cm at the lip. It is deemed unlikely that the clinical situation is due to tube placement. Does tube length at the teeth determine position tip adequately on all occasions? This is discussed, as is the possibility of tube movement during patient positioning.
>
> The team agree that this is a knowable unknown, either via auscultation or by fibreoptic bronchoscopic observation. Auscultation is performed with decreased air entry noted on the left side. The endotracheal tube is withdrawn to 19 cm at the teeth before air entry becomes equal. Peak airway pressure drops to 23 cmH_2O and the oxygen saturation increases to 97 per cent with a drop in FiO_2 to 0.5. The need for fibreoptic bronchoscopic confirmation is discussed and discounted at this moment, but the need for it to be available in case of any further issue is made by the trainee (a safe-to-fail plan).

The Cynefin framework has been used as a cognitive aid to discuss and plan immediate complex situations including hostage rescue teams and military special forces units. Its use as a cognitive aid, as with difficult airway management or allergy guidelines, helped the team to work through the issue and avoid compliancy affecting decision making. The action to the probe – withdrawing the endotracheal tube to 19 cm – was surprising. It also gave us a framework in which to identify and manage possible changes and develop safe-to-fail plans. In an informal debrief it was discussed that a recently published article concerning the tracheal accordion may have unconsciously acted as an agent in our situation[22].

Finally, to truly consider complexity, we need to ask what events occurred to bring about the presence of a complexity framework, designed by a Welsh ex-senior IBM director, on a wall of on operating theatre in Coffs Harbour to be used by a mediocre UK-trained specialist anaesthetist. That is the beauty of complexity.

CONCLUSION

Complexity has been described in healthcare in terms of organisation, coordination and leadership[22-24]. Its use appears scarce in clinical practice or medical education. Hopefully we have increased the reader's awareness and interest in complexity theory and its possible application to anaesthetic practice.

Medicine has a habit of colonising domains such as safety science (patient safety), decision-making theory (medical decision making) and error management (medical error). The common injunction to interventions proven in other domains from the medical establishment is that the medical sphere is somehow different. We hope that we have shown the possibility of using a tool originally designed for policy strategy, knowledge and organisation management, without modification, in several aspects of clinical practice and education.

While there is an increased awareness of human and cognitive factors, we are not the first to suggest that a "Lake Wobegan" or Kruger-Dunning effect has a larger effect on anaesthetic practice than anyone would like to accept[25,26]. Human factors affect my colleagues, not me. In terms of complexity theory there is no plausible way that can be true; a fact we should be able to admit. We continue to pursue linear Newtonian-Cartesian solutions to clinical issues, but cry "it's more complex than that" when it goes wrong. Can we change practice at such a level? We will see.

REFERENCES

1. Peak D, Frame M. Chaos under control: the art and science of complexity. New York: WH Freeman and Co,1994.
2. Chopra V, Bovill JG, Spierdijk J, Koornneef F. Reported significant observations during anaesthesia: a prospective analysis over an 18-month period. BJA. 1992;68(1):13–17.
3. Chopra V, Bovill JG, Spierdijk J. Accidents, near accidents and complications during anaesthesia. A retrospective analysis of a 10-year period in a teaching hospital. Anaesthesia. 1990;45(1):3–6.
4. Duff RS, Hollingshead AB. Sickness and society. New York: Harper & Row, 1968.
5. Schimmel EM. The hazards of hospitalization. Ann Intern Med. 1964;60(1):100–110.
6. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study I. NEJM. 1991;324(6):370–376.
7. Brennan TA, Hebert LE, Laird NM, Lawthers A, Thorpe KE, Leape LL, et al. Hospital characteristics associated with adverse events and substandard care. JAMA. 1991;265(24):3265–3269.
8. Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. Med Care. 2000;38(3):261–271.
9. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The quality in Australian health care study. MJA. 1995;163(9):458–471.
10. Donaldson L. An organisation with a memory. Clin Med 2002;2(5);452–457.
11. Bogner, MS. Stretching the search for the why of error: the systems approach. J Clin Eng. 2002;27(2):110–115.
12. Kurtz C F, Snowden, DJ. The new dynamics of strategy: sense-making in a complex and complicated world. IBM Syst J. 2003;42(3):462–483.
13. Dekker, S. Drift into failure: from hunting broken components to understanding complex systems. Farnham, England: Ashgate, 2011.
14. Boisot, M. Connecting the dots: from data processing to pattern processing. Omnipedia. 2004;6:13.
15. Dekker S, Bergström J, Amer-Wåhlin I, Cilliers P. Complicated, complex, and compliant: best practice in obstetrics. Cogn Technol Work. 2013;15(2):189–195.
16. Cilliers P, Spurrett D. Complexity and post-modernism: Understanding complex systems. London: Routledge, 1998.
17. Snowden DJ, Boone ME. A leader's framework for decision making. Harv Bus Rev. 2007;85(11), 68-76, 149.
18. Luhmann N. A sociological theory of law [translated by: Elizabeth King and Martin Albrow]. London: Routledge, 1985. p. 63.
19. Wikipedia. Domains of the Cynefin framework [Internet]. 2011. From: https://en.wikipedia.org/wiki/Cynefin_framework#/media/File:Cynefin_framework,_February_2011_(2).jpeg. Accessed 27 September 2017.
20. Kearns SK, Sutton, JE. Hangar talk survey: using stories as a naturalistic method of informing threat and error management training. Hum Factors. 2013;55(2):267–277.
21. Herway ST, Benumof JL. The tracheal accordion and the position of the endotracheal tube. Anaesth Intensive Care. 2017;45(2):177–188.
22. Wikström E, Dellve L. Contemporary leadership in healthcare organizations: fragmented or concurrent leadership. J Health Organ Manag. 2009;23(4):411–428.
23. Plsek PE, Greenhalgh T. Complexity science: the challenge of complexity in health care. BMJ. 2001;323(7313):625–628.
24. Matlow, AG, Wright JG, Zimmerman B, Thomson K, Valente M. How can the principles of complexity science be applied to improve the coordination of care for complex pediatric patients?. Qual Saf Health Care. 2006;15(2):85–88.
25. McIntosh CA. Lake Wobegon for anesthesia… where everyone is above average except those who aren't: variability in the management of simulated intraoperative critical incidents. Anesth Analg. 2009;108(1):6–9.
26. Kruger J, Dunning D. Unskilled and unaware of it: how difficulties in recognizing one's own incompetence lead to inflated self-assessments. J Pers Soc Psychol. 1999;77(6):1121–1126.

Management

Informed consent in the age of peri-operative medicine: Is it possible?

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INTRODUCTION

Increasing demands of throughput pressure, greater complexity of surgery and older patients with multiple medical problems have required a response as to how we provide anaesthesia and surgical care. The concept of perioperative medicine is emerging as both a philosophy and a pragmatic approach to redesigning care around the needs of the patient in a truly holistic sense. The underlying concept is one of continuity based on recognising and managing the specific requirements and individual needs of patients as unique individuals. Entirely new concepts with attendant fields of clinical practice and research are evolving, including "frailty", "pre-habilitation" and "patient-reported outcomes". At a practical level, whole new specialties of peri-operative medicine and protocols for enhanced recovery after surgery are becoming the norm across a range of subspecialties[1,2]. The typical models that have emerged consist of multidisciplinary teams, including anaesthetists, internal medicine specialists, surgeons, geriatricians, physiotherapists, and dietitians, among others. Increasingly, the direct engagement of the patient's primary care physicians will also assume greater importance in these processes as we move from the focus of surgery being what the acute hospital wants to do to patients, versus what the patient and resource providers want from our healthcare system as a way of optimising overall health outcomes.

Within this new paradigm of organised care delivery, there are many challenges for each of the team members. Role delineation around such traditional tasks of acute pain management and drug and fluid prescribing are being revisited and there are entirely new areas such as oversight of fitness training and health optimisation pre-surgery which have had no traditional custodians. A number of questions arise: who will have the discussion around the merit of having a surgical intervention or not in the context of the potential adverse impact on overall quality of life? Is anyone discussing and documenting those important factors in the patient's life that may be impacted by the stay in hospital that are not on the standard list of potential complications? And in the event of something going wrong, who in the team is going to be held accountable for what was said or not said should there be a mismatch between the patient's expectations and the outcome? More importantly, who listened to what those expectations were in the first place? In this context, the concept of informed consent becomes something more than a pre-operative recitation of potential complications. It is a more focused and individualised process that requires all members of the healthcare team to have a common understanding of what the patient views as important at each phase of the journey from initial referral, through preoperative workup, inpatient stay and resumption of daily life.

It is very clear that central to the success of this model of care is effective communication. This applies not only to that between an increasingly diverse group of healthcare providers each with their own jargon and mental models, but also for each member of the peri-operative team with the patient and their support network. Content must be consistent and at all times cognisant of the specific needs of each individual patient. Staying on message requires a straightforward generic skill set which each member of the team can use which incorporates the core quality of effective listening to what the patient is saying, not only in terms of the content but the underlying emotional and psychological drivers. This paper presents a brief summary of the concept of informed consent and then one such model which may be helpful in providing the perioperative team with a simple and relevant tool for effective communication.

INFORMED CONSENT

Over the past two decades there has been increasing demand by regulators and medico-legal forces to impose ever-greater complexity through the introduction of exhaustive checklists, and protocols. The recently published guidelines on informed consent of the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and in some jurisdictions in Australia are illustrative of this philosophy, in which a seemingly endless list of things that might possibly go wrong must be discussed and documented pre-operatively[3]. This approach has four significant problems: 1) it fails to address individualised priorities, 2) it can create, or exacerbate, information anxiety through content overload, 3) when negative communications are presented they can have nocebo effects with the potential to adversely affect patient perceptions, emotions and behaviour, and 4) it does not in practice absolve the healthcare provider from any future claim of negligence should something go wrong, just because someone said it could happen. Collectively, these elements seem counter to the fundamental principle of medical practice which still remains primum non nocere, first, do no harm. It would appear that the interpretation of "harm" has to a large degree been hijacked by forces which have focused entirely on technical misadventure and essentially ignored the harm that is done to people who are unnecessarily alarmed or confused by the provision of information that is of little or no relevance to them.

The recent Montgomery case in the United Kingdom[4] has been cited as supporting the view that the process of providing information about medical complications in some way reduces the likelihood of successful litigation[3], i.e. it constitutes the creation of a form of waiver for any future action should something go wrong. This interpretation has been directly rejected by numerous jurisdictions, including in the United States which is generally perceived as a highly litigious environment. As one example, a recent ruling of the Supreme Court of Missouri, found that the provision of informed consent as evidenced by a signed consent form was not only irrelevant, but in fact was at risk of confusing the jury. It was the fact of the injury itself and the standard of care being established as being below an acceptable standard that were important. Indeed, the court noted that its ruling was consistent with other similar higher courts as follows, "This Court joins the chorus of other state supreme courts and holds that evidence of alleged informed consent is irrelevant and can only mislead the jury in a medical malpractice case based on negligent performance of care and treatment[5]."

This interpretation reinforces the principle that the most effective component of risk management is in fact good quality clinical care. Simply providing a list of things that could go wrong to someone is no defence and may lead the practitioner to the false conclusion that they are safe from litigation as any complication that subsequently occurs has been pre-empted. The provision of information then becomes relevant where the individual patient has an express wish to proceed or not with a medical intervention based on an adequate discussion of the issues of value and relevance to that individual.

These considerations are further complicated by the legal concepts of "material risk" and the somewhat challenging notion of the "reasonable person". Material risk is one that a reasonable person would wish to know in that particular patient's circumstances. This clearly strikes at the nature of defining what is important on an individualised basis. We also question whether it is appropriate to define a "reasonable person" as this will always be idiosyncratic, and open to speculation or even abuse. Secondly, even if one accepts that a reasonable person can be identified, patients cannot always be expected to behave in a reasonable fashion, or think logically, when ill, stressed or distressed. A "reasonable person" may have little capacity to appreciate future realities until actually presented with the situation, such as the person refusing blood products until they are actually about to die.

These complexities invite the need to find a simple and effective means of reaching a shared understanding.

LAURS OF COMMUNICATION

Effective interactions can be seen to conform to the LAURS of communication:

- Listening reflectively
- Acceptance
- Utilisation
- Reframing
- Suggestion

These LAURS of communication are an easy structured way to remember the key concepts of effective therapeutic communication when our usual strategies or words are either not working or not coming to mind easily. The application of the LAURS concept may occur as individual components or as a whole.

Listening reflectively

The three steps to improving communication skills:

Step 1: Listen

Step 2: Listen

Step 3: Listen

What is reflective listening?

Learning how to teach and utilise communication more effectively in clinical practice requires one skill above all others, namely to listen[6-8].

What are the steps for effective listening?

1. Ensure you have heard the words correctly.
2. Note whether you are thinking about your response to the patient rather than listening to what the patient is saying.
3. Resist the temptation to interrupt or second guess what the patient needs to hear.
4. Be comfortable with silence or pauses.
5. Check in to seek clarification regarding your understanding of what the patient means, and their understanding of what you mean (see below).

As doctors, we are used to telling patients what we need them to do rather than listening and responding to their needs. Listening to what patients or colleagues are saying involves more than hearing what one thinks has been said. It is not just about being silent while the patient is talking.

There are four questions to ask when listening reflectively. First, did you hear what was said? Second, did you understand what was meant? Third, does the patient know that he/she has been heard? Finally, does the patient know he/she has been understood? To determine the answer to these questions requires a 'checking in' process. Please note: this takes seconds rather than minutes.

How to listen

Patient: "I don't want to feel anything during the Caesarean. Will I feel any pain?"

Anaesthetist: "By saying 'you don't want to feel anything' does this mean that if you don't feel any pain and are comfortable will that be OK for you?"

Patient: "Yes."

Anaesthetist: "Once the spinal anaesthetic is working, I expect you to be comfortable throughout the procedure but if not, let me know and we will do everything we can to help things proceed as easily and safely as possible for you! Have you any questions or other concerns?"

Listening for content

This concept involves hearing the words. For example, a woman came for elective Caesarean section – for grade IV placenta praevia – with a list of demands, as she had desperately wanted "natural childbirth". Her demands included: "I want three support people in the room during my operation," having been told that it was hospital policy only to have one person in the OR during a Caesarean; "I want the drapes down for the entire procedure", having been told that this was not sterile and wouldn't be allowed for safety reasons. She wanted her partner "to video the procedure and birth" despite video cameras being prohibited in the theatre.

The content of these statements was interpreted by the anaesthetic registrar as having to meet these demands literally or else...!

Listening for process

How could these words be reconciled with hospital policy and safe clinical practice? The answer began by listening not only to the actual words but their meaning and what was really being asked. The woman was in fact asking for some sense of control and choice over what was happening to her and her baby.

Listening and "checking in" for meaning

For this woman, the meaning of the various statements began to be understood by gaining patient rapport. The first step was accepting the importance to her of having any concerns and wishes addressed as fully as possible in the context of her and the baby's safety.

"I want three support people in the room during my operation." When the woman was asked what the role of each person was, she said that she wanted her partner to "see the baby being born", and her two best friends to be with her to "provide support" through the operation.

These requests were addressed by asking: "Would it be OK if one friend was with you for part of the operation and the other could take over at a time you decided was best for you?" It transpired that the partner did not want to be in the operating room and the woman was informed that "he could still be there to see the baby being born" as there was a glass partition where he could observe the baby being born.

When asked why she wished the drapes to be down she replied that she wanted this so as "to see the baby being born". This was easily addressed as this is standard practice and she was informed that as soon as the baby was about to be born, "we will lower the drapes for you so that you can see the baby being born". Finally, she was informed that as many still pictures as she liked could be taken by her partner or support person. There was no further mention of video.

Acceptance

Acceptance of another person's alternate reality is sometimes a difficult concept for anaesthetists to grasp. It is the concept of being open-minded and having a non-judgmental attitude to other people. This can be a hard, philosophical issue, especially if the patient's beliefs run counter to those of the anaesthetist and seem illogical or even stupid. There is little point arguing with patients logically if they are stressed or distressed, as their responses are primarily subconscious. They are frequently unable to accept reason or logic at this time.

Patients may present to the anaesthetist with behaviours and perceptions which run counter to our own beliefs and experiences. Take for example patients with tattoos and body piercings who state that they have a needle phobia. One might be tempted to dismiss the patient's concern by saying, "We'll only use a small needle and in any event the tattoos and piercings would have been much more painful! So don't worry, you'll be fine", or "There is nothing to worry about". Such statements invariably are unhelpful as there is disparity between the anaesthetist's and the patient's perception of the experience. Acceptance of alternate realities is a fundamental prerequisite for communicating effectively and is a core communication skill when attempting to gain patient rapport. In this example, the anaesthetist by accepting the patient's reality of having a severe fear of needles can then explain strategies to finish the procedure as safely and comfortably as possible taking into account this issue. The concern can be addressed by saying something like, "There are lots of strategies we use in this situation that can be helpful so you can feel more relaxed about this – is that OK?" or "A lot of people with this problem have concerns. However, they are usually surprised how much easier it is finishing up placing the drip than they had previously thought."

Another example is the patient who may have an "irrational" fear that they will certainly die if they have an anaesthetic. Acceptance of alternate realities is a fundamental prerequisite for communicating effectively and is a core communication skill when attempting to gain patient rapport. In this example, the anaesthetist invariably has usually accepted that there is some element of risk during anaesthesia. It is implicit in the pre-anaesthetic check of drugs and equipment that, no matter how simple the procedure or healthy the patient, an adverse life-threatening event can occur at any time. However, one might be tempted to dismiss the patient's concern by saying something like, "Don't worry, you'll be fine", or, "There is nothing to worry about". Such statements invariably are unhelpful as there is disparity between the anaesthetist's and the patient's perception of risk. The concern can be addressed by saying something like, "Is there anything I can do to help you feel more relaxed about this?" or "A lot of people have these concerns. However, you are fit, the surgery is minor, and my job is to ensure your safety and comfort in a way that allows you to relax and wake up in recovery surprised that it is a little easier than you might have thought." A truism would be that the patient would not be advised to undertake the surgery if it was not believed that the benefits outweigh any risks. In contrast, in a patient with a recent myocardial infarction having a Whipple's procedure, the realities of anaesthetist and patient will be congruent and it is therefore much easier to accept the patient's concern. Acknowledging the same concern and engendering empathy is harder when there is discordance between the patient and anaesthetist or the surgeon and anaesthetist's differing realities, as this frequently leads to miscommunication and conflict. This is particularly so when there is a strong emotional attachment to a belief. Anger is usually a demand for recognition of emotions, and the patient or a colleague may be indirectly expressing that they do not feel that they have been listened to or their viewpoint appreciated. When appropriate, venting of the patient's emotions can be encouraged. The anaesthetist's emotions may also need recognition as a subconscious response such as anger or frustration. Once recognised, the anaesthetist can interrupt a usual behavioural pattern and make a choice as to whether to continue with their own current behaviour or not. This break in the normal pattern of one's own subconscious behaviour allows logical consideration as to whether some other more useful communication strategy could optimise patient care (a third reality).

Awareness, mindfulness, emotional intelligence, self-reflection and taking responsibility for communications that are not going well, are all fundamental techniques that can be used to gain mastery of the challenging situations that anaesthetists increasingly find themselves confronted with.

A temporary acceptance of the patient's beliefs or emotions, no matter how strange they appear, allows the anaesthetist to gain rapport and then move on to a situation that is more therapeutic for the patient. For example, a patient in established labour was shouting at the anaesthetist as he entered the room. She stated that there was no way she could sit up to allow epidural catheter placement for analgesia. The dialogue continued:

Woman: "I can't sit up. It's too painful!"

Anaesthetist: "That's OK, you don't have to sit up during this contraction but in a moment when you are ready for the epidural to be placed as comfortably and as quickly as possible, you will find you can do this."

Woman: "I can't, I can't, I can't!"

Anaesthetist: "I know you can't just now, but knowing that the epidural can be working for you sooner, you will find you can sit up and stay still as soon as you are ready to feel comfortable."

The anaesthetist acknowledges the present reality of the patient's inability to sit still and, has utilised an alternate reality focusing on the patient's goal of comfort. In addition, the anaesthetist is expressing a belief in the patient that she can do more than she thinks she can in the very near future, within one or two contractions, without her necessarily appreciating consciously this future reality herself until she finds herself doing it!

Another example is the pain patient who is severely distressed and expressing pain, despite having no obvious organic basis or diagnosis for being in this position. Unless we accept the patient's reality of being in pain and believe that what they are saying is true, we are not allowing ourselves the opportunity to engage with them and treat their problem.

Utilisation and speaking the patient's language

Our perceptions are frequently communicated in the form of sensory perceptual language, usually of the three main senses: visual, kinaesthetic, and auditory. Visual language incorporates phrases such as "I'm not looking forward to my surgery" or "I see what you mean". Kinaesthetic phrases include "It doesn't feel right" or "It's like a weight off my shoulders". Examples of auditory language are "I hear what you say" or "That sounds clear to me." Much less commonly, gustatory or olfactory language is utilised, such as "It leaves a bad taste in my mouth" or "It doesn't smell right."

Utilising the patient's perceptual world is likely to increase rapport and allow the anaesthetist to reframe negative perceptions and experiences. For example, a patient might say that he/she is not looking forward to an anaesthetic and is worried about not waking up. Rather than respond with a platitude such as, "Of course you will wake up" or "It's very unlikely that will happen", the anaesthetist can use this perceptual language and reframe it into something useful such as, "You may not be looking forward to the anaesthetic but you can look forward to waking up in recovery."

Developing an ear for patients or colleagues preferred communication modality and style can lead to engagement with other people in a way that increases the chances of being heard and understood. Almost anything a patient or colleague says or does can be utilised therapeutically. The only limiting factor here is the anaesthetist's imagination.

For example, when the anxious patient asks whether you will be in theatre there all the time or asks: "How will you know if I'm asleep?" These concerns can be utilised by explaining all the different types of monitors in some detail and then utilising the experience. For example:

Utilising patients' concerns

Patient: "How will you know I'm OK?"

Anaesthetist: "When you are lying in the operating room we will position a number of monitors to ensure you are as safe and comfortable as possible throughout the procedure, for when you wake up in the recovery room. For instance, we will place some ECG stickers on your chest and a blood pressure cuff on your arm to monitor your heart, a pulse monitor on the finger to check the oxygen level in the blood. Knowing how closely we are looking after you will help you relax."

Utilising patient strengths

All patients will have strengths and abilities, qualities and experiences that have been used effectively in other contexts such as at work, at school or playing sports. These can be utilised and emphasised in the context of the challenge anaesthesia and surgery represents. If patients have had good or successful experiences while in hospital previously, these can be focused upon. For example, the patient who has managed to mobilise effectively on the day of previous similar surgery. This success can be encouraged by saying that now the patient knows what to do for this success to be repeated.

Reframing

The reframe is a concept whereby a patient's concern that is generating a thought, perception or behaviour that is unhelpful, for example, anxiety is reframed in a way that generates a thought, perception or behaviour that is helpful or therapeutic, for example, relaxation. If an anxious patient is stating that he is very stressed that there will be "too many people" in the operating room, the anaesthetist can reframe this concern by utilising this perception. A reframe can be communicated that "Every person in the operating room will have a job to ensuring your safety and comfort". Then, no matter how many people there are in the room the patient can be reassured that there will be only enough people to do their job and no more.

Principles of suggestion

Suggestions are verbal or non-verbal communications that lead to subconscious, non-volitional responses in mood, perception or behaviour. Patients and people generally are in large part subconscious beings. At times, the ability of people to respond to communications in a subconscious way is termed suggestibility. Suggestibility increases when patients are highly anxious, distressed or in pain. It also increases in pregnancy[9,10] and is higher in the paediatric population[11]. We tend to focus on and associate with what is being suggested. This is highly

relevant in the recovery room after surgery, when the patient is repeatedly asked what their pain scores are. This encourages an association of the surgery with injury, rather than the healing process of recovery.

The importance of expectancy and how positive expectancy can enhance the anaesthetic experience is a highly relevant communication tool in the practice of anaesthesia.

Positive suggestion
A positive suggestion is a communication that elicits a positive therapeutic response. For example: "Most people find it is more comfortable than they thought" is an indirect positive suggestion to elicit the perception of comfort.

Negative suggestions
Lang et al have shown that the ubiquitous use of language with negative emotional content is likely to increase patients' anxiety, pain and distress[12]. There is increasing evidence that the current paradigm for the delivery of informed consent is not working in the best interests of patients or their carers.

CONCLUSION

Words can hurt but they can also help. Using LAURS as a basis of informing patients in a way that is therapeutic to them is likely to enhance their anaesthesia care and focus on aspects that are important to the individual patient in front of the anaesthetist. As we move further into the world of peri-operative medicine, communication skills will be increasingly important. One particular challenge will be to ensure that the peri-operative care team communicates with each other and has the capability to listen to the individual needs of patients.

REFERENCES

1. Rawlinson A, Kang P, Evans J, Khanna A. A systematic review of enhanced recovery protocols in colorectal surgery. Ann R Coll Surg Engl. 2011;93(8):583–588.
2. Melnyk M, Casey RG, Black P, Koupparis AJ. Enhanced recovery after surgery (ERAS) protocols: time to change practice?. Can Urol Assoc J. 2011;5(5):342–348.
3. Yentis SM, Hartle AJ, Barker IR, Barker P, Bogod DG, Clutton-Brock TH, et al. AAGBI: consent for anaesthesia 2017: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia. 2017;72(1):93–105.
4. Montgomery v Lanarkshire Health Board. UKSC 11 [Internet]. 2015. Available from: https://www.supremecourt.uk/decided-cases/docs/UKSC_2013_0136_Judgment.pdf. Accessed 30 March 2017.
5. Wilson v Patel. MOSC No. SC95890 [Internet]. 2017. Available from: https://www.courts.mo.gov/file.jsp?id=112955. Accessed 28 July 2017.
6. Cericola SA. Communication skills: the art of listening. Plast Surg Nurs. 1999;19(1):41–42.
7. DiBartola LM. Listening to patients and responding with care: a model for teaching communication skills. Jt Comm J Qual Improv. 2001;27(6):315–323.
8. Willen J. The skills of listening: a review of helpful communication techniques. Am J Hosp Care. 1986;3(4):39–41.
9. Tiba J. Clinical, research and organisational aspects of preparation for childbirth and the psychological diminution of pain during labour and delivery. Br J Exp Clin Hypn. 1990;7(1):61–64.
10. Alexander B, Turnbull D, Cyna A. The effect of pregnancy on hypnotizability. Am J Clin Hypn. 2009;52(1):13–22.
11. Olness K, Gardner GG. Some guidelines for uses of hypnotherapy in pediatrics. Pediatrics. 1978;62(2):228–233.
12. Lang EV, Hatsiopoulou O, Koch T, Berbaum K, Lutgendorf S, Kettenmann E, et al. Can words hurt? Patient provider interactions during invasive procedures. Pain. 2005;114(1–2):303–392.

The anaesthetist as a leader and manager: Priorities, dilemmas and solutions

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INTRODUCTION

Development of professional and leadership attributes by clinicians is essential for the promotion of quality patient services and care[1-4]. Establishing an understanding of organisational and management issues provides insight into the conflicting priorities of hospital executive, managers, clinician managers and clinicians. Similarly, executive and managers must appreciate the importance of engaging clinicians in decisions that affect service delivery and patient care. This article will examine principles of, and evidence supporting, the professional aspects of anaesthetic practice, the conflicting priorities of clinicians and managers and the importance of clinical engagement in organisational decisions and management.

BACKGROUND

In 2004 the Australian and New Zealand College of Anaesthetists (ANZCA) introduced professional attributes and practice modules into the anaesthesia curriculum including: medical expert, communicator, collaborator, manager, health advocate, scholar and professional[5]

The 2013 ANZCA curriculum defines these competencies as “Roles in Practice” and outlines learning outcomes within each domain of the framework[6]. This is underpinned by the CanMEDS framework, developed by the Royal College of Physicians and Surgeons of Canada in the 1990s, its most recent revision being in 2015[7].

The recently released ANZCA guide, *Supporting Anaesthetists’ Professionalism and Performance: A guide for clinicians* expands on these roles indicating behavioural aspects that are consistent with each domain (table 1)[8]. The Royal Australasian College of Surgeons (RACS) and the Royal Australasian College of Physicians (RACP) introduced performance frameworks in 2008 and 2011 respectively[9,10]. This indicates a growing appreciation of the requirement for an understanding of the professional attributes and behaviours that are considered essential for competent medical practice.

Competence in these areas provides a framework for clinical practice as well as equipping clinicians with insight to deal with broader institutional management issues and regulatory frameworks. The clinician as a manager is a role that is often perceived as unpalatable by those who choose to enter medicine to be clinicians[11], however they are not mutually exclusive. These roles are important at many levels:

- Day-to-day clinical anaesthetic practice.
- Responsibilities in anaesthetic department portfolios.
- Participation in hospital organisational and safety and quality initiatives.
- Head of department.
- Anaesthetists with executive roles within hospitals and health services.
- Sole specialists in rural and regional hospitals without ANZCA input.
- Insight into industrial relations and conflicts.
- Development of leadership skills.

Table 1. ANZCA Roles in practice and patterns of behaviour[8]

ROLE	PATTERN OF BEHAVIOUR
Medical expert	Demonstrating medical skills and expertise
	Monitoring and evaluating care
	Managing safety and risk
	Proactively making decisions
Communicator	Developing rapport and trust
	Eliciting and synthesizing information
	Discussing and communicating options
	Effectively communicating information
Collaborator	Documenting and exchanging information
	Establishing a shared understanding
	Playing an active role in clinical teams
	Working to prevent and resolve conflict
Leader and manager	Setting and maintaining standards
	Leadership that inspires others
	Supporting others
	Promoting efficiency and cost effectiveness
Health advocate	Caring with compassion and respect for patient rights
	Promoting health and responding to patient needs
	Responding to community and population needs
	Demonstrating cultural awareness and sensitivity
Scholar	Showing commitment to lifelong learning
	Facilitating the learning of others
	Critically evaluating and applying information
	Fostering scientific inquiry in anaesthesia
Professional	Having awareness and insight
	Observing ethics and probity
	Maintaining health and well-being
	Adhering to regulatory framework of practice

FRAMEWORKS

Frameworks provide structure, guiding principles and a common language to support and develop skills and competence in practice[12]. The emergence of frameworks internationally for the inclusion of non-technical skills into medical education for both medical students and specialist training is a development that acknowledges the importance of these skills for safe patient care. Individual frameworks exist in many countries for leadership, for performance and for inter-professional collaboration[3,13,14]. Considering the crowded curricula for medical and specialist training the need for an integrated framework incorporating all of these attributes must be considered.

Health LEADS Australia is the leadership framework that has been adopted by Health Workforce Australia[15]. It outlines the capabilities that are required for leadership development: Leads self, Engages others, Achieves outcomes, Drives innovation, Shapes systems, while emphasising that all health workers should strive to achieve these capabilities with a move to distributed leadership in health. The ANZCA *Professionalism and Performance Framework* encourages this by describing a desired behaviour as "(recognising) the benefits of shared leadership models where all members can assert their individual leadership qualities"[8(p11)]. This is a shift away from earlier leadership models where "heroic" leaders made and implemented decisions either by not recognising the importance of engaging clinicians or by not being able to engage them[11]. Contemporary leadership and management in health has shifted from hierarchical models with attempts to promote clinician engagement[12].

MANAGERS AND LEADERS

Management and leadership are terms that are often used together although there are differences between the functions and attributes of each role[16], recognising that there is much debate as to how to differentiate these terms[17]. However, effective managers need leadership skills. Anaesthetists should be encouraged to develop leadership and management skills and become competent in the behaviours set out in the ANZCA *Professional and Performance Framework*[8] acknowledging the evidence that this promotes improved levels of quality care and patient safety and better organisational outcomes[1,17,18]. It is recognised that not all anaesthetists will become managers as involvement in management roles tend to be resisted by clinicians[11].

The clinical anaesthetist has a role as a leader and manager in daily practice and service development and some clinicians will have portfolios such as supervisors of training, administration and rostering, safety and quality, drugs and therapeutics. Others may undertake the transition into roles that have greater leadership and management responsibilities, while maintaining part-time clinical duties. These roles include head of department and directorate leadership responsibilities within the hospital executive team.

THE CLINICIAN MANAGER

In Australia in the 1990s hospitals were restructured into clinical directorates providing opportunities for clinicians to have a greater role in hospital management[19]. While there is some debate as to whether this restructuring has increased efficiency[20], engagement of clinicians in organisational decisions has been shown to have a positive effect on organisational outcomes including patient safety and financial performance[21,22]. Braithwaite and Westbrook demonstrated that this desired effect of clinical engagement has not necessarily been achieved among doctors, with a perception that the development of clinical directorates has created greater division between doctors and managers[23]. Negative attitudes towards clinicians in management roles develop as they are perceived by their clinical colleagues to be more focused on budgetary matters than quality care[24,25].

The transition from clinician to manager, whether as a "hybrid" clinician manager or in a non-clinical capacity has the advantage of affording the opportunity to influence system change, while providing some challenges. These challenges include the different tasks, roles, relationships and skills that are required in management settings. In 1993 Prideaux undertook a qualitative study investigating the difficulties associated with the clinician to manager transition[26]. He concluded that there was some "surprise about aspects of the new job (and that) most of the surprises were disappointments"[26(p47)]. He suggested that facilitation of the transition could be improved with:

- Supportive organisational systems.
- Supportive colleagues.
- Formal courses in management.
- Supportive groups.

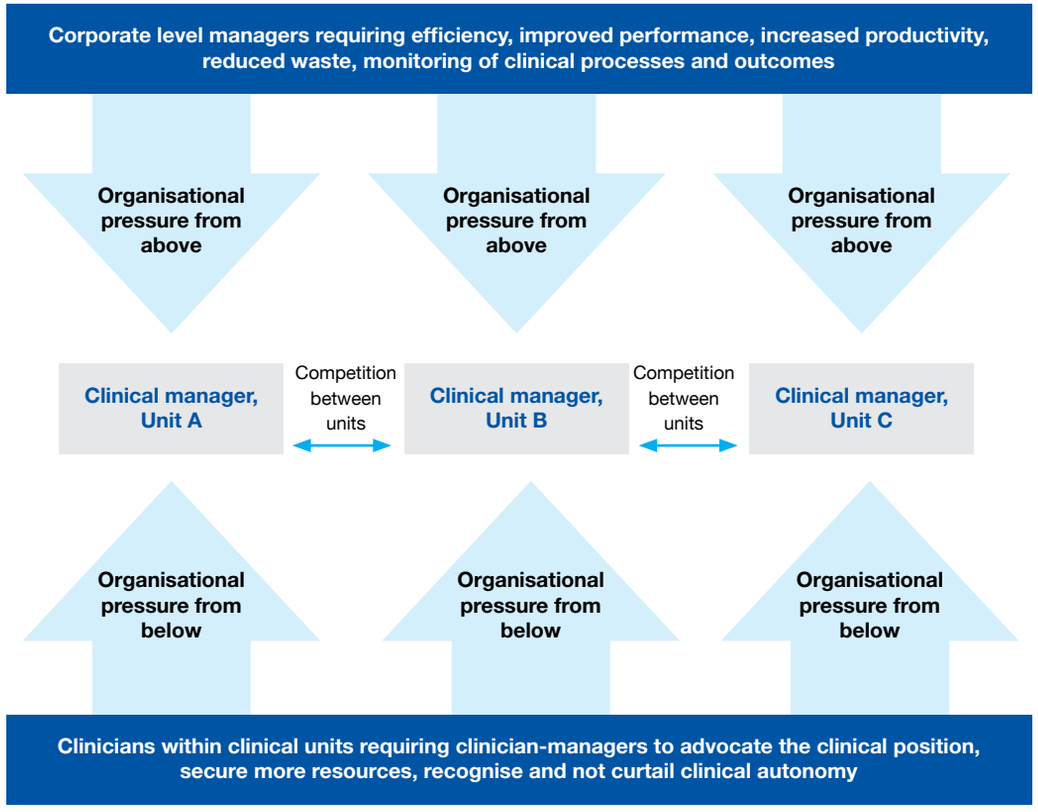
Despite the contemporary shift to distributed leadership, and the recognition that clinicians have a significant role to play in management, the health management literature continues to highlight and affirm the ongoing challenges[24,25,27-32]. Chan et al propose that there should be international collaboration to introduce leadership training into medical curricula, for both everyday leadership competencies in clinical practice and as preparation for leadership roles[3]. A conceptual paper published by Kippist and Fitzgerald highlighting the differences between manager and clinician roles arose out of their representation on an expert panel at the 2008 ANZCA Annual Scientific Meeting in Sydney where hybrid clinician managers expressed concern at their lack of training for and reluctance to take up managerial roles[29]. The need for succession planning to prepare clinicians for management roles has been advocated with a view to attracting clinicians who have enthusiasm for the role[33]. Mintzberg argues that in order to be an effective manager and leader there must be both a "will" and a "zest" to manage[34]. The reluctance by clinicians to enter into management roles along with their lack of preparation and conflicting priorities must be addressed in order to enhance clinician engagement and improve health care management[33].

Training and competence in leadership and management along with the other roles described in professional frameworks, such as collaborator and communicator, are not sufficient to address the conflicting priorities of clinicians and managers. An understanding of the structural, economic and political context in which health service delivery decisions are made is required to address the conflict that is associated with the clinician manager role. A study undertaken in Norway, Canada and Uganda demonstrated that many clinicians lacked knowledge of priorities that were set at government or hospital executive level[35].

CONFLICTING ROLES AND PRIORITIES

The rising cost of healthcare precipitated by improved technology and treatments, the ageing population, increasing community expectations and a broadening in the number of treatable diseases continues to put pressure on hospital budgets[36]. Despite health funding reforms and restructuring of hospital management Australian hospitals continue to suffer from budget and performance issues[33,36]. Inevitably clinicians in management roles whether as clinical directors, heads of department or other management portfolios will have the responsibility of assisting with budgetary compliance. This, along with the need to ensure compliance with other imposed regulatory requirements creates an environment in which there may be conflict between the clinician and managerial role[28]. The complex relationships in which clinician managers are engaged include demands from the organisational executives, the expectations of the clinicians within their unit and the requirement for collaboration with other units[28]. These complex relationships are summed up in figure 1. In addition to this, clinicians in dual roles tend to see themselves as clinicians primarily, with the managerial role as secondary[33].

Figure 1. Schematic diagram of some lateral and hierarchical power and relationship issues facing clinician-managers[28,37]



Prideaux lists categories in which there are differences between the responsibilities of clinician and of manager[26]. These include tasks, role, relationships, orientation, decision processes and skills. The ambiguities inherent in the dual role of clinician and manager are summarised in table 2.

Table 2. Paradoxes of the hybrid clinician-manager role[38]

CLINICAL ROLE	MANAGERIAL ROLE
Clinician	Manager
Professional language	Management language
Medical career	Management position
Clinical values	Management objectives
Individuality	Collaboration
Clinical colleague	Clinician manager
Clearly defined role	Lack of role clarity and structure
Clinical qualifications	Lack of management education
Full/part-time position	Part-time position
Medical community	Management community

The challenge of conflicting priorities that influence decision making and prioritisation are inherent in understanding the nature of the difficulties of the dual clinician and manager role[24]. Tensions that exists between clinicians and non-clinicians in executive roles within the hospital system promote a "them and us" culture and inhibits cooperation[25,39]. This originates from a difficulty in reconciling the practice of healthcare with the business of healthcare particularly when setting priorities[29]. Table 3 outlines the conflicting influences on priority setting.

Table 3. Clinician manager conflicts in priority setting

CLINICAL ROLE	MANAGERIAL ROLE
Individualised care	Distributed care
Patient care focus	Budget focus
Practice of healthcare	Business of healthcare
Social focus	Market driven
Quality	Volume
Evidence based	Empirically driven

Individualised versus distributed care

The medical expert role arising from years of medical and specialist training promotes concentration on individual patient care with the desire to provide the best care possible for each patient, whereas managers have a responsibility to ensure that resources are distributed effectively for all patients. Skirbekk et al demonstrated that managers were more concerned with the resources available for future patients while doctors, understandably were concerned about current cohort of patients in their care[24]. This is particularly apparent with the managers' emphasis on throughput to ensure that there are available beds and resources for future patients.

Patient focus versus budget focus

Clinicians seldom consider cost when choosing patient treatment, however, when in management positions they are required to be mindful of budget constraints, show accountability and ensure equitable distribution of resources[24]. This causes tension between the clinician manager and the clinicians with whom they work. The literature on variation in healthcare delivery and low value care suggest a need to address priority setting and reflect on individual practice[36,40,41], but the autonomous nature of clinicians encourages resistance to imposed disinvestment and attempts at rationing of resources by managers[42].

Practice of healthcare versus business of healthcare

The responsibility of managers in healthcare to ensure adherence to regulatory requirements and budget considerations tends to put them at odds with clinicians who have an individual patient focus and tend to view management from a clinical rather than organisational perspective[24,43]. The transition from this patient focus to an organisational and strategic focus requires a change in the mindset of clinicians who take up management roles[44]. Mintzberg argues against treating healthcare as a business and suggests that co-operation is required, not competition[45], citing the American experience where the cost of healthcare administration is twice that of

other OECD countries[46]. Contemporary healthcare organisational models, particularly in the context of activity based funding (ABF), promote this business approach to healthcare.

Market driven versus social focus

The growth of neoliberalism has led to the introduction of market forces into healthcare, the theory being that this promotes efficiency[29,47]. However, there is an argument that this leads to an increase in administration costs[46]. An example of the market system is ABF, also known as casemix funding which was first introduced in the US in 1983 and has been adopted by Australia, the UK and several other European countries[48]. Hospitals are paid according to the number of patients they treat based on a unit price, which is weighted according to complexity[49]. The aim of this form of funding is to reduce hospital costs, promote efficiency and transparency, reduce length of stay and promote shorter waiting times[50]. This focus on the patient as a revenue generator for the hospital[50] is at odds with the focus of clinicians who tend to use social worth criteria for prioritising patient care[35].

Quality versus volume

In order to promote the efficiencies that are intended with ABF there is a focus on increased patient throughput and decreased length of stay, although studies that have analysed the effect of ABF on these parameters have been inconclusive[50]. This focus on volume and throughput is perceived by clinicians as detrimental to patient care and could possibly increase the patient readmission rate[24,50]. Skirbekk et al demonstrated that clinicians felt that they were under pressure to spend less time with patients than they believed necessary[24]. The context of this for anaesthetists is that there is perceived pressure from management to minimise preoperative assessment and optimisation, reduce cancellations and encouragement of rapid theatre throughput which may affect patient safety.

While managers also have the responsibility to ensure that safety and quality regulatory requirements are adhered to, the measurable nature of patient throughput, the pressure of budgetary constraints and the requirement to meet performance targets influences the prioritising of activity measures. Moral distress is experienced by both clinicians and managers when faced with prioritising scarce resources[51,52]. It is understandable that those in a dual clinician manager role experience low job satisfaction and problems with commitment to the organisation[53].

Evidence based versus empirically driven

The practice of evidence-based medicine based on randomised controlled trials is the gold standard in the clinical setting[54]. It is recognised that randomised controlled trials are not feasible for the study of clinician manager complexities, but there is a dearth of evidence to guide management practices[28,54]. Where evidence is available, it appears that managers do not often use this to guide their decisions, the main barrier being that much of the research is considered to be irrelevant to their practice[54,55]. Liang et al have developed a framework to support evidence-based decision-making that requires the involvement of government departments, healthcare organisations, professional and training organisations, research institutes and universities[55]. Clearly this would require significant integration of these organisations to translate the evidence into guiding management practices in the domain of resource allocation. Robinson et al demonstrated that when evidence-based frameworks are used for priority setting this promotes transparency and enhanced clinician engagement, although engagement of the acute sector was problematic[56].

THE WAY FORWARD

Having considered the challenges, conflicts and ambiguities faced by clinicians in the complex field of healthcare organisational management, investigation of strategies to mitigate the conflict is essential for ensuring safe and efficient delivery of care. By recognising that those who work in the healthcare sector have a common goal we should ensure that we focus on co-operation rather than differences. The introduction to the ANZCA performance framework for anaesthetists claims that the purpose of this framework is "to assist (anaesthetists) in improving their practice of anaesthesia, perioperative medicine and pain medicine"[8(pii)]. There is, however, a much broader focus within the attributes described in the framework (table 1) and consideration of solutions to the dilemmas described so far will provide some context to this broad focus.

Leadership

Leadership theory has evolved over the past century from one that concentrates on individual traits to current theories of transformational, authentic and collective or distributive leadership that have a more holistic view[57,58]. Contemporary leadership research examines not only the individual traits that are inherent in good leadership, but also the relationships between leaders and followers along with a move towards collective or distributive leadership[58-60].

In healthcare there are benefits to doctors having medical management and leadership positions contributing to the development of clinical directorates as discussed previously[1,34,61]. The doctor manager's authoritative position as a medical expert provides clinical input into the prioritisation of services as well as allowing an interface between non-clinician managers and clinicians[43]. While this requirement for clinicians in management has been acknowledged, it is accompanied by a recognition that heroic leadership in healthcare is outdated.[45] In order for governance of health services to be effective there needs to be distributed or collective leadership, justifying the need to encourage all clinicians to develop leadership attributes[3,60,62]. These leadership attributes are considered essential for day to day clinical practice[3,8] along with the recognition that collaborative leadership and decision-making strengthens the professional bureaucracy with respect to clinician input into organisational concerns[43,60]. The American College of Healthcare Executives has identified leadership development as one of the core domains for promoting a culture of safety in healthcare[63], recognising that safety and quality in patient care is dependent on the broader aspects of healthcare organisational considerations, and are not merely process driven.

West et al, in advocating collective leadership in healthcare in the NHS describe it as a culture in which "responsibility and accountability function simultaneously at both individual and collective levels"[60(p14)]. The promotion of enhanced medical leadership, both in leadership positions and collectively, which in effect encourages engagement of medical staff, has been shown to improve organisational outcomes in the UK[60].

Medical engagement

An engaged medical workforce creates a high performing organisation and safer more productive patient-centred care[21,22]. Medical workforce engagement must be seen as reciprocal, being defined as:

> "The active and positive contribution of doctors within their normal working roles to maintaining and enhancing the performance of the organisation which itself recognises this commitment in supporting and encouraging high quality care"[21(p115)].

West and Dawson include motivation, commitment and satisfaction as characteristics of workforce engagement[64] and this could be used to advantage in ensuring that engagement strategies are aligned with professional goals[43]. These characteristics are more difficult to measure than those used by Spurgeon et al in their Medical Engagement Scale (MES)[21], a tool that has been shown to have a reliable relationship with organisational outcomes in the UK and Australia[17]. Parameters measured in this scale are presented in table 3.

Table 4. Medical Engagement Scale[21(p115)]

Metascale 1	Working in a collaborative culture
Subscale 1	Climate for positive learning
Subscale 2	Good interpersonal relationships
Metascale 2	Having purpose and direction
Subscale 3	Appraisal and rewards effectively aligned
Subscale 4	Participation in decision-making and change
Metascale 3	Feeling valued and empowered
Subscale 5	Development orientation
Subscale 6	Work satisfaction

It is clear from this MES that engagement of the medical workforce requires more than just being involved in decision making. It is necessary to consider the job dimensions that lead to motivation including meaningful work with skill variety[65]. Job design has been shown to influence motivation[66], emphasising the importance of job plans, particularly for clinicians working in the public sector. Annual appraisal of clinicians should be viewed as a meaningful aspect of engagement, not as a "box-ticking" exercise. Effective performance monitoring with goal setting, evaluation of previously set goals and meaningful data-driven feedback is a significant driver of employee engagement[18,22]. Consideration of areas of interest and expertise should be explored to shape job design and work plans as well as identifying opportunities for involvement in service improvement.

Ensuring aspects of engagement are acknowledged requires leadership, not just at executive level, but also within departments to ensure that trusting relationships are developed, staff contributions are recognised, innovation is supported along with helpful feedback and transparent information sharing[60]. This will contribute not only to the performance of the organisation, but will also promote success in the implementation of change and innovation at the organisational level[43,67]. Kippist and Fitzgerald demonstrated that engagement of clinical colleagues by doctors in management positions, mainly at the head of department level, promotes collaboration and assists with change initiatives[43]. However, they advocated for more clarity and definition within the head of department role.

Education

The promotion of the development of leadership skills for all doctors, makes it essential that leadership training, along with inter-professional considerations is embedded in medical training at the undergraduate and postgraduate level[3]. The debate as to whether leaders are born or made continues in the leadership development literature and it is acknowledged that the evidence base for leadership development is lacking[58]. There is an argument, however, that teaching leadership theories promotes leadership development[58]. It is necessary to

distinguish between "leader development" and "leadership development", the former focusing on the individual attributes and competencies required for leadership positions and the latter being more about the process of leadership, the relationships and team influences within this process and the context in which it occurs[59,68,69]. It is in the realm of collective leadership that leadership development for all doctors is promoted, recognising that formal leadership positions require a different focus. Ham states that leadership development for collective leadership "entails refocusing on the education and training of clinicians to achieve a new equilibrium between autonomy and accountability"[4(p1979)].

The admission by doctors in management positions of their lack of preparedness for the task[29,31,33] has prompted the call for formal education of clinicians who enter into management positions along with the introduction of credentialing processes[61,70]. Mintzberg argues that because there are natural leaders in society, leadership and management are not sciences that can be taught[34], but the evidence to support this argument is contradictory[46,58]. Considering that the skill and knowledge requirements for managing within the complex healthcare system are quite different from the clinical domain of doctors, lack of knowledge of systems, budgets, regulatory requirements, management language and policies are barriers to effective management by clinicians[29,33,55]. This, along with the lack of application of evidence-based decision-making and priority setting[55] would support the need for formal training. Considering the reluctance of clinicians to enter into management positions, the "them and us" discourse between clinicians and managers[25] and the unfortunate language around management being perceived as "the dark side"[71,72], succession planning and mentoring must be embedded within management training[33].

Inter-professional collaboration

The need for inter-professional education and collaboration and the breaking down of professional barriers for safe and effective healthcare is recognised internationally[18,60,73,74]. In order for progress to be made in this realm, it is essential to recognise and break down professional barriers between clinical professions and between clinicians and managers, acknowledging that there is a tendency towards "tribalism" within professional groups[75]. The clinician/manager divide needs to be addressed by acknowledging that managers need insight into the professional identity of clinicians, while clinicians need to have some appreciation of the organisational objectives faced by managers. Clinicians in dual roles should be at the forefront of this inter-professional engagement process[43], but the role of all clinicians in this process should not be ignored[76]. In an exploration of the qualitative literature on high performing hospitals, Taylor et al identified seven themes contributing to this high performance, two of which are, "receptive and responsive senior management" and "interdisciplinary teamwork"[77(p7,16)].

A systems approach to change[36,43] along with priority setting[35] and relationship-buiding[62] within a culture of transparency and trust are required to enhance engagement and collaboration between professions. Communication to clinicians of the rationale behind policy decisions and implementation is vital for enhancing co-operation and engagement[24,35]. This could be achieved with the practice of evidence informed decision making, recognising the complexity of this[55], and the provision of opportunities to revise and challenge these decisions[35].

CONCLUSION

This article has sought to contextualise the attributes in table 1 from the ANZCA publication *Supporting Anaesthetists' Professionalism and Performance: A guide for clinicians*[8], while highlighting the complexities and ambiguities that relate to this. The behavioural markers that are exemplified within the guide, particularly within the domains of collaborator, scholar and professional support this point. These include contributing to health service management processes, the promotion of shared leadership and having awareness and insight. Awareness of the contribution of leadership, clinician engagement and inter-professional collaboration towards quality patient care and a positive workplace culture in contemporary practice is essential for both trainee and specialist anaesthetists.

REFERENCES

1. Daly J, Jackson D, Mannix J, Davidson P, Hutchinson M. The importance of clinical leadership in the hospital setting. J Healthc Leadersh. 2014;2014(6):75-83.
2. Dickson G, Owen K, Sebastian A, Fulop L, Dadich A, Fitzgerald A, et al. Health leads Australia and implications for medical leadership. Leadersh Health Serv. 2014;27(4):355-370.
3. Chan M-K, de Camps Meschino D, Dath D, Busari J, Bohnen JD. Collaborating internationally on physician leadership development: why now? Leadersh Health Serv. 2016;29(3):231-239.
4. Ham C. Improving the performance of health services: the role of clinical leadership. Lancet. 2003;361(9373):1978.
5. ANZCA. The 2004 ANZCA training program. Module 2, Professional attributes [Internet]. Australian and New Zealand College of Anaesthetists, 2006; From: http://www.anzca.edu.au/documents/anzca-curriculum-module-2-2004-09092013.pdf. Accessed 25 April 2017.
6. ANZCA. ANZCA anaesthesia training program: curriculum. 2016. From: http://www.anzca.edu.au/documents/anaesthesia-training-program-curriculum.pdf. Accessed 25 April 2017.
7. RCPSC. CANMEDS framework [Internet]. The Royal College of Physicians and Surgeons of Canada, 2015; From: http://www.royalcollege.ca/rcsite/canmeds/canmeds-framework-e. Accessed 23 April 2017.
8. ANZCA. Supporting anaesthetists' professionalism and performance: a guide for clinicians. 2017. From: http://www.anzca.edu.au/documents/supporting-anaesthetists-professionalism-and-perfo.pdf. Accessed 6 May 2017.

9. RACS. Surgical competence and performance. 1st ed. Melbourne: Royal Australasian College of Surgeons, 2008.
10. RACP. Supporting physicians' professionalism and performance guide. Sydney: SPPP Project Office, The Royal Australasian College of Physicians, 2012.
11. Fulop L. Leadership, clinician managers and a thing called "hybridity". J Health Organ Manag. 2012;26(5):578-604.
12. Bish M. Leadership and management frameworks and theories. In: Leggat SG, Day GE, editors. Leading and managing health services: an Australasian perspective. Melbourne: Cambridge University Press, 2015.
13. Thistlethwaite JE, Forman D, Matthews LR, Rogers GD, Steketee C, Yassine T. Competencies and frameworks in interprofessional education: a comparative analysis. Acad Med. 2014;89(6):869-875.
14. Gordon M, Baker P, Catchpole K, Darbyshire D, Schocken D. Devising a consensus definition and framework for non-technical skills in healthcare to support educational design: a modified Delphi study. Med Teach. 2015;37(6):572-577.
15. Health Workforce Australia. [Internet] Health LEADS Australia: The Australian health leadership framework. 2013. From: https://www.aims.org.au/documents/item/352. Accessed 6 August 2017.
16. Stankunas M. Concepts of leadership and management in health services. In: Leggat SG, Day GE, editors. Leading and managing health services. Melbourne: Cambridge University Press, 2015.
17. Spurgeon P, Long P, Clark J, Daly F. Do we need medical leadership or medical engagement? Leadersh Health Serv. 2015;28(3):173-184.
18. Taylor N, Clay-Williams R, Hogden E, Braithwaite J, Groene O. High performing hospitals: a qualitative systematic review of associated factors and practical strategies for improvement. BMC Health Serv Res. 2015;15:244.
19. Braithwaite J, Westbrook MT. A survey of staff attitudes and comparative managerial and non-managerial views in a clinical directorate. Health Serv Manag Res. 2004;17(3):141-166.
20. Braithwaite J, Westbrook MT, Hindle D, Iedema RA, Black DA. Does restructuring hospitals result in greater efficiency-an empirical test using diachronic data. Health Serv Manag Res. 2006;19(1):1-12.
21. Spurgeon P, Mazelan PM, Barwell F. Medical engagement: a crucial underpinning to organizational performance. Health Serv Manag Res. 2011;24(3):114-120.
22. Lowe G. How employee engagement matters for hospital performance. Healthc Q. 2012;15(2):29-39.
23. Braithwaite J, Westbrook M. Rethinking clinical organisational structures: an attitude survey of doctors, nurses and allied health staff in clinical directorates. J Health Serv Res Policy. 2005;10(1):10-17.
24. Skirbekk H, Hem MH, Nortvedt P. Prioritising patient care: the different views of clinicians and managers. Nurs Ethics. 2017: 0969733016664977.
25. Buchhorn H, Shannon EA. From service provider to service manager: exploring the transition experience. Asia Pac J Health Manage. 2014;9(3):24-30.
26. Prideaux G. Making the transition from health professional to manager. Aust Health Rev. 1993;16(1):43-50.
27. Lawson J, Rotem A, Bates PW. From clinician to manager: an introduction to hospital and health services management. Sydney: McGraw-Hill, 2003.
28. Braithwaite J. An empirically-based model for clinician-managers' behavioural routines. J Health Org Manage. 2004;18(4):240-261.
29. Kippist L, Fitzgerald A. Are managers from Mars and doctors from Venus? 22nd ANZAM Conference –Australian & New Zealand Academy of Management; Auckland 2008.
30. Fulop L, Day GE. From leader to leadership: clinician managers and where to next? Aust Health Rev. 2012;34(3):344-351.
31. Spehar I, Frich JC, Kjekshus LE. Clinicians' experiences of becoming a clinical manager: a qualitative study. BMC Health Serv Res. 2012;12(421):0.
32. Leggat SG, Harris MG, Legge D. The changing role of the health service manager In: Harris MG, editor. Managing health services concepts and practice. 2nd ed. Sydney: Mosby Elsevier, 2006.
33. Kippist L. Bridges or barriers? Succession planning for doctor managers. Int Employ Relations Rev. 2013;19(2):24.
34. Mintzberg H. Wrong people. Managers not MBAs: a hard look at the soft practice of managing and management development. San Francisco: Berrett-Koehler, 2005.
35. Kapiriri L, Norheim OF, Martin DK. Priority setting at the micro-, meso-and macro-levels in Canada, Norway and Uganda. Health Policy. 2007;82(1):78-94.
36. Scott IA. Ten clinician-driven strategies for maximising value of Australian health care. Aust Health Rev. 2014;38:125-133.
37. Braithwaite J. An empirically-based model for clinician-managers' behavioural routines. J Health Organ Manage. 2004;18(4):240-261. Figure 3, Schematic diagram of some lateral and hierarchical power and relationship issues facing clinician-managers; p. 249.
38. Brandis S, Fitzgerald A, Avery M, McPhail R, Fisher R, Booth J. The emergence of new kinds of professional work within the health sector. In: Wilkinson A, Hislop D, Coupland C, editors. Perspectives on contemporary professional work: challenges and experiences. Cheltenham: Edward Elgar Publishing, 2016.
39. Glouberman S, Mintzberg H. Managing the care of health and the cure of disease—part i: differentiation. Health Care Manage Review. 2001;26(1):56-69.
40. Australian Commission on Safety and Quality in Health Care. Australian atlas of healthcare variation [Internet]. 2016; From: http://www.safetyandquality.gov.au/atlas. Accessed 7 May 2017.
41. Scott IA, Soon J, Elshaug AG, Lindner R. Countering cognitive biases in minimising low value care. Med J Aust. 2017;206(9):407-411.
42. Elshaug AG, Hiller JE, Tunis SR, Moss JR. Challenges in Australian policy processes for disinvestment from existing, ineffective health care practices. Aust NZ Health Policy. 2007;4(1):23.
43. Kippist L, Fitzgerald JA. Professional identity: enabler or barrier to clinical engagement? Employment Relations Record. 2014;14(2):27.

44. Rasa J. Networking. In: Day GE, Leggat SG, editors. Leading and managing health services. Melbourne: Cambridge University Press, 2015.
45. Mintzberg H. Managing the myths of health care. World Hosp Health Services. 2012;48(3):4-7.
46. Himmelstein DU, Jun M, Busse R, Chevreul K, Geissler A, Jeurissen P, et al. A comparison of hospital administrative costs in eight nations: UU costs exceed all others by far. Health Affairs. 2014;33(9):1586-1594.
47. McGregor S. Neoliberalism and health care. Int J Consum Stud. 2001;25(2):82-89.
48. O'Reilly J, Busse R, Hakkinen U, Or Z, Street A, Wiley M. Paying for hospital care: the experience with implementing activity-based funding in five European countries. Health Econ Policy Law. 2012;7:73-101.
49. Independent Hospital Pricing Authority. IHPA [Internet]. 2015; From: http://www.ihpa.gov.au/internet/ihpa/publishing.nsf.
50. Palmer KS, Agoritsas T, Martin D, Scott T, Mulla SM, Miller AP, et al. Activity-based funding of hospitals and its impact on mortality, readmission, discharge destination, severity of illness, and volume of care: a systematic review and meta-analysis. PLoS ONE. 2014;9(10).
51. Førde R, Aasland O. Moral distress among Norwegian doctors. J Med Ethics. 2008;34(7):521-525.
52. Mitton C, Peacock S, Storch J, Smith N, Cornelissen E. Moral distress among health system managers: exploratory research in two British Columbia health authorities. Health Care Anal. 2011;19(2):107-121.
53. Kippist L, Fitzgerald A. Organisational professional conflict and hybrid clinician managers. J Health Org Manage. 2009;23(6):642-655.
54. Leggat SG, Jepson DM. Evidence-based practice. In: Day GE, Leggat SG, editors. Leading and managing health services. Sydney: Cambridge University Press, 2015.
55. Liang Z, Howard PF, Leggat SG, Murphy G. A framework to improve evidence-informed decision-making in health service management. Aust Health Rev. 2012;36(3):284-289.
56. Robinson S, Williams I, Dickinson H, Freeman T, Rumbold B. Priority-setting and rationing in healthcare: evidence from the English experience. Social Sci Med. 2012;75(12):2386-2393.
57. Bolman LG, Deal TE. Reframing organisations: artistry, choice, and leadership. 5th ed. San Francisco: Jossey-Bass, 2013.
58. Avolio BJ, Walumbwa FO, Weber TJ. Leadership: current theories, research, and future directions. Ann Rev Psychol. 2009;60:421-449.
59. Edmonstone J. Developing leaders and leadership in health care: a case for rebalancing? Leadersh Health Serv. 2011;24(1): 8-16.
60. West M, Eckert R, Steward K, Pasmore B. Developing collective leadership for health care. London: The King's Fund, 2014.
61. Dwyer AJ. Medical managers in contemporary healthcare organisations: a consideration of the literature. Aust Health Rev. 2010;34(4):514-522.
62. Fitzgerald L, Ferlie E, McGivern G, Buchanan D. Distributed leadership patterns and service improvement: evidence and argument from English healthcare. Leadersh Q. 2013;24(1):227-239.
63. American College of Healthcare Executives. Leading a culture of safety: a blueprint for success. 2017. From: http://www.npsf.org/page/cultureofsafety. Accessed 10 May 2017.
64. West MA, Dawson JF. Employee engagement and NHS performance. London: The King's Fund, 2012.
65. Hackman JR, Oldham GR. Motivation through the design of work: test of a theory. Organ Behav Human Perf. 1976;16: 250-279.
66. Courtney M, Whelan AK, Majoor J, Ibrahim JE, Day GE. Work design in health care. In: Harris MG, Associates, editors. Managing health services: concepts and practice. Australia: Elsevier, 2006.
67. Wutzke S, Benton M, Verma R. Towards the implementation of large scale innovations in complex health care systems: views of managers and frontline personnel. BMC Res Notes. 2016;9(1):327.
68. Kean S, Haycock-Stuart E. Understanding the relationship between followers and leaders. Nurs Manag (Harrow). 2011;18(8):31-36.
69. Schyns B, Kiefer T, Kerschreiter R, Tymon A. Teaching implicit leadership theories to develop leaders and leadership: how and why it can make a difference. Acad Manage Learn Educat. 2011;10(3):397-408.
70. RACMA. PACE: The RACMA strategic plan 2014 – 2016 [Internet]. Royal Australasian College of Medical Administrators, 2015. From: http://www.racma.edu.au/index.php?option=com_docman&task=doc_view&gid=1576. Access 6 August 2017.
71. Chandrasiri S. Transitioning to the dark side: evidence-based strategies for managing the critical challenges confronting new clinician managers [Internet]. Royal Australasian College of Medical Administrators, 2015; From: http://www.racma.edu.au/index.php?option=com_content&view=article&id=784:transitioning-to-the-dark-side-evidence-based-strategies-for-managing-the-critical-challenges-confronting-new-clinician-managers&catid=144:the-quarterly-2015&Itemid=457. Accessed 6 August 2017.
72. Spurgeon P, Clark J, Ham C. Medical leadership: from the dark side to centre stage. London ; New York: Radcliffe Pub., 2011.
73. World Health Organisation. Framework for action on interprofessional education & collaborative practice. Geneva: Health Professions Network Nursing and Midwifery Office within the Department of Human Resources for Health, 2010.
74. Greenfield D, Nugus P, Travaglia J, Braithwaite J. Factors that shape the development of interprofessional improvement initiatives in health organisations. BMJ Qual Safety. 2011;20(4):332-337.
75. Braithwaite J. Between-group behaviour in health care: gaps, edges, boundaries, disconnections, weak ties, spaces and holes. A systematic review. BMC Health Serv Res. 2010;10:330.
76. Dickinson H, Bismark M, Phelps G, Loh E. Future of medical engagement. Aust Health Rev. 2016;40(4):443-446.
77. Taylor N, Clay-Williams R, Hogden E, Braithwaite J, Groene O. High performing hospitals: a qualitative systematic review of associated factors and practical strategies for improvement. BMC Health Serv Res. 2015;15(1):244.

A guide to the electronic roster

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Dr Mulrooney is a consultant anaesthetist and has extensive experience in managing departments of anaesthesia having previously been chair of the anaesthetic department at the University Hospitals Coventry and Warwickshire NHS Trust for eight years. In addition he was co-clinical director of surgery and oncology at the same hospital. He developed an interest in the role of computers in rostering in the mid-1990s and conceived the role of the relational database with respect to skills-based anaesthesia rosters.

DECLARATION OF INTEREST

Dr Peter Mulrooney has an interest in an e-rostering program and the company that has developed it.

BACKGROUND

Rostering is the process of appropriately assigning individuals to individual tasks. Integral to this process is due consideration of availability, job plan, contractual obligation, skills, training and safe working hours.

There is a compelling case for automating these tasks to control the high number of constantly moving variables to achieve high levels of consistency. Rostering software exists, but unfortunately the appropriate software is hard to find. Clinical governance demands skills-based solutions.

In 2010, the National Audit Office in the United Kingdom emphasised the need for e-rostering in order to improve efficiency in the NHS[1]. That this has not been reliably adopted was made clear in a more recent report on operational productivity and performance again in the UK[2].

Two recent reports demonstrate the serious consequences of poor rostering. In one, the coroner highlighted “an unsatisfactory and casual attitude to rostering” following two deaths in Adelaide[3]. The second report was the working hours report by the Australian Medical Association published in July 2017[4] that concluded that there are still too many doctors working unsafe shifts. It highlighted that fatigue and stress remain prevalent in public hospitals.

HISTORY

The roster is seen as a time-consuming impost. Pen and paper have been the mainstay of rostering for many years. In a surprising number of manpower-heavy environments this is still the case. This includes clinical departments and ward nursing. Surprisingly, major hotel chains also fall into this category.

The arrival of the basic software spreadsheet was regarded as the answer, but it was slowly recognised that the relative inflexibility of the options available meant that a high degree of knowledgeable manual interaction was still required. In other words, an experienced practitioner had to be removed from their primary duties to attend to this.

Unfortunately, the population of the relevant field in the spreadsheet is often regarded as the binary measure of success. The effectiveness of the roster so produced is difficult to monitor in its entirety (clinical governance, training and supervision etc.). It also ignores the effort required to achieve this end and moreover it also fails to comprehend that this manual input is subjective and not reliably reproducible.

Basic programmable software has subsequently become available in an attempt to increase the flexibility of the spreadsheet approach, such as Microsoft Access for the Excel spreadsheet. Unfortunately, this approach is limited by the underlying architecture of the spreadsheet itself. Effectively the rostering issues must fit the limited spreadsheet capability and does not allow the skills-based diary approach that is required.

THE CURRENT SITUATION

Specific electronic rostering (e-rostering) systems are now proffered, but their quality and functionality is highly variable. Moreover, clinicians (even departmental enthusiasts) are ill-equipped to critically evaluate them. Superficially similar software may appear to offer what is required, but the entirety of the process must be considered from the departmental input, the hardware requirements, the security, the setup requirements, the IT issues, the data access and availability, the automaticity and the reliability in maintaining clinical governance standards.

The spreadsheet approach has much to commend it on the basis of familiarity. The limited options with respect to the variables make the set-up relatively straightforward and rapid. However, these very limitations preclude the full functionality that a clinical department realistically needs to manage and record the required information for full automation and clinical governance. Just as relevantly, it inhibits the delegation of management of the roster to a non-clinician.

The financial implications of this latter point can be defined on the basis of the loss of clinical time engendered by the need for input from clinicians. At the most basic level half a day per week of consultant time would be

required to run a clinical roster. This cost is easy to calculate. If a senior trainee is also required, then there is a further cost. If this time can be released back to clinical activity, the cost advantages are obvious.

The executive appreciates that their massive staffing costs are ill-defined but have no objective tool for their measurement. Departments have lacked the ability to provide the relevant data. The executive and the department have to square this circle.

A searchable relational database can address all these issues. Fully programmable database "languages" such as Oracle© (Oracle Corporation) and 4th Dimension© (4D SAS) have long been available and are utilised by major organisations and industries. For example, 4th Dimension has been relied upon by the US Air Force, IBM and major retailers all of whom require flexibility, reliability and security. Indeed functional relational database developments should have consigned the spreadsheet roster approach to history. However, this is still doggedly pursued because of the apparent ease of use. Rules, targets, skills, availability, shift/on-call duties, training and records together with all the disparate elements of the departmental "tribal" memory are essential to managing the electronic roster, but they are too complex to address in a spreadsheet.

DATA IMPLICATIONS

The manual approach, be it pen and paper or the spreadsheet, generates a pattern of assignments that are subjective and generate very limited usable data.

The semi-automated spreadsheet approach suffers from many of the same data limitations of the manual approach, particularly with respect to reproducibility. In addition, neither approach allows meaningful data interrogation.

With some of the early relational databases, data remained inaccessible to the user and was difficult even for the software producer to mine. The vendor also took advantage of the user's naivety in not having defined the detail of the data access required. Access was also almost on the basis of a ransom.

Allowing data to remain at the whim of the vendor limits security. Data must remain 100 per cent in the hands of the user. It can potentially be utilised in manning, efficiency and payroll reports. It also enables projection of the effects of service changes. A locked system denies the purchaser from accessing the data and, therefore, prevents analysis of that data. The purchaser should have unfettered access to all data by right.

Well-designed fully automated systems, while being demanding in the set-up phase, by definition, generate useful data as a by-product. If an outcome is reproducible, then the data associated with this process is relevant. The information generated will detail individual staff records, departmental performance, skill mix and training. This type of information addresses the current accountancy approach to departmental management by providing the full story.

Similarly, systems for accurate collection of operating suite case data can be used to predict operating room demand and enhance staff resource allocation[5,6]. Security and data protection for such software programs is vital. A single, standalone un-networked computer may appear to be secure, but strict password security is required and the loss of multi-user access severely inhibits any useful function. Security could be afforded via the hospital intranet run via on-site servers and/or virtual servers. Initial analysis might suggest that this is the ideal, however, the very security required leads to rigidity of such a system and may prevent a user access from outside the hospital and thus denying the potential efficiencies of universal access by the department. Moreover, as demonstrated in the UK, the intranet is still vulnerable to ransomware denying data access. Additionally, the costs associated with maintaining the latest hardware, software and data backup within an individual internal environment may be prohibitive.

A newer option is the "cloud". There is understandably a degree of nervousness regarding the security of this approach, however, it should be borne in mind that the cloud is a generic term and does not describe the many features available. For instance, the security levels of banking payment systems are taken as read. This same security is available for an e-rostering system. This is simply a matter of coding the feature into the relational database. The security reservations are valid but they are controllable.

GUARANTEEING GOVERNANCE

As mentioned above, fatigue and stress remain prevalent. Reports suggest that cancellation due to double-booking can be ameliorated by integrating staffing processes. Corporate reinsurance rates can be reduced with governance compliant rosters produced in advance, as experienced in a 700-bed hospital in the north Midlands of the UK. Defined rules prevent unconsciously (or consciously) breaching governance standards. The software needs to be able to handle the detail involved.

Departments must consider individual's skills, availability and the task complexity. The key is self-evident – the appropriate control of the available resources and the management of unexpected unavailability. Assigning a name to a duty or task is insufficient, the individual must be available and the skills appropriate.

A pre-rostering strategy is vital. Controlling specialist staff availability by limiting planned absences based on individual's skills (e.g. paediatrics, neurosurgery, obstetrics, cardiothoracics) helps protect coverage of required

tasks. This lends itself to automation, which is best controlled within an electronic diary as either a standalone tool or a feed into the full electronic roster.

The diary approach minimises the task of assignment to fixed or float sessions, on call, or shifts. Identification of non-clinical sessions can be built in. This enables identification of individuals on non-clinical duties who can be re-assigned in an emergency. Pre-rostering alone provides the basis of a semi-automated system with at least 30 per cent automation. Achieving more requires incremental levels of data entry. Up to 95 per cent automation is possible.

MANAGING THE IMPLEMENTATION OF AN E-ROSTERING SYSTEM

Specifications

The spreadsheet has the advantage of familiarity, however, even utilising software modification, there are too many variables in matching multiple skills to many complex tasks at different locations on different days and times for this approach to work. Especially when training modules, absences, on-calls and shifts need to be integrated.

The "one size fits all" software has the advantage of simplicity in setting up. However, the easier the set-up, the lower the degree of automation and the greater the need for day-to-day direct specialist input. These programs are designed for apparent ease of use and low or zero maintenance; however, they do not truly cater for the skills, specialties, training modules and governance that are essential elements in rostering.

The other major issue with such programs is the nature of the data produced and what access is provided. In the absence of relevant data being inputted during the set up, such data will, by definition, be wholly absent for future reporting. Hence, future data requirements should form part of the assessment of such programs.

In addition, the generic one size fits all hospital-wide rostering system cannot satisfy the complexities of many clinical departments where unique skill sets must be accommodated. Moreover, the generic version will be subject to the committee approach where a "democratic" view will emerge that does not meet the skill requirements of particular specialties. Specifying local requirements to ensure governance will be necessary. However, this does not preclude linking to a hospital wide system where it is available, if a relational database structure is utilised.

Dedicated relational database software is designed from the ground up to enable multiple elements to be defined and brought into play simultaneously when generating a roster. The structure lends itself to a modular approach such that additional functionality can be added as required. In addition, every defined element is available as data from which reports can be generated.

The software should include many agreed reporting requirements, but should also remain open to data mining software such as Crystal Reports© (SAP SE).

Data delivers transparency. However, some thought may be required to simplify a barrage of data from a complex high-end SQL database. Some suppliers deliver elements in spreadsheet form, which means the data can be reprocessed for reports. For the rostering output, it is possible to go further by linking part of the database to a spreadsheet such that a finished roster is run into a spreadsheet format that can be modified by users with password controlled access. Every time a change is saved it can ripple back to the database thus maintaining the core data integrity for reporting purposes.

The specification of an e-rostering system must be clear. Advice should be sought since the widespread unfamiliarity with relational databasing and network/cloud issues diminishes the chances of success. Guidance by the vendor alone may not be ideal. Policing the functionality of the project is vital.

THE ENGINE

Departmental stand-alone computer

Standalone desktop PCs have the necessary power, but with disadvantages. Secure access necessitates repeated log ins if multiple users are involved. Inevitably shortcuts will be taken, compromising security and audit. The integrity of the system information must be guaranteed. However, the data should be accessible from multiple locations. Networking is preferable, but is only the first step. Unless one is using a single machine to run pre-rostering and a diary system, the lack of networking is a liability.

In addition, where rostering solutions are controlled by a single departmental enthusiast and a single un-networked system, then the critical safety paradigm exists: that of the single point failure (the failure of a single element destroying the functionality of the entire system).

In-house network and the cloud

The move from the stand-alone desktop to the intranet may mean loss of control and the data retreating behind the walls of the IT department, however, it makes some security sense to run a "closed" conventional client/server within the in-house system. Data security is not merely a preference; it is a legal requirement. However, this results in loss of flexibility in terms of access and achieving a usable interface with the program from outside the intranet is often nigh on impossible, for example, access from home.

The browser based approach (Internet Explorer/Edge, Chrome, Safari etc) is the norm on the internet, but security reservations exist when utilising the common “http” addresses. Safety may mean staying away from browser delivery systems that have gained popularity in the recent past in favour of applications designed to work in the cloud. Most Microsoft applications now run on the cloud without a browser. The likes of ebay and Amazon persist with browsers because the cost per user is negligible. However, browsers can still be safely utilised to deliver reports where rostering information is published to the net rather than allowing access to the program itself.

The cloud provides many advantages. Secure access can be provided via “https” access i.e. credit card level safety. Systems that sit on secure servers out in the “ether” can access software system out of hours seven days a week. Information from the roster system can be published to “the net” and accessed for general departmental use. For example, leave requests can be managed remotely. To apply, staff can use a form or e-mail a request to a server address monitored 24 hours a day by the system and picked up. Provided no program rules are breached, automatic notification of approval can occur.

The cloud also offers cost reductions, adaptability, and accessibility. External virtual servers can maintain high data security with low cost options. Round the clock external back-up and support combined with the ability to increase speed and hard drive space make a compelling argument.

The advantages of the cloud are clear. It offers users the opportunity to utilise low cost hardware updated, maintained and supported by reliable providers with secure servers. The IT department involvement is negligible. Users can also negotiate free updates and software costs in an annual cost. The goal, predictable overheads for hardware and software with ability to change as required.

The potential downside to the cloud approach is that it depends on the internet speeds locally available.

The IT department

What is needed from the IT department is installation of the software and a server or gateway to a cloud server. It is vital to have support from the hospital executive for the project.

The IT department may be a bottle neck when seeking to install software. Allowable software must make it on to a “white-list” before being installed on hospital systems. One malfunctioning piece of software can bring down the whole system. The cloud approach using servers and software “off-site” decreases the IT load and costs. Security must be maintained and IT must ensure this with external and highly secure external filtering.

In addition, the workload associated with a true ODBC/SQL relational database is not appreciated. Hence, integral to setting up a functional automated system is the manual data input resource required. IT departments are often self-funding and may charge for this kind of resource. Upgrades and support is far cheaper outside the rigid world of the in-house department. In addition, they are busy managing legacy programs or integrating disparate/incompatible Windows systems.

Testing

There can never be enough testing prior to adoption. Once again, the advantage of automation becomes apparent. Automated software never tires or gets bored.

WHY DO PROJECTS FAIL?

Projects fail at a departmental level when high expectations flounder on the high investment in time necessary. Accountability is paramount and timelines and milestones must be defined. Task management from outside the department may be advisable as multitasking clinicians cannot concentrate on the detail of the project.

There are multiple reasons for the failure of IT projects within the health/public sector. The executive may not grasp the complexity of the issues and may not identify the need for qualified experts to facilitate such a project. While individuals may grasp the essential concepts, the process fails because their enthusiasm may not be shared.

The lack of detailed specification provides a potential vendor with a wide target. Additionally, the project team may be permanently on the back foot addressing a system not properly specified whilst themselves not understanding the technical complexities. Failure to ensure that adequate time and resources are provided during the set-up will inhibit reaching agreed milestones.

It should also be appreciated that determined individuals within a department can inhibit the progress of implementation of such projects.

MANAGEMENT OF THE FUNCTIONING E-ROSTER

An e-roster must be designed such that a non-clinical administrator can run the system. The software should be sufficiently comprehensive to automatically enforce the departmental clinical governance standards and should seamlessly integrate with a powerful departmental e-diary. A relational database allows all of this.

All departmental events, commitments, absences, etc., need to be entered into this diary. Having set absence limits on the basis of skills or seniority, the administrator is immediately informed as to adverse repercussions

of a booking. The roster should remain live at all times even if already published, so late unavailability can then be identified and addressed without having to re-generate the entire roster. This approach ensures the accuracy of the data.

Every member of the department should have access privileges linked to passwords to provide control. Each department will have its own priorities.

Ultimately, whoever manages the day-to-day e-roster, a clinician must ultimately underwrite all activities. A comprehensive automated software package will be able to reflect the detail needed by the department and will highlight any problem that defies automation. Anaesthesia departments frequently have a clinician with responsibility of overseeing or assisting with theatre management. Such clinicians have the corporate knowledge and a detailed understanding of the complexity of operating room resourcing[7] and are logical choices to become custodians of these systems.

E-ROSTER OUTPUT

Relevant data can be disseminated in multiple report forms. All delivery systems are available from texting and e-mails to mobile apps. These can be driven from the software and auto-updated. Immediacy is delivered by auto-texting. Emailing has the advantage of economy.

Individuals can be informed directly as to their future assignments and late changes can be automatically forwarded. Departments can receive the complete roster via email or by linkage to a TV screen in the relevant areas. This reduces the administrative requirements considerably.

DATA FOR DEPARTMENTAL MANAGEMENT

The priority is total access and control of data. Consider a supplier going bankrupt or a more attractive system becoming available. The historical data must be available for migration to the new system.

Powerful relational data bases generate an incredible amount of information which must remain available for the user to access. One hospital in the midlands of England was able to save a major management consultancy firm two days’ work by mining the data in their rostering system and thus justified the entire project.

The data needed to achieve full automation also enables more accurate projections of the implications consequent to changes of duties/commitments or staffing numbers.

Obviously backups of data needs thought and the cost advantage of the cloud again becomes clear. Exporting data for departmental reports and spreadsheets is a major advantage.

DATA FOR HOSPITAL MANAGEMENT

Automation via e-rostering enables the rapid projection of the effects of either a net increase of tasking or a net decrease of manpower. Multiple variations can be generated in minutes and the statistical output generated in seconds. In effect, “real time” simulations can be demonstrated to the executive. More importantly, with a skills-based e-rostering program, the projections take into account clinical governance, training needs and the effect of historical absence rates (sick leave, study leave, etc.).

Moreover, with the generation of increasing numbers of projected rosters (dozens or tens of dozens) at the click of a button, the cumulative effect of minor discrepancies will become apparent. The ability to assign reasons for any cancellation of a task automatically generates relevant statistics and sometimes surprising results, for example, the anaesthesia department is not always the source of all problems.

DATA FOR LINKING TO OTHER HOSPITAL APPLICATIONS

Hospitals have myriad software program spanning multiple generations of operating systems. For example, MS-DOS applications and even Windows 3.0 software programs still operate today. Bridging these types of programs, some of which may be used for payroll and human resource applications, with an e-rostering program in order to automatically feed in data is realistically only possible with ODBC/SQL type software. A modified spreadsheet will not manage this.

When assessing a system, users should ensure that the control of data output remains in their hands and not only be available on request and at a cost. The minimum requirement should be data output to recognised spreadsheet with an agreed format. Better still, a data mining utility should have to accessor interrogate the database. The ultimate solution is an SQL link. However, some constraints for reasons of commercial sensitivity may be imposed.

CONCLUSION

Anaesthetists have much to contribute to the safe and efficient use of operating suites and other dedicated areas wherein anaesthesia services are required. Computerisation and implementation of the anaesthesia record, theatre management and decision-support systems, and even educational activities, have been developed and adopted by our specialty. Clearly, E-rostering has unarguable advantages over historic pen and paper

systems. Identifying the appropriate functionality of the software presents the potential end-user with a multiplicity of choices with many traps for the uneducated purchaser. Choosing the best platform to run the software also presents a number of challenges that need to be addressed. However, armed with the appropriate information and knowing which questions to ask, the user now has a better chance of success.

GLOSSARY

Access privileges are the delegation of authority over a computer system. This allows a user to perform an action.

Additional functionality (tasks) can be applied as and when required (see also Modular approach).

Amazon is the most widely known site for buying commodities and services across the internet. They are also leaders in the push for "cloud" services using their own worldwide virtual server network at attractively low prices.

App is short for "application" – which is another name for a computer program usually run on a mobile device.

Back-up is the copying and archiving of computer data.

Browser with Internet Explorer or Chrome. A web browser is a software application for retrieving, presenting and passing information resources on the Internet. Because of its ubiquity, it is an obvious target for hacking notably via use of plug-ins, small Java-based mini applications. Microsoft's Internet Explorer and Google's Chrome are the best known browsers.

Clinical governance is a framework through which hospitals are accountable for continually improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.

Crystal Reports is a business intelligence application, currently marketed to small businesses by SAP SE. It is used to design and generate reports from a wide range of data sources.

Data mining is the practice of re-using data extracted from a database in different ways typically in Excel spreadsheets or reports.

ebay is a massive internet auction site that is accessible worldwide.

e-diary is a computerised diary of varying complexity ranging from a series of logged events to an interactive diary that provides feedback in the form of interactive advice on the implications of actions such as allowing a requested leave breaks safety rules.

Emailing is the act of communicating text messages between computers, smart phones, tablets and other devices anywhere in the world or in this case around the hospital. A universal format ensures that any machine can read and respond to messages.

e-rostering is the act of generating a roster from a set of rules defined on a computer. These range from the simple to advanced systems that approach 100 per cent automation.

Ether is computer speak for out on the internet.

Gateway is a term to describe a link to another network or the internet. IT departments look to control these points to maintain security.

Generic rostering systems are simple "do it all" systems aimed at the general market. Hospital skills for example particularly when "batched" are beyond their capabilities. Medical rostering particularly in the larger specialist departments such as radiology and anaesthesia need many more variables than are found in such systems.

Hospital wide intranet is a private network accessible only to an organisation's staff. A wide range of information and services from internal IT systems are available that would not be available to the public from the internet.

Http and **https** is a hyper text transfer protocol. The "s" at the end of "https" stands for "secure". Both are the protocol over which data is sent between your browser and the website that you are connected to. It means all communications between your browser and the website https files are encrypted or sometimes known as credit card level.

Legacy-based systems are frequently tied to an older specific version of an operating system.

Milestones are a significant stage or event in the development of something in this case goals set to be achieved before moving forward.

Modular approach is the ability to progress as far along the road to automation as desired at a pace to suite. An e-diary is the first step then the ability to allocate manually from available and qualified staff. The next stage would be to add higher levels of automation firstly through fixed sessions then then training modules, shifts and on calls on to full automation.

MS-DOS was the main operating system for IBM PC compatible personal computers during the 1980s and the early 1990s, when it was gradually superseded by operating systems offering a graphical user interface (GUI), in various generations of the graphical Microsoft Windows operating system.

Multiple generations of operating systems. In hospitals, most computers run a version of Microsoft Windows. The most recent is Windows 10 but the most widely adopted was Windows XP from a few generations back.

Networking is the act of connecting computers to allow the various pieces of equipment to communicate with one another, as well as with other networks. In the UK there is still a reliance on N3 a national standard for networking between hospitals.

ODBC stands for Open Database Connectivity and is a standard application programming interface for accessing database management systems. It is independent of database systems and operating systems. By using ODBC statements in a program, you can access files in a number of different databases, including Access, dBase, DB2, Excel, and Text.

Off-site refers to sites, services or facilities outside the hospital environs.

Pre-rostering describes the numerous activities, normally diary based, that contribute to allowing maximum flexibility of staff by controlling leave to ensure that as far as possible suitably skilled staff are available to carry out the tasks required in any one day. Targets or maximum away limits can be set to avoid the embarrassment of having enough staff but without the necessary qualifications.

Ransomware is a type of malicious software virus that threatens to publish the victim's data or perpetually block access to it unless a ransom is paid.

Real time simulations are provided via fully automated software systems that can be generated quickly and in volume to identify the snowball effect of absences and its effect on safe working hours and consequent availability.

Relational database is structured to recognise relations between stored items of information.

Spreadsheet is an interactive computer application for organisation, analysis and storage of data in tabular form. Most people are familiar with the market leader Excel.

Server is software or hardware that provides functionality for other programs or devices, called "clients". This architecture is called the client–server model, and a single overall computation is distributed across multiple processes or devices. Servers can provide various functionalities, often called "services", such as sharing data or resources among multiple clients, or performing computation for a client. A single server can serve multiple clients, and a single client can use multiple servers.

Skills-based systems exploit an ability to define skill sets and then to define those necessary for a particular task. Staff are assigned manually or automatically according to those defined skills.

Software is all information processed by computer systems, programs and data. Computer software includes computer programs, libraries and related non-executable data, such as online documentation or digital media. Computer hardware and software require each other and neither can be realistically used on its own.

Standalone PC is a desktop or laptop computer used on its own without requiring a connection to a network.

Texting is the act of composing and sending electronic messages, in rostering this should be the last resort to communicate change as costs can mount up unnoticed.

The cloud is a series of internet links to hardware and offered as a utility via the internet.

Virtual server is a server (computer and various server programs) at someone else's location that is shared by multiple website owners so that each owner can use and administer it as though they had complete control of the server as if it is many servers.

Whitelist is a list of items that are granted access to a certain system or protocol. When a whitelist is used, all entities are denied access, except those included in the whitelist.

Windows systems or simply **Windows**, is a family of operating systems developed by Microsoft. It consists of several families of operating systems, each of which cater to a certain sector of the computing industry. Windows 3.0 originated in 1989 and is the third major release of Microsoft Windows, and was released on May 22, 1990. It became the first widely successful version of Windows and a rival to Apple Macintosh and its graphical user interface (GUI) front. It was followed by Windows 3.1.

REFERENCES

1. National Audit Office. Department of Health: management of NHS hospital productivity. Report by the Comptroller and Auditor General. HC 491. Session 2010–2011. London: The Stationery Office, 2010. From: https://www.nao.org.uk/wp-content/uploads/2010/12/1011491.pdf. Accessed 2 October 2017.
2. Department of Health. Operational productivity and performance in English NHS acute hospitals: unwarranted variations. London: Department of Health, 2016. From: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/499229/Operational_productivity_A.pdf. Accessed 2 October 2017.
3. Prosser C. Royal Adelaide Hospital appoints another stroke specialist after patient deaths, inquest hears. ABC News Online, 2 August 2017. From: http://www.abc.net.au/news/2017-08-02/rah-appoints-another-stroke-specialist-after-patient-deaths/8766874. Accessed 12 September 2017.
4. Australian Medical Association. Managing the risks of fatigue in the medical workforce: 2016 AMA Safe Hours Audit. Canberra: Australian Medical Association, 2017. From: https://ama.com.au/system/tdf/documents/v1%202016%20AMA%20Safe%20Hours%20Audit%20Report.pdf?file=1&type=node&id=46763. Accessed 12 September 2017.
5. Tiwari V, Furman WR, Sandberg WS. Predicting case volume from the accumulating elective operating room schedule facilitates staffing improvements. Anesthesiology. 2014;121(1):171-183.
6. Stepaniak PS, Heij C, Mannaerts GH, de Quelerij M, de Vries G. Modeling procedure and surgical times for current procedural terminology-anesthesia-surgeon combinations and evaluation in terms of case-duration prediction and operating room efficiency: a multicenter study. Anesth Analg. 2009;109(4);1232-1245.
7. Levine WC, Dunn PF. Optimizing operating room scheduling. Anesthesiol Clin. 2015;33(4):697-711.