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Invited papers and selected continuing education lectures

Editor:
Richard Riley
Department of Anaesthesia and Pain Medicine
Royal Perth Hospital
Pharmacology and Anaesthesiology Unit
School of Medicine and Pharmacology
University of Western Australia
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College of Intensive Care Medicine

Dr Richard Riley
Western Australia

Professor David Story
Victoria

Dr David Sturgess
Queensland

Dr Sharon Tivey
New South Wales

Dr Gerald Toh
South Australia
Preface

Welcome to the 2015 edition of Australasian Anaesthesia (the Blue Book).

This edition of the Blue Book provides a diverse range of topics for your interest and I thank the authors and regional editors for their valuable contributions.

Please remember that bonus materials may be found on the ANZCA website (www.anzca.edu.au/resources/collegepublications or use the QR code with your digital device). The authors have generously allowed their articles to be available in this way to maximise distribution of their work.

We have again produced the Blue Book in both digital and hard copy formats. While anecdotally many anaesthetists favour the digital format as they amass vast electronic libraries on their portable devices, there are still a number of you who prefer a hard copy. It is wonderful to be able to offer both formats. ANZCA and other medical colleges are constantly faced with the challenges of providing access to the latest medical information. Publications provide a more traditional means of educating and informing and more recently social media has been used to communicate with members about meetings, drug alerts, employment opportunities and other events. Perhaps we may have an article on this very topic in 2017!

I hope you enjoy this edition and I’d also like to thank ANZCA’s Publications Manager Liane Reynolds for her support.

Please thank our authors personally if you can – and also consider writing yourself for a future edition.

Dr Richard Riley
Editor, 2015 Australasian Anaesthesia
Re-examining rapid sequence induction

ANDREW GOLDBERG, MBBS, BBNSC
Registrar, North Western Training Scheme, Melbourne, Australia.
Dr Andrew Goldberg is a junior anaesthesia registrar with interests in junior medical staff education and clinical ultrasound.

IAN HARLEY, MBBS, FANZCA, FRCA
Staff specialist, Austin Hospital, Melbourne, Australia.
Dr Ian Harley's other interests include cardiac anaesthesia and intraoperative echocardiography.

INTRODUCTION

Rapid sequence induction (RSI) is an anaesthetic technique that is used to minimise the risk of pulmonary aspiration during induction of anaesthesia.

It has traditionally involved:
- Preoxygenation.
- Cricoid pressure.
- Predetermined doses of thiopentone and suxamethonium.
- Intubation as soon as the suxamethonium has caused paralysis (often indicated by fasciculations).
- No bag and mask ventilation before intubation.
- Inflation of the tracheal cuff and confirmation of tracheal intubation by end tidal CO₂ before removal of cricoid pressure.

The proposed advantages of RSI include:
- Reduced likelihood of aspiration.
- If the patient’s trachea cannot be intubated, then there is a relatively rapid return of spontaneous ventilation due to the short duration of action of the drugs used.

The disadvantages of RSI include:
- Increased risk of awareness due to the dosage of induction agent being predetermined and not titrated.
- Haemodynamic instability due to non-titration of drug doses.
- Some specific disadvantages/contraindications of using suxamethonium (spinal cord injuries, burns, cholinesterase deficiencies).

The risk of aspiration can vary between high and remote, even in emergency situations, so the reduction in risk of aspiration by RSI must be weighed against other risks and disadvantages of the technique.

With the introduction of new drugs, particularly propofol, rocuronium and sugammadex, and with thiopentone falling into disuse, various modifications of the RSI technique are increasingly being used, depending on circumstances and personal preferences.

In this article we discuss the various combinations of drugs that are used in modified rapid sequence induction and the evidence for any advantage or disadvantage:
- Propofol versus thiopentone.
- Suxamethonium versus rocuronium.
- The use of short-acting opioids to supplement induction agents.

The studies we have looked at all suffer from the problem of comparing two drugs for efficacy in doses that are decided arbitrarily. If a study shows one drug to be superior to another in achieving an end point at two particular doses, it does not mean that if the doses were altered, the results might not be reversed. Having said that, some studies do use a range of doses and a fundamental of ANZCA training is to know what dose ranges to use in order to achieve the desired effect while minimising unwanted side effects.

PROPFOFOL VERSUS THIOPENTONE

Hypotension is a side effect of both thiopentone and propofol induction. Indeed, it may be seen with induction of anaesthesia in general, and is of particular concern in RSI due to the non-titration of induction doses and the haemodynamic instability of many emergency patients.

Thiopentone has traditionally been thought to cause less hypotension compared with propofol post-induction, and this is probably true when 5mg/kg of thiopentone is compared with 2.5mg/kg of propofol1,2. Some recent studies comparing 2mg/kg of propofol with 5mg/kg of thiopentone3,4 showed less haemodynamic effect from the propofol, highlighting the difficulty in comparing two drugs with dose-dependent side effects.

A systematic review examined a number of studies that compared the use of rocuronium with either propofol or thiopentone and found that satisfactory intubation conditions are possible with either combination5; however, the dose of rocuronium required was increased when thiopentone was used. It is not surprising that the laryngoscopic views attained are comparable when there is sufficient neuromuscular blockade. However, in the absence of complete neuromuscular blockade, propofol appears to be more effective at blunting airway reflexes and improving laryngoscopy grade6.
Regarding speed of onset, although studies have found that both propofol and thiopentone have a similar time to loss of consciousness, time to BIS <50 may be quicker with thiopentone (52 seconds vs 65 seconds, p = 0.01). However, this does not reflect the use of propofol. This difference in speed of onset may represent a reduced risk of awareness during rapid sequence induction with propofol compared with thiopentone. Thiopentone is no longer manufactured in Australia. It is imported and although the imported product is not registered in Australia, it is distributed under an exemption granted by the TGA and will likely be available for the foreseeable future at a 13-fold price differential between thiopentone ($0.73 per 500mg vial) and propofol ($0.76 per 200mg vial), which makes an economic argument in favour of the use of propofol. In spite of the limited availability, obstetric anaesthesia appears to be the last area of practice in which thiopentone is used regularly. In the situations using thiopentone outside of obstetric practice, it remains the obstetric induction agent of choice for many anaesthetists in the UK. There is, however, growing evidence for the safety of propofol in obstetric anaesthesia. Despite ongoing use in obstetrics, ANZCA trainees are often unfamiliar with the use of thiopentone, which may be due to its limited availability and expense. This lack of experience may result in incorrect drug use and drug errors if thiopentone is used. Common drug errors reported during obstetric anaesthesia involve confusion between thiopentone and antibiotic syringes and the presence of phenotypes with atypical anticholinesterases (0.01 per cent, with varying prevalence among specific groups). Thiopentone is contraindicated in burns, recent spinal injuries and penetrating eye injuries, so avoidance of suxamethonium in some situations is not controversial.

The use of non-depolarising muscle relaxants has also been avoided in the past, due to problems caused by the relatively large doses required to produce the onset time of suxamethonium and the time taken for spontaneous recovery. In the elderly, the trachea being difficult to intubate and the risk of aspiration. In situations where propofol is contraindicated due to allergy or preference, then there is still a role for thiopentone. In situations where there are no contraindications to suxamethonium, a rapid-sequence induction using a predetermined dose of propofol and suxamethonium is probably the first choice for most anaesthetists in most situations and the bulk of evidence in the literature supports this.

In situations where there is absolute, or even relative, contraindications to the use of suxamethonium, then rocuronium has been shown to be a good substitute.

Alfentanil has an onset time in the same order as induction agents and its use may increase depth of anaesthesia. This is because if propofol is contraindicated due to allergy or preference, then there is still a role for thiopentone. However, with thiopentone having limited routine use and limited availability, the experience in its favour and the preference of some traditional anaesthetists will become easier to ignore.

REFERENCES


CONCLUSION

RSI remains an important tool in protecting the airway during induction in emergencies and other situations in which appropriate anaesthetic agents are likely.

The principles of the traditional RSI still hold true, but today there are options of induction agents, muscle relaxants and whether or not to include short-acting opioids, which means that one type of RSI is not suitable for all situations.

There are no contraindications to suxamethonium, a rapid-sequence induction using a predetermined dose of propofol and suxamethonium is probably the first choice for most anaesthetists in most situations and the bulk of evidence in the literature supports this.

However, with thiopentone having limited routine use and limited availability, the experience in its favour and the preference of some traditional anaesthetists will become easier to ignore.

SUXAMETHONIUM VERSUS ROCURONIUM

Suxamethonium is a depolarising muscle relaxant characterised by a rapid onset that is defined by muscle fasciculations, and a quick offset that theoretically precedes halothane desaturation in the apnoic patient. It is, however, the only depolarising muscle relaxant available, and its utility is supported by a long history of use, and if paralysis is not required post-induction, then the use of neurotigmine and an anticholinergic can be avoided. There is also evidence that the addition of alfentanil to this regimen has some advantages, though less so if there is any evidence that the addition of alfentanil to this regimen has some advantages, though less so if there is no evidence that the addition of alfentanil to this regimen has some advantages, though less so if


Which videolaryngoscope do you choose?

WILLIAM PIERRE L BRADLEY, MBCHB, FANZCA
Specialist anaesthetist, Department of Anaesthesia and Perioperative Medicine, The Alfred, and adjunct senior lecturer, Academic Board of Anaesthesia and Perioperative Medicine, Monash University, Melbourne.

Dr William Pierre L Bradley is a past chair of Airway Management Special Interest Group and divides his time between public and private practice. His interests are the perioperative management of the complex patient, simulation education and human factors. Recently he chaired the working party for the new ANZCA professional document PS61 Guidelines for the Management of Evolving Airway Obstruction: Transition to the Can’t Intubate Can’t Oxygenate Airway Emergency. He has been involved with Epworth Anaesthetic Risk Management Committee and the development of the Epworth difficult airway trolley.

JOHN MOLONEY, MBBS, MEMERGH, GRADCERTEMERGH (AEROMEDRETRIEVAL), GRADCERTARTS (WRITING), ACCAM FANZCA, DAME
Specialist anaesthetist, Department of Anaesthesia and Perioperative Medicine, The Alfred, and adjunct clinical associate professor, Academic Board of Anaesthesia and Perioperative Medicine, Monash University, Melbourne.

Associate Professor John Moloney is a staff specialist anaesthetist at The Alfred, where he is the head of trauma anaesthesia. He is the acting chair of the ANZCA Trauma Special Interest Group and sits on the Royal Australasian College of Surgeons Trauma Committee. He is the senior field emergency medical officer for Health Displan Victoria and retrieval physician and critical care co-ordinator for Adult Retrieval Victoria. His special interests are cardiothoracic medicine and anaesthesia, trauma, disaster response, retrieval medicine and human factors.

IAN RICHARDSON, BSC (HONS), MBCHB (HONS), FRCA, FANZCA
Specialist anaesthetist, Department of Anaesthesia and Perioperative Medicine, The Alfred, Melbourne.

Dr Ian Richardson has dual accreditation in intensive care medicine and anaesthesia. He graduated from the University of Manchester with honours in medicine, experimental immunology and oncology. He has undertaken a trauma anaesthesia fellowship at The Alfred and a fellowship in retrieval medicine with CareFlight and Ambulance Service NSW. He divides his time between The Alfred and Monash Health while maintaining an interest in retrieval medicine.

Introduction
Since the introduction of the Weiss video-intubating laryngoscope1, there has been a proliferation in number and type of videolaryngoscopes. Anaesthetists, other providers of critical care and managers need to consider multiple factors when purchasing these devices. These considerations can be broadly divided into those affecting the success of the device in the hands of the laryngoscopist and device technical considerations.

Selection considerations for videolaryngoscopes include:
1. Type of blade.
2. Operating environment.
3. Portability – size, power source, video display.
4. Reliability.
5. Robustness.
6. Integration.
7. Expense – capital, disposables and maintenance.

Blade Selection
Videolaryngoscope are available with Macintosh or hyper-angled type blades, which can be further subdivided into channelled and non-channelled blades2.

Laryngoscopists are generally comfortable using a Macintosh blade. Using a familiar technique, the Macintosh-style videolaryngoscopes provide an improved view, with additional benefits in a difficult intubation scenario1. In an educational setting, Macintosh-style blades can enhance learning for trainee or inexperienced personnel, while reinforcing standard Macintosh intubation techniques3-5. Learning and reinforcing basic intubation skills may be becoming more difficult. Exposure to intubations is decreasing for many trainees due to constraints relating to safe working hours6-9, increased use of alternative airway devices, such as laryngeal mask airways, and increasing out-of-theatre clinical requirements. For training purposes, the laryngoscopist uses the standard direct view of the larynx, while the educator views the video screen, enabling appropriate discussion on blade handling and tube manipulation techniques to optimise the intubation.

The hyper-angled videolaryngoscope is the device of choice as the secondary blade after a failed intubation with a Macintosh-type blade and bougie10-11. It may be the device selected as the primary blade in a suspected difficult intubation. Hyper-angled devices are less familiar to most users. For optimal success these require a different intubation technique12. Rather than entering the right side of the mouth and sweeping the tongue across to the left, they use a midline “point and shoot” technique with a channelled device or a midline, guided technique with a stilette angulated endotracheal tube in an un-channelled device. It may be difficult to use a bougie in the
un-channelled hyper-angled device and novice users should avoid this. Subjectively, the hyper-angled blade can make intubation harder in easy intubation cases (Cormack and Lehane grade 1 and 2). Both of the challenges in hospital and pre-hospital medicine is maintaining the currency of skills. The techniques required to use an ideal scope should therefore be easily mastered and maintained, with the progression from novice to master laryngoscopist being rapid. Ideally, this would mean the minimum volume of practice is required to make and maintain that transition16,17. As a consequence, there is a tendency for pre-hospital organisations to use a conventional Macintosh-blade device in the knowledge that the technique is familiar to many and that the required skills are being maintained in other areas of the laryngoscopist’s clinical practice. Unfortunately, a single device to handle a difficult intubation in all these conditions and their associated challenges is currently not on the market. Australian clinicians feed back their experiences to manufacturers, there is progress towards that ideal.

We believe every intubating scope should have access to both a Macintosh-type and hyper-angled-type videolaryngoscope as this may be one device system with interchangeable blades or as a standard Macintosh laryngoscope and a hyper-angled-videolaryngoscope. In addition, we recommend having a work-based training programme with the devices to overcome the learning curves, there may be limited experiences to over appropriate use of the devices, even by senior staff18,19. Specifically, the look in the mouth-screen-mouth-screen four-step approach20 should be taught for insertion of the videolaryngoscope and endotracheal tube to minimise the risk of iatrogenic injury.21,22,23. Critical training can make intubation harder in easy intubation cases (Cormack and Lehane grade 1 and 2).

Perspectives
We offer a word of caution not to forget awake techniques when supraglottic oxygenation is anticipated to be difficult, in addition to a potentially difficult intubation. Also we add a plea, that it should be clearly documented what type of device is used and the grade of view obtained, so that there can be no confusion with a standard Macintosh-blade device in the knowledge that the technique is familiar to many and that the required skills are being maintained in other areas of the laryngoscopist’s clinical practice. Unfortunately, a single device to handle a difficult intubation in all these conditions and their associated challenges is currently not on the market. Australian clinicians feed back their experiences to manufacturers, there is progress towards that ideal.

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Tracheal extubation: Strategies for predicting and managing extubation of the difficult upper airway in the non-obstetric adult patient

FAYAVAR A AJVADI, MD, FANZCA
Staff specialist, Department of Anaesthesia and Perioperative Medicine, Royal Brisbane and Women's Hospital, Brisbane, Queensland. Staff specialist, Department of Anaesthesia, The Princess Alexandra Hospital, Brisbane.
Dr Fayavar Ajvadi was awarded FANZCA in 2012 after fulfilling provisional fellowships in airway management and paediatric anaesthesia. He completed further training in cardiothoracic anaesthesia and trans-oesophageal echo at Mount Sinai Hospital, New York, in 2012-13.

MICHAEL J EDWARDS, BSC, MBBS, FANZCA, PG DIP ECHO
Staff specialist, Department of Anaesthesia and Perioperative Medicine, Royal Brisbane and Women's Hospital, Brisbane.
Dr Michael Edwards' special interests include difficult airway management, vascular surgery and echocardiography.

KEITH B GREENLAND, MBBS, MD, FANZCA, FHKAM (ANAESTHESIOLOGY)
Consultant anaesthetist, Wesley Anaesthesia and Pain Management, Auchenflower, Brisbane. Honorary Associate Professor, Department of Anaesthesiology, University of Hong Kong, Hong Kong SAR.
Associate Professor Keith Greenland has published several publications on difficult airway management, including an MD thesis titled “A reappraisal of adult difficult airway management, theoretical and practical aspects”.

MICHAEL G IRWIN, MB CHB, MD, FRCA, FHKAM (ANAESTHESIOLOGY), FANZCA
Professor and head, Department of Anaesthesiology, University of Hong Kong, Queen Mary Hospital, Hong Kong SAR.
Professor Michael Irwin is professor and head, Department of Anaesthesiology, University of Hong Kong, Chief of service in Anaesthesia at Queen Mary Hospital and at HKU Shenzhen Hospital, China. He is the president of the Society of Anaesthetists of Hong Kong, and past president of the Hong Kong College of Anaesthesiology, where he is also a member of the education and examination committees and is chief censor. Professor Irwin has published more than 180 articles in peer-reviewed scientific journals and is a regular invited journal reviewer. He is an editor of a number of journals including Anaesthesia, Expert Opinion on Pharmacotherapy, Perioperative Medicine, CPD Anaesthesia (UK), Pain Research and Treatment, Hong Kong Medical Journal, Anaesthesia and Intensive Care Medicine. He is chair of the organising committee for the World Congress of Anaesthesia 2016. Research interests include intravenous anaesthesia, pharmacology, acute pain management and organ preconditioning. He is part of the Faculty of 1000 Medicine in the field of cardiovascular medicine in anaesthesia: basic science.

ANDRE VAN ZUNDERT, MD, PHD, FRCA, EDRA, FANZCA
Professor in Anaesthesiology, School of Medicine, The University of Queensland. Senior staff specialist, Department of Anaesthesia and Perioperative Medicine, Royal Brisbane and Women's Hospital, Brisbane.
Professor Andre Van Zundert is a senior staff specialist at the Royal Brisbane and Women’s Hospital. He is the head of the Discipline of Anaesthesiology and Burns, Trauma, Critical Care Research Centre at the University of Queensland. Professor Van Zundert is widely published with special interests in obstetric anaesthesia, regional anaesthesia and difficult airway management.

INTRODUCTION
Most research and algorithm development in airway management has focused on facilitating safe tracheal intubation, with relatively little attention paid to extubation. According to the latest American Society of Anesthesiologists (ASA) closed claims report, the odds of death or brain damage from airway management associated with induction of anaesthesia decreased by 27 per cent in 1993-99 compared with 1985-93. In contrast, death or brain damage associated with emergence or recovery did not change significantly between the same period1. The incidence of complications associated with extubation may actually now exceed those occurring during intubation2. Extubation complications of the “normal” airway are uncommon. However, occurrence is increased with procedures in proximity to the airway, particularly with emergency surgery. Case reports of potentially preventable post-operative airway compromise leading to death or severe disability in conditions such as Ludwig's angina highlight deficiencies in understanding by medical and nursing staff of the sequence of clinical parameters indicative of the compromised airway3-4, and lack of practical and effective plans to appropriately address them5. In the field of critical care, a higher rate of extubation complications occurs with reports between 2 and 25 per cent. This may be attributable to other factors, including duration of intubation and ventilation, severity of underlying disease, prolonged sedation, generalised weakness (endogenous or iatrogenic) and cardio-respiratory or neurologic compromise6-7.
The ASA Task Force on the Management of the Difficult Airway regards the concept of an extubation strategy as a logical extension of the intubation strategy and strongly supports developing a preconceived plan for extubation of the difficult airway. This strategy depends on the type of surgery, the condition of the patient and the skills and preferences of the practitioner. The focus should ideally be towards assisting the practitioner to identify potentially difficult extubations based on patient history, anatomy, possible functional impairment, oedema and type of surgery. This approach should include tests to identify patients who are suitable for extubation and use devices that allow safe re-intubation as required.

The Difficult Airway Society (DAS) published its landmark consensus papers on tracheal extubation. It has a very comprehensive overview of the patho-physiology of problems arising during emergence and extubation period and highlights the importance of advanced planning for extubation. The stepwise approaches appear in three self-explanatory flow charts, “basic algorithm”, “low-risk algorithm” and “at-risk algorithm”, which describe the process in four steps: plan for extubation; prepare for extubation; perform extubation and post-extubation care. This work and highlights the importance of advanced planning for extubation. The stepwise approaches appear in three self-explanatory flow charts, “basic algorithm”, “low-risk algorithm” and “at-risk algorithm”, which describe the process in four steps: plan for extubation; prepare for extubation; perform extubation and post-extubation care. This work provides practitioners with useful guidelines and a valuable resource for future research.

The use of the three-column model may further assist the anaesthetists and trainees to understand the different nature of airway anatomy in difficult airway and help them to incorporate this knowledge in the context of the clinical scenarios to plan for extubation.

**MATERIALS AND METHODS**

The PubMed database was used to identify publications relevant to tracheal extubation of the difficult airway between the years 1980 to 2011. “Extubation” is not a MeSH term so the following key words were used for the literature search:

- Intubation, intratracheal/adverse effects.
- Intubation, intratracheal/complications.
- Intubation, intratracheal/contraindications.
- Intubation, intratracheal/instrumentation.
- Tracheal extubation.
- Extubation criteria.
- Extubation failure.
- Extubation readiness.

Any articles involving paediatric or obstetric patients were excluded. Articles involving pathophysiology of the lower airway were excluded (for example, bronchospasm or desaturation post-extubation in the intensive care unit). Articles involving extubation of patients without known difficult upper airway problems were excluded.

**DEVELOPING A STRATEGY FOR SUSPECTED HIGH-RISK EXTUBATION**

The need for a stepwise strategy for safe extubation has been outlined previously. Such a strategy should aim to maintain oxygenation, minimise complications and reduce the risk for re-intubation, but include a safe plan to do so if necessary.

Rescuing the airway following tracheal extubation can be extremely difficult for several reasons. Firstly, it is difficult to predict when respiratory compromise may develop. This is a particular problem outside normal working hours or in remote locations when airway expertise may not be immediately available or the provision of airway management equipment may not be ideal. Secondly, patients may have already experienced an episode of respiratory compromise resulting in depletion of their oxygen reserve, which limits the time available to secure the airway. Finally, airway distortion may render intubation challenging, especially in an already anxious and hypoxic patient.

An extubation strategy should aim for adequate oxygenation, minimal complications and a safe plan to secure the airway in case of airway compromise after extubation. This strategy will depend on the surgical and medical condition of the patient and the airway status, as well as on the skills and preferences of the practitioner.

The extubation plan should include:

1. A method for predicting patients at high risk for extubation.
2. Physical assessment of the airway.
3. Airway monitoring after extubation.
4. Development of an airway management plan, including airway devices to facilitate oxygenation and possible re-intubation.

The purpose of many guidelines and algorithms is to direct the clinician on a management pathway that minimises judgment and adverse results. However, the clinician’s judgment at the time is still important in the provision of optimal patient care.
Figure 1. Three-column model for direct laryngoscopy

Modified from Greenland, K.B. Reappraisal of adult airway management, Australasian Anaesthesia, a publication of the Australian and New Zealand College of Anaesthetists. The anterior (triangle) and posterior (solid line) columns of the model for direct laryngoscopy influence the shape of the middle (airway passage) column (dotted line). In addition, the middle column may have intrinsic changes where the configuration is distorted by loss of pharyngeal muscle tone (due to sedative drugs or muscle relaxants), mucosal oedema or airway tumours.

An extubation strategy based on this anatomical definition and the nature of the changes in configuration of the columns, allows the prediction of high-risk patients and the development of specific management strategies. However, difficulty of intubation based on anatomical landmarks is not the sole predictor in the decision for extubation. For example, a patient with either an anterior (for example, retrognathia) or a posterior (for example, ankylosing spondylitis) column problem during intubation may still be suitable for immediate extubation after uncomplicated surgery if the risk of airway compromise is otherwise deemed low. A useful strategy is to insert a laryngeal mask airway (LMA) behind the ETT before tracheal extubation\(^1\). The ETT can then be removed and the supra-glottic airway becomes an airway conduit. The placement of the supra-glottic device is performed prior to removal of the ETT so it can be correctly sited prior to extubation. The LMA is left in place until the patient can maintain his or her own airway\(^2\). Delayed extubation is often recommended in situations where there is a middle column problem. There are two broad situations following anaesthesia when this may occur. Firstly, patients with difficult airways undergoing prolonged anaesthesia and requiring moderate to large doses of long-acting opioids. Hypnotic drugs and opioids separately and in concert depress genioglossus and pharyngeal muscle tone and diminish airway protective reflexes. This loss of tone impacts on the middle column configuration and, when combined with anterior and/or posterior column problems, may make immediate extubation dangerous. Ventilation in the intensive care unit post-operatively allows time for the effects of the anaesthetic drugs to dissipate and provides safer extubation conditions.

The second is when anaesthetic and/or surgical factors, such as prolonged head-down position, massive fluid resuscitation, airway soft tissue trauma or submandibular abscesses, may cause airway mucosal swelling. This anatomical distortion of the middle column requires delay of extubation until the swelling has resolved (Figure 2).

Figure 2. Causes of airway mucosal swelling based on Starling forces and reduced lymphatic drainage

- **Increased hydrostatic pressure**
  - e.g. pre-eclampsia
  - prolonged head down
  - large volume resuscitation

- **Reduced lymphatic drainage**
  - e.g. radiotherapy to submandibular area

2. PHYSICAL ASSESSMENT OF THE AIRWAY

Evaluation and preparation of the patients considered a possible risk for extubation failure should be methodical and comprehensive. Physical assessment of the airway should include: 1. direct laryngoscopy; 2. cuff-leak test; 3. fibreoptic visualisation or often a combination of these tests.

**Direct laryngoscopy**

Direct laryngoscopic visualisation of the airway may provide useful information about supra-glottic and glottic structure and function, particularly in cases with suspected change in the airway configuration due to surgery or underlying pathology. With head and neck surgery, sub-mandibular infection and thermal injury to the airway, post-operative airway mucosal swelling may occur insidiously and present a problem for monitoring and re-intubation. The Cormack and Lehane laryngoscopy grading should be considered as a “snap shot” of the upper airway at intubation, but may not correlate with ease of re-intubation at a later time. In addition, a Magill-shaped tracheal tube (ETT) may push the glottic opening posteriorly giving a deceptively better laryngoscopic view compared to the view after it is removed. This may contribute to difficulties should re-intubation be required. Finally, the tube may compress airway mucosal swelling so that the airway is stented open. After the tube is removed, the oedema fluid may redistribute leading to delayed airway occlusion.

**Cuff-leak test**

Several authors have suggested conducting a cuff-leak test before extubation as an assessment of airway patency\(^2\)-\(^5\). Careful suctioning of the sub-glottic and supra-glottic areas should precede this test. The cuff is deflated and the tube lumen is occluded in order to assess the air leak around the tube during spontaneous ventilation. The cuff-leak test may be performed quantitatively, by measuring the volume of the leak, or qualitatively by listening for an audible leak. The flow around the tube may be generated by respiratory effort in a conscious patient or by a positive pressure of 20mmHg through the ETT. Leak is calculated by measuring the difference between the inspiratory tidal volume with the cuff inflated and the expiratory tidal volume when deflated. The test is positive (failed) when the leak volume is less than 110ml. A positive predictive value of 80 per cent for failed extubation occurs when the test is conducted 24 hours prior to the extubation after extended critical care intubation\(^1\). This may suggest the necessity for surgical access to the airway as a longer term bridging measure before final extubation\(^1\).

A failed cuff-leak test does not necessarily indicate the extubation will fail and, if used as a sole indicator for extubation, may lead to unnecessary delays\(^6\). Judicious fluid management and intravenous corticosteroid therapy may be beneficial in suitable cases\(^3\)-\(^6\).

**Evaluation via fibreoptic bronchoscopy and nasendoscopy**

The fibreoptic bronchoscope (FOB) is useful for visualising airway anatomy and function at several levels\(^7\)-\(^20\). With distorted airway anatomy, vocal cord paralysis or tracheomalacia, FOB can assist the operator to assess the airway prior to extubation. There has been a report of tube entrapment (surgical suture through the ETT cuff) complicating the extubation process identified and remedied with FOB\(^2\). Nasendoscopy also can be used to assess supra-glottic swelling and oedema\(^2\), although interpretation is subjective and somewhat dependent on operator experience. This can be particularly useful with a borderline cuff-leak test.

Appropriate patient selection and explanation, upright positioning and administration of an anti-sialagogue may assist FOB assessment of the upper airway. Unfortunately, the presence of the ETT may limit adequate inspection of the surrounding structures.
3. DEVELOPMENT OF AN AIRWAY MANAGEMENT PLAN

The airway management plan must include an extubation strategy that specifically focuses on allowing continuous oxygenation and ventilation while facilitating early and safe re-intubation if required. Options for management of a high-risk extubation may include the placement of an extraglottic device or an airway exchange catheter.

Exublation of the trachea with an extraglottic device in place:

An extraglottic device may be used as an airway conduit following extubation. A flexible bronchoscope can be advanced through the device allowing inspection of laryngeal anatomy and function. This method is particularly useful when fibroptic assessment of vocal cord function is required. Airway access can be achieved if the fibroptic bronchoscope is loaded with an Aintree catheter (Cook Critical Care, Bloomington, IN) and directed through the extraglottic device. The FOB and the extraglottic device are then removed and an ETT is railroaded over the Aintree catheter. The safety of this method is questionable with suspected peri-glottic oedema, as resulting distortion of the middle column, may make placement of the extraglottic device difficult.

Airway exchange catheter:

Airway exchange catheters (AEC; Cook Critical Care, Bloomington, IN) are small hollow semi-rigid tubes made of radio-opaque polyurethane. They are designed to increase safety while changing an ETT and maintain oxygenation. They have also been used to maintain airway access after extubation, allowing re-intubation if needed. The concept of re-intubation of the trachea using this technique after a failed extubation is not new. Badger and Chang described successful use of a “jet-stylet” as an airway conduit to facilitate re-intubation in 1987. Bemunof also recommended extubation over a jet stilette in order to maintain airway access in case re-intubation was required. In a series of 36 patients who were intolerant of extubation within 120 minutes, four patients between two and four hours, and the largest AEC (19 FG), although an excellent conduit for airway access, is tolerated by only 50 per cent of patients.11

The AEC should be an integral component of any difficult airway extubation strategy. Most studies have examined the size 11 and 14 FG AEC and showed both to be well tolerated by patients. The largest AEC (19 FG), although an excellent conduit for airway access, is tolerated by only 50 per cent of patients.1

Following the decision to use an AEC assisted extubation, after conventional criteria for extubation are met, a lubricated AEC should be carefully inserted through the ETT to the same depth as the tip of the ETT to avoid stimulation of the carina. The ETT can then be removed over the AEC, while maintaining the exchange catheter at the same depth in the trachea. High concentration oxygen can be administered via a modified oxygen mask or through the AEC lumen. The proximal AEC should be secured to the patient’s forehead with adhesive tape to reduce the risk of dislodgement. The tip should be occluded with tape and clearly labelled to ensure it is not mistakenly used for enteral feeding. Patients should remain fasted while the AEC is in situ.

Optimal duration of placement of an AEC:

The ideal duration of continuous airway access post-extubation is variable and depends on the patient’s clinical status. Removal is often based solely on the clinician’s assessment of the patient. In Mort’s study, 36 out of 354 patients in whom the AEC was removed, subsequently required re-intubation within seven hours.12 Eighteen of these 36 patients were intolerant of extubation within 120 minutes, four patients between two and four hours, and 14 patients required re-intubation beyond four hours. The majority of these patients required three or more laryngoscopy attempts and the use of accessory devices and/or techniques during re-intubation. This contrasts with only one patient with the indwelling AEC who required three attempts.

A study in 2004 examined 36 patients after maxillofacial and neck surgery where an AEC was left in situ for a mean of 10.4 hours (range four-24 hours). Four of the 36 cases required re-intubation and all were successful using an 11 FG airway exchange catheter.

Although peri-glottic oedema contributing to airway compromise usually develops within the first 45 minutes after extubation, laryngeal oedema as late as eight hours post-extubation has been reported.15 It may be advisable to extend the duration of continuous airway access to 12 hours or even longer in patients with cardiopulmonary or neurological compromise.16 At this point, there is not enough evidence to confidently recommend a specific duration for leaving an AEC in situ post-extubation.

Advantages:

It has been suggested that by facilitating safer re-intubation after earlier extubation the AEC may reduce complications related to prolonged intubation. This also may be more cost effective.17,18 The AEC also provides a method for the continuous administration of oxygen with less hypoxic episodes during re-intubation when compared with other techniques.19 Several studies have shown improved cardio-respiratory stability during re-intubation when the AEC is used.20,21 The AEC also has been used for jet ventilation and for CO2 monitoring.22

Disadvantages:

Inadventitious removal of AECs has been reported requiring the use of other methods to secure the airway.10,11 Inability to advance an ETT over the AEC due to excessive airway oedema also has been reported.23 Barotrauma occurred in five out of 45 patients when jet ventilation was used via the AEC.24 Other reported complications include lung abscess, direct airway trauma and lung laceration.25,26

Other methods:

Cannula cricothyroidotomy is recommended for emergency tracheal oxygenation and/or ventilation in the current ASAA Practice Guideline for management of the difficult airway. Accurate identification of the cricoid membrane is reportedly poor, possibly due to the infrequent practice.27 This makes the routine use a problem unless training can be improved.

Elective insertion of a cricothyroid cannula prior to intubation and securing it in place in a controlled environment may be beneficial for the management of a difficult airway during both intubation and extubation by providing a route for oxygenation and the possibility of airway access via the Selldinger manoeuvre.28 However, subsequent use of the cannula may be a problem due to cannula displacement after intubation. Further work is required in this area.

4. AIRWAY MONITORING FOLLOWING EXTUBATION

For every potentially difficult airway, extubation should be considered a trial with a clear plan for how and when re-intubation should occur.

Disadvantages:

Inadvertent removal of AECs has been reported requiring the use of other methods to secure the airway.

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Advantages:

It has been suggested that by facilitating safer re-intubation after earlier extubation the AEC may reduce complications related to prolonged intubation. This also may be more cost effective.
Suggested extubation strategy:
The flow diagram below has been constructed based on the principles of the extubation strategy outlined above (Figure 4). It assesses the patient based on their pathophysiological and anatomical parameters, as well as whether they had a pre-existing difficult airway. The airway assessment represents the point at which the airway is assessed by direct laryngoscopy, leak test or fibreoptic visualisation. The authors favour the use of the AEC due to its relative ease of use, ability to deliver oxygen, its use as a conduit for re-intubation and its tolerance by the patients over extended periods of time. Patients with an AEC in-situ should be observed in a high dependency unit/intensive care unit environment where their airway status can be continuously assessed and there is expertise to intervene should the patient’s condition change.

Figure 4. A suggested difficult airway extubation decision-making process illustrating the inter-relationship of key issues

CONCLUSION
The overwhelming attention paid to difficult airway during intubation has led to difficult extubation being neglected. The development of staged strategies for the identification and management of difficult airways during emergence and recovery from anaesthesia or in intensive care may improve patient safety and is strongly recommended. Airway assessment with the identification of early warning signs, and the need for close monitoring in a high dependency unit with staff who can effectively diagnose and manage upper airway obstruction with difficult airway equipment, are integral components of an effective extubation strategy.
Maintaining continuous airway access with the AEC can be an important component of an extubation strategy.
The AEC appears to increase the first-pass success rate of tracheal reintubation and decrease the incidence of complications. It may also be cost effective, allowing a margin of safety for earlier extubation and reducing prolonged intubation with its associated complications. However, the incidence of AEC facilitated re-intubation failure and complications, although low, does still exist.

Antireye™ assisted fibreoptic intubation through extraglottic devices and cricothyroidotomy may have a role as alternative management strategies. Well-designed prospective randomised trials are needed to develop effective and practical extubation strategies, techniques and training.
Staff education focusing on airway monitoring, early detection of airway compromise, and familiarity with rescue equipment is crucial for successful management. Problems often develop in an unfamiliar and suboptimal environment with anxious and/or hypoxic patients. Occasionally, there is a need for education and training of medical and nursing staff working in such environments. This should include familiarisation with difficult extubation algorithms, teaching of clinical signs, and use and interpretation of equipment such as AEC and capnography. Regular simulation workshops further reinforce the practical application of this knowledge.

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Competing interests:
FA Ajavid, MJ Edwards and KB Greenland purchase emergency surgical airway equipment from Cook Medical Pty Ltd for teaching purposes.

REFERENCES
Muscle relaxation in laparoscopic surgery: How deep is deep enough?

THOMAS LEDOWSKI MD, PD, DEAA, FANZCA

Thomas Ledowski is Professor of Anaesthesiology at the University of Western Australia and is consultant anaesthetist at Royal Perth Hospital. He has a keen interest in neuromuscular blocking agents and their reversal, as well as the monitoring of peri-operative nociception.

CONFLICT OF INTEREST DISCLOSURE

Thomas Ledowski has consulted for and accepted a research grant from MSD. However, none of the aforementioned has been related to this publication, and MSD has not in any form been involved in the preparation of this manuscript.

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INTRODUCTION

Harold Griffith and Enid Johnson famously were the first to describe the routine use of a neuromuscular blocking agent (NMBA), curare, in anaesthesia practice1. Three years later, when reviewing 1000 cases of curare use at the Homeopathic Hospital in Montreal, Griffith described the new drug as “dramatically successful”2. However, despite being hailed the “second revolution in anaesthesia” by many, NMBA also became notorious for their predominant side effect, the impairment of respiratory function2. Though this was initially thought to be a problem only during the operation, Beecher and Todd3 soon described a sixfold increase in postoperative mortality after the use of NMBA. Despite this evident problem, NMBA have remained in our portfolio until today, not at least because they allowed surgical techniques previously thought to be impossible4. However, from the outset Griffith suggested to avoid curare-related side effects by reducing its dose, recommending the combination with cyclopropane anaesthesia2.

Though the anaesthetic technique has certainly changed since the days of Griffith and Johnson, the idea to “balance” anaesthesia between hypnosis, analgesia and muscle relaxation has remained nearly unchanged. In this context, NMBA usually play only a minor part, and most anaesthetists (if monitoring the depth of neuromuscular block at all) aim for a moderate depth of block of one to four twitches in the train-of-four (TOF). The latter also applies to the field of laparoscopic surgery – although most anaesthetists seem to agree that some degree of paralysis is necessary to achieve adequate surgical conditions, the depth of muscle relaxation required is largely unknown. As a result, most laparoscopic procedures are likely performed under moderate or shallow neuromuscular block.

Lately, however, some studies have suggested that only deep neuromuscular blockade may achieve best operating conditions during laparoscopic surgery. As deep neuromuscular block cannot be safely reversed with neostigmine, the technique has clear implications for the method of reversal (sugammadex) and may thus also impact on healthcare economics.

Therefore it is the aim of this short review to investigate what depth of neuromuscular block may achieve optimum surgical conditions and best patient outcomes.

DEFINITIONS

According to the revised guidelines for Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents5 the following definitions apply for the description of the depth of neuromuscular block:

- Intense neuromuscular block is reflected by no twitch in neither TOF nor post-tetanic count (PTC) stimulation pattern. The depth of intense block can currently not be adequately monitored.
- Deep block results in ≥1 twitch in the PTC, but no twitch in the TOF.
- Moderate block, frequently also called “surgical depth of block” will allow one to three twitches in the TOF to be elicited.
- Shallow block (>3 TOF twitches) will seamlessly progress into recovery from NMBA, with a TOF ratio of >0.7 signifying recovery of the diaphragm and >0.9 recovery of the pharyngeal muscles. A TOF ratio >0.9 is therefore defined as the threshold for sufficient neuromuscular recovery.

HOW DEEP IS DEEP ENOUGH?

Two recent review articles have investigated the matter6,7, with conflicting results. While a systematic review by Madsen et al.7 concluded that neuromuscular block per se marginally improved operating conditions, and that deep block was superior to a moderate level of block, the second review by Kopman and Naguib6 found little or no evidence for improved surgical conditions under deep neuromuscular blockade. This apparent contradiction is largely resolved when only studies fulfilling certain inclusion criteria are analysed.

When investigating the effect of NMBA on laparoscopic operating conditions, it is important to distinguish between studies comparing “no” versus “moderate” or “deep” block and those comparing different depths of block (usually “moderate/shallow” versus “deep”). Without using a “no” block group as control. It is also critical to note whether a specific study used a clear description of outcome parameters (that is, surgical conditions on numeric
rming scale) and whether the depth of neuromuscular block was monitored at all. The allocation to treatment arms should also be randomised as well as observers ideally be blinded. In view of many old studies which are still quoted in current reviews it is desirable to only include publications in which the described anaesthetic is comparable with today’s standards of care.

Disappointingly, the above excludes >95% of all trials published about the topic. Only six studies ultimately qualify for further analysis10,11, with three aiming to compare “no” versus “deep” block10,11 and three comparing “moderate” versus “deep” block10,11,12.

**NO BLOCK VERSUS DEEP BLOCK**

Three studies investigated surgical conditions under “no” versus “deep” block. Deep muscle relaxation improved surgical space at a given intra-abdominal pressure (IAP), or allowed a reduction of IAP without impairing operating conditions. Deep muscle relaxation resulted in a significantly increased working field with sporadic muscle contractions, movements, or both10,11,12.

**MORPHINE OR MELANIE?**

In the largest and probably best-designed of these three studies, Blomberg et al13 examined the effect of deep paralysis on surgical conditions during laparoscopic cholecystectomies. Fifty patients were randomly assigned to receive either no or deep neuromuscular block. Investigated outcome parameters were signs of inadequate muscle relaxations (inadequate neuromuscular relaxations, inadequate ventilation, or breathing and coughing against the ventilator), the frequency of rescue doses of rocuronium (0.3mg/kg) and the overall rating (0-10 numeric rating scale) of operating conditions by the surgeon at the end of the procedure. All patients received deep anaesthesia monitoring with capnometry under desflurane/oxygen anaesthesia. Signs of inadequate anaesthesia were significantly more often found in the “no” block group (12/25 patients versus 1/25 patients; p<0.001), resulting in an absolute risk reduction of 0.44 (0.23-0.65) and a number needed to treat of 2.3 (1.5-4.4). Rescue rocuronium was significantly more often found in the “no” block group (12/25 patients versus 1/25 patients; p<0.001), resulting in a trend towards a higher success rate with “deep” block: 15/25 versus “moderate” block13.

No Blcok Versus Deep Blcok

The attempt was made to perform all procedures at an IAP of 8 mmHg. Surgical space ratings were done by blinded assessors using a four-point scale. Optimum conditions throughout the duration of the procedure were found in the “deep” block group (4/4 patients at all time points) whereas in the “no” block group only 2 patients (8%) were rated as “excellent” (scores at the low end of the scale; scores 1-3); deep block resulted in 99 per cent of scores at the high end of the scale (scores 4 and 5). The authors also asked 12 experienced anaesthetists to rate operating conditions based on visual analog scale ratings from the study according to the 1-5 scale used by the surgeons. Despite the poor agreement between ratings of the same images by anaesthetists and surgeon. Although the study was well designed, it was relatively small. Furthermore, the described differences appear – at least on first sight – relatively small, with 80 per cent of operating conditions in the “moderate” group (4/4 patients) and 99 per cent of conditions in the “deep” block group (P<0.001).

**Surgical space**

Intraoperative, intra-abdominal space (distance from trocar insertion at the skin to the promontory) was assessed by the surgeon at two different levels of IAP of 8 and 12mmHg and at non-paralysed versus deep block respectively. Independent of the level of IAP, muscle relaxation resulted in a significant increase of intra-abdominal space. Intra-operative surgical conditions were found in the “deep” block group (4/4 patients at all time points) whereas in the “no” block group only 2 patients (8%) were rated as “excellent” (scores at the low end of the scale; scores 1-3). The third study in this context was published by Dubois et al 14. The authors randomised 105 patients scheduled for laparoscopic hysterectomies into either “deep” block (TOF maintained < 2) or “shallow” (initial bolus of rocuronium 0.6mg and further relaxant only if surgical conditions unacceptable) block. The surgeon scored the quality of the surgical field every 10 minutes as excellent (1), good but not optimal (2), poor but acceptable (3), or unacceptable (4). For the “shallow” and “deep” groups respectively, the maximum surgical field scores were 1 in 21 and 34 patients, 1 in 13 and 30 patients, 2 in 11 and 11 patients, 3 in 4 and 5 patients and 4 in 14 and 0 patients. A trend towards higher scores (+ worse conditions) was demonstrated in “shallow” block group (P<0.001). Surgical field scores of 2, 3 and 4 (not excellent ratings) occurred only when the TOF was at least 2 and 3 respectively.

**Discussion**

A similar investigation is reported by Martini et al 15. Twenty-four patients were randomised into either “deep” or “moderate” neuromuscular blockade for a laparoscopic prostatectomy or nephrecomy. One surgeon rated the operating conditions into five categories – excellent being 5 and unacceptable 1. Overall, significantly better ratings were obtained in the “deep” block group (4.7 ± 0.4) versus 3.6 ± 0.6 in the “moderate” block group (P < 0.05).

**Rescue rocuronium**

In contrast, rocuronium was used significantly more often in the “moderate” block group (12/25 patients versus 1/ 25 patients; p<0.001), resulting in a significantly higher number of rescue doses of rocuronium (0.3mg/kg) and a trend towards a higher success rate with “deep” block: 15/25 versus “moderate” block (P<0.001). This indicates that the surgeon was not blinded to the state of muscle relaxation.

**Conclusions drawn from this publication about patient care in 2015 should hence be viewed seriously awkward.**

Furthermore, it has since been recognised that nerve stimulation at the adductor pollicis brevis muscle may be important in high-risk patients (such as bariatric, or those with significant adhesions from previous surgery) or procedures (such as robotic surgery), where even small movement may have catastrophic consequences.

**MODERATE/SHALLOW VERSUS DEEP BLOCK**

Summary

Three studies compared “shallow”- (possibly the standard depth of block during laparoscopic surgery, see above) versus “deep” block. All studies found better operating conditions under “deep” versus “moderate” or “shallow” block. The maximum of surgical block differences were relating small, they may be important in high-risk patients (such as bariatric, or those with significant adhesions from previous surgery) or procedures (such as robotic surgery), where even small movement may have catastrophic consequences.

The attempt was made to perform all procedures at an IAP of 8 mmHg. Surgical space ratings were done by blinded assessors using a four-point scale. Optimum conditions throughout the duration of the procedure were found in the “deep” block group (4/4 patients at all time points), whereas in the “no” block group only 2 patients (8%) were rated as “excellent” (scores at the low end of the scale; scores 1-3). The study failed to demonstrate a significant difference between groups in the number of procedures performed at an IAP of 8 mmHg (P = 0.08). The study concluded towards a higher success rate with “deep” block versus “shallow” block (P<0.05) and a trend towards a higher success rate with “deep” block versus “moderate” block (P = 0.06). Furthermore, operating conditions during dissection of the gall bladder rated about 10 per cent better when “deep” block was performed. The authors concluded that “deep” block marginally improved surgical conditions for laparoscopic cholecystectomy.

**Ultrasound for laparoscopic surgery**

Intraoperative, intra-abdominal space (distance from trocar insertion at the skin to the promontory) was assessed by the surgeon at two different levels of IAP of 8 and 12mmHg and at non-paralysed versus deep block respectively. Independent of the level of IAP, muscle relaxation resulted in a significant increase of intra-abdominal space. Intra-operative surgical conditions were found in the “deep” block group (4/4 patients at all time points), whereas in the “no” block group only 2 patients (8%) were rated as “excellent” (scores at the low end of the scale; scores 1-3); deep block resulted in 99 per cent of scores at the high end of the scale (scores 4 and 5). The authors also asked 12 experienced anaesthetists to rate operating conditions based on visual analog scale ratings from the study according to the 1-5 scale used by the surgeons. Despite the poor agreement between ratings of the same images by anaesthetists and surgeon. Although the study was well designed, it was relatively small. Furthermore, the described differences appear – at least on first sight – relatively small, with 80 per cent of operating conditions in the “moderate” group (4/4 patients) and 99 per cent of conditions in the “deep” block group (P<0.001).

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Based on the need for an (ideally) paralysed abdominal wall and diaphragm during laparoscopic surgery, and based on the “deeper than usual” level of neuromuscular block needed to achieve this goal, many anaesthetists aim to combine a modest-shallow depth of block with deep anaesthesia in order to facilitate NMBA reversal at the end of surgery. As propofol has no significant muscle-relaxing properties, NMBA would ideally need to be combined with volatile anaesthetic agents that are known to have significant muscle-relaxing properties, both by direct action on skeletal muscle as well as by an interaction with NMBA[18-19]. This would principally follow Griffith’s advice to combine curare and cyclopropane anaesthesia[20]. Though volatile anaesthetic agents “boost” the effects of NMBA by about 20-30 per cent, a study by Tanmoto and Oikikola[21] suggests that this may less reliable than it appears. Though the authors concluded that “as anaesthesia deepened, less intense block was required”, they also stated “individual variation, certain 'overdosing' of neuromuscular blocking drugs is necessary to guarantee adequate muscle relaxation of abdominal muscles during all stages of upper abdominal surgery[22]. Depth of anaesthesia appears therefore not to be sufficiently predictable to maintain satisfactory surgical conditions. In light of ongoing intense research into the possible side effects of “too deep” anaesthesia[23], deep anaesthesia may be somewhat counter-intuitive strategy to save on the dose of NMBA and improve surgical conditions.

CONCLUSION

Good evidence exists for the beneficial effect of deep (versus no) muscle relaxation on surgical working conditions during laparoscopic surgery. However, the ideal depth of neuromuscular block has still not been defined. Recent publications have shown a small but significant benefit for deep vs. moderate-shallow depth of block. A continuously monitored and maintained deep-to-moderate neuromuscular block appears superior to a one-off dose of an NMBA with subsequent spontaneous awakening. Whether such differences are crucial for everyday routine surgery is yet unknown. However, deep block may be advisable for difficult cases for which sudden patient movements could have catastrophic consequences.

The impact of deep block on postoperative patient outcomes has been much less investigated. However, lower IAP has shown to have significant outcome benefits (such as less organ damage and less postoperative pain), and continuous monitored deep-moderate block may assist in keeping the IAP as low as possible. Whether or not deep vs. moderate block is used in a specific case ultimately remains a point of discussion between surgeon and anaesthetist. Continuous neuromuscular monitoring, as well as ongoing communication between the involved parties, remain of utmost importance.

REFERENCES


Perioperative iron deficiency anaemia – a review with a regional flavour

RYAN HUGHES, MBBS
Launceston General Hospital, Australia.
Dr Hughes is a second-year anaesthetic registrar at the Launceston General Hospital. His passion for all activities outdoors has kept him in Tasmania since completing his medical degree in 2010.

ALHOSSAIN KHALAFALLAH, FRACP
Launceston General Hospital and University of Tasmania, Australia.
Professor Khalafallah completed his postgraduate study in haematology at the University of Heidelberg, Germany. He has extensive clinical and academic experience in hospitals and universities both abroad and in Australia and is widely published in scientific and clinical research. Professor Khalafallah’s main research interest focuses on translational research that leads to improving patient outcome. This includes the field of iron metabolism and management of anaemia in different settings.

DANIEL ARAS, FANZCA
Launceston General Hospital, Australia.
Dr Aras is an anaesthetist representative on the Launceston General Hospital Transfusion Committee and has a particular interest in preoperative patient optimisation. He also develops software for clinical decision-making support, audit and research purposes.

INTRODUCTION
Launceston General Hospital (LGH) is a public, regional tertiary referral hospital and the second-largest in Tasmania. It has a catchment of some 150,000 patient population, with some specialties servicing a total of 250,000 – the entire north of the state. It has an obstetric unit delivering about 1500 women a year and most surgical specialties are represented, with the exception of cardiac and neurosurgery. Tasmanians suffer a greater burden of comorbid disease, and have a lower life expectancy than residents of most other Australian states and territories.

This article aims to summarise the epidemiology and pathophysiology of iron deficiency anaemia (IDA), the therapeutic options, rationale for our process of haematinic optimisation in the perioperative and maternity setting and our prospects for the future in promoting a system for appropriate patient blood management in obstetrics and surgery at the LGH.

WHY PATIENT BLOOD MANAGEMENT?
The goal of patient blood management (PBM) is to improve patients’ clinical outcomes. While not the primary aim, minimising or avoiding blood transfusion can be considered another desirable result.

Red blood cell transfusion in the perioperative period is associated with increased mortality following cardiac and non-cardiac surgery. This has been demonstrated in short-term outcomes as well as in five-year follow-up data. There has been much debate about the cause of this and it is still not clear whether blood transfusion per se or the series of physiologic insults that lead to blood transfusion are the cause of the increased mortality.

Blood transfusion is associated with increased morbidity; there is a clear association with postoperative infections and increased length of hospital stay. The term transfusion-associated immune modulation (TRIM) has been coined to describe the range of immune changes that occur due to blood transfusion. TRIM encompasses changes to cellular immunity, as well as alteration of cytokine expression, such that malignant tumour growth is favoured. Observational evidence suggests that there is a link between cancer recurrence and administration of blood products.

Blood transfusion is expensive. Figure 1 outlines the list prices for some commonly used blood products. These costs are list prices only, and the true cost of administration is much higher. The average cost of administration of a unit of packed red blood cells is estimated to be three to four times the unit cost of the product. The cost of blood transfusion is shared between the States and Commonwealth of Australia. The Commonwealth funds the majority (63 per cent) of the cost of procurement and distribution of blood, with the states and territories responsible for the remainder. The state services are also responsible for the costs of administration and any complications. There has been a paradigm shift away from blood transfusion across Australia, with many hospitals implementing transfusion management programs to meet National Blood Authority Guidelines introduced in 2012. PBM programs have implemented preoperative, intraoperative and postoperative strategies built on three conceptual “pillars” promoting an approach aimed at “optimising red cell mass”, “minimising blood loss and bleeding” and “harnessing and optimising physiological reserve of anaemia”. Most of this article pertains to “optimising red cell mass”.

Perioperative iron deficiency anaemia – a review with a regional flavour
ANAEMIA AND IRON DEFICIENCY

Defined values for normal haemoglobin (Hb) level may vary by laboratory and population; however, most authors agree anaemia should be defined as Hb <120g/L for non-pregnant women. In a pregnant woman at greater than 20 weeks gestation, a Hb of <110g/L is considered anaemic. In adult men at all ages, anaemia is defined as Hb less than 130g/L.

Figure 2 shows the rate of anaemia in the non-pregnant Australian population. Under the age of 65, the anaemia rate is less than 4 per cent – about 6 per cent in females and 2 per cent in males. This risk increases to 16 per cent over the age of 75. The rate of anaemia among patients presenting for major elective surgery is unclear. In pregnant women, the prevalence of IDA is estimated to be about 15 per cent in the developed world.

Anaemia is an independent risk factor for morbidity, mortality, hospitalisation and a decreased quality of life. Preoperative anaemia is an independent risk factor for postoperative morbidity and mortality, as well as being associated with an increased likelihood of blood transfusion.

Iron deficiency is the most common cause of anaemia in patients presenting for major elective surgery. This cohort of patients is typically elderly with multiple comorbid conditions. Diabetes, cardiac failure, cancer and chronic renal impairment are associated with a greater risk of concurrent anaemia than are other comorbidities.

It is important to recognise that IDA is only a late feature of iron deficiency, which should itself be considered a pathologic state. Insufficient stored iron due to lack of intake progresses to iron deficient erythropoiesis that can ultimately lead to IDA. Pathogenesis of IDA due to chronic blood loss is explained, as most stored iron in the form of ferritin is used in hyperactive erythropoiesis. When iron stores become severely depleted, erythropoiesis becomes inadequate, leading to IDA.

Iron deficiency is the most common cause of anaemia in patients presenting for major elective surgery. This cohort of patients is typically elderly with multiple comorbid conditions. Diabetes, cardiac failure, cancer and chronic renal impairment are associated with a greater risk of concurrent anaemia than are other comorbidities.

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CURRENT STRATEGY TO ASSESS IRON DEFICIENCY

Full blood count including Hb and blood film, as well as blood indices such as mean corpuscular volume (MCV), mean corpuscular Hb concentration (MCHC) and red cell count (RCC) values allowing the diagnosis of microcytic anaemia is considered a good screening tool for IDA. However, in areas of the world where haemoglobinopathies are prevalent, these indices will indicate microcytosis, so iron studies (in particular the ferritin level) remain the surrogate marker for IDA.

The degree of iron deficiency is classified according to ferritin level into:

- Severe iron deficiency if the serum ferritin level is below 15 or 30μg/L (some variation between laboratories).
- Moderate iron deficiency if the serum ferritin level is 30-50μg/L.
- Mild iron deficiency if ferritin is 50-100μg/L.

A low transferrin saturation <20 per cent (or <15 per cent in some studies) also indicates iron deficiency. Ferritin can be considered the surrogate marker for iron deficiency, but serum ferritin is an acute phase reactant often raised in cases of inflammation or infection.

Therefore, a concurrent test for inflammatory markers such as C-reactive protein (CRP) is advisable in cases of anaemia with raised ferritin, to exclude reactive causes. Iron deficiency is unlikely if the ferritin level is above 100μg/L.

In conditions associated with inflammation, the expression of the plasma protein, hepcidin, is increased. Hepcidin impairs absorption of dietary iron and inhibits the use of stored iron. Hepcidin expression associated with inflammation thus can cause an iron sequestration disorder in which iron storage may be normal as assessed by ferritin level, but the transferrin saturation is low. These patients are not iron deficient per se, but are unable to access their iron stores appropriately. There is no benefit from oral iron (due to expression of hepcidin), but intravenous iron therapy might help.

Other complementary tests in iron studies, such as serum iron and iron-binding capacity, are helpful in confirming the diagnosis of IDA and are outlined in Figure 3.

Figure 2. Population risk of anaemia by age group, persons 12 years and over

Figure adapted from Australian Health Survey: Biomedical Results for Chronic Diseases, 2011-12

Figure 1. List price per unit of some commonly used blood products

<table>
<thead>
<tr>
<th>Product</th>
<th>Cost per unit (AUD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>365</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>296</td>
</tr>
<tr>
<td>Platelets</td>
<td>391</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>40</td>
</tr>
</tbody>
</table>

Figure 3. Laboratory evaluation of iron status

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal range/ diagnostic values</th>
<th>Details</th>
<th>Access</th>
<th>Other details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>30-300 mcg/L and it is lab-specific.</td>
<td>Ferritin is an acute phase reactant and can be increased in patients with inflammation, liver disease, chronic infection, autoimmune disorders, and some types of cancer.</td>
<td>Readily available in most laboratories.</td>
<td>Acute phase reactant.</td>
</tr>
<tr>
<td>Transferrin saturation (TSAT), iron binding capacity and serum iron</td>
<td>In healthy people, about 20-40% of available transferrin sites are used to transport iron. Total iron-binding capacity (TIBC) is commonly used with iron level to evaluate iron status. Both tests are used to calculate transferrin saturation, which is a functional marker of iron status rather than just iron or TIBC alone.</td>
<td></td>
<td>Readily available in most laboratories.</td>
<td>More reliable than ferritin.</td>
</tr>
<tr>
<td>Hepcidin</td>
<td>Not standardised – see comments.</td>
<td>A hepatic derived plasma protein that regulates intestinal iron absorption. Released when adequate or high iron stores binding and down regulating intestinal ferroportin, reducing dietary absorption. When stores are low, release is suppressed leading to an increase of iron efflux from enterocytes into the blood.</td>
<td>Available only in a few laboratories and not yet widely used.</td>
<td>Easily detected in urine, hepcidin estimation seems a potentially accurate test that reflects the actual iron status.</td>
</tr>
</tbody>
</table>
irons therapy

oral preparations

oral iron therapy is common treatment for IDA, despite having significant limitations relating to intake and absorption. The most common cause of oral iron therapy failure is non-compliance because of side effect–related patient intolerance. The side effects of oral iron therapy include gastrointestinal disturbances (colicky pain, nausea, vomiting, diarrhoea and constipation) and occur in up to 50 per cent of patients taking oral iron preparations.20

mouth is mainly composed of ferrous iron. Unfortunately, there are low and variable absorption rates, limited by ingestion of certain foods or by mucosal luminal damage and needing an acidic medium for optimum absorption.21–23. Ferric compounds were introduced to avoid such obstacles, but the available compounds are generally less soluble and have poor bioavailability. A new oral ferric polymaltose compound (Vifor Pharma Inc., Zürich, Switzerland) appears to have less side effects and better absorption. This promising results warrant further clinical trials to confirm the effectiveness and utility of this new oral iron polymaltose in the treatment of IDA.

the usual recommended oral ferrous sulphate dose for the treatment of iron deficiency is at least 80mg daily of elemental iron, which is equivalent to 250mg of oral iron sulphate tablets (Abbott, Australasia Pty Ltd).

Intravenous preparations

Parenteral iron is seen as an attractive option in the treatment of IDA. It is likely to be more popular due to the introduction of new and relatively safe intravenous iron preparations that allow substantial doses of iron to be administered intravenously in a single treatment.24

First-generation intravenous iron preparations (dextran complexes) had serious side effects, including anaphylaxis, limiting their use in the treatment of IDA. Iron sucrose was released in the 1990s and is safer, but its maximum weekly dose of 600mg limits its use. More recent formulations, such as iron polymaltose and carboxymaltose complexes, are better tolerated and can be used for rapid repletion of iron stores25–27. Nevertheless, intravenous iron remains underutilised because of previous concerns with tolerability of the older intravenous iron preparations and in spite of increasing evidence of the safety of the newer preparations, both in pregnant and general populations.13,25–27.

cost analysis

The cost of intravenous iron therapy is that of the product itself, plus the cost of administration in a day procedure or outpatient setting. The cost of iron polymaltose and carboxymaltose are similar (despite the higher product cost of carboxymaltose), as less nursing time is required to administer the carboxymaltose. There are small costs for expendables, clerical work and disposal of waste (Figure 4). Intravenous iron therapy is much cheaper than transfusing even one unit of blood.

Figure 4. Costing for iron supplementation courses of comparable efficacy (AUD)

<table>
<thead>
<tr>
<th>Product</th>
<th>Cost per unit</th>
<th>Administration time</th>
<th>Cost (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulphate</td>
<td>$0.3 per tablet</td>
<td>6-9 months</td>
<td>$54–89</td>
</tr>
<tr>
<td>Iron polymaltose</td>
<td>$100 (for 1g)</td>
<td>2.5 hours</td>
<td>$375</td>
</tr>
<tr>
<td>Iron carboxymaltose</td>
<td>$232 (for 1g)</td>
<td>15 minutes</td>
<td>$300</td>
</tr>
</tbody>
</table>

Evidence

iron therapy in obstetrics

A randomised controlled trial of oral versus intravenous iron for the treatment of mild-moderate IDA in pregnancy was conducted at LGH between 2007 and 2009 and published in 2010.28 Both oral and intravenous iron therapy were effective in treating IDA in pregnancy and the intravenous iron group had a statistically lower rate of anaemia (16 per cent) at term compared to the oral iron group (29 per cent).

A protocol was introduced concurrently so that all women referred to the obstetric clinic received a full blood count and iron studies in their first trimester, allowing for timely identification and treatment of IDA of pregnancy. The hospital’s current protocol is that pregnant women are routinely screened for iron deficiency; those with moderate to severe iron deficiency are given intravenous iron, while those with mild iron deficiency are treated with oral iron. This protocol of timely iron in the obstetric population at the LGH has approximately halved since the completion of the project in 2009.

Preoperative iron therapy

Preoperative oral iron therapy has been shown to be effective in the treatment of IDA.29–32. Most of the data to support this statement is derived from trials of orthopaedic patients, in which one month of oral iron therapy preoperatively improved preoperative haemoglobin, postoperative haemoglobin and decreased the need for blood transfusion. The timeframe required for intravenous iron to be effective is unclear. There is some evidence from small orthopaedic trials to suggest that in neck-of-femur fracture fixation, joint replacement and spinal surgery, an iron infusion less than four days preoperatively decreased the need for blood transfusion and decreased rates of wound infection.33,34

Preoperative erythropoiesis-stimulating agents (ESA)

Studies investigating the efficacy of ESAs for the treatment of preoperative anaemia commonly combine ESAs with iron therapy. Available evidence suggests that in non-cardiac surgical patients treatment of IDA with ESAs offers no added benefit over treatment with iron therapy alone in relation to postoperative haemoglobin levels and blood transfusion.35

Patients who have chronic kidney disease, or those who are anaemic and have had nutritional deficiencies ruled out, may benefit from preoperative ESA therapy.36 This should be arranged in consultation with a haematologist and renal physician.

Postoperative iron therapy

Postoperatively, the erythropoietic response to blood loss is blunted by the systemic inflammatory response to surgery.37,38 As alluded to earlier, the expression of hepcidin impairs absorption of oral iron such that postoperative oral iron therapy fails to increase haemoglobin concentration.39 There is contradictory evidence for intravenous iron therapy for the treatment of postoperative anaemia with several small trials in the setting of cardiac and orthopaedic surgery demonstrating no benefit37;40; while one observational study showed a decrease in transfusion rate post– joint replacement.38

Regional flavour – preoperative screening, diagnosis and treatment of IDA

Patients attending the LGH may come from distances of up to 250km and several hours by road. For many, this is a daunting and expensive journey not to be repeated without good reason. The current LGH practice is that often a surgical date is given, followed by an appointment in the preoperative assessment unit. Only those patients perceived to be at special risk are seen in the preoperative assessment unit by an anaesthetist. When there may only be a couple of weeks between preoperative assessment and booked surgery, the choice between a month of preoperative iron therapy or a same-day 15-minute intravenous infusion is simple. Many a patient has languished on the surgical waiting list for a year or more and to add further delay is distressing. Worse, the patient will have already made work and family arrangements for the original surgical date. Iron cannot be added to an operation that can be scheduled to occur in the near future.

In 2010, the LGH undertook an industry-funded trial of use of point-of-care testing to minimise the need for repeat visits or delayed return for patients requiring preoperative iron infusions. A Pronto 7 with Rainbow 4D Sensor probe (Masimo) was used to screen patients on arrival in the preoperative assessment unit. Patients found to have a low haemoglobin (less than 10g/dL, iron studies sent for urgent full blood count and iron tests after their appointment. If they were found to be anaemic and iron deficient, they would be referred to the day procedure unit for an intravenous iron infusion after anaesthetic assessment. Iron carboxymaltose (Ferrinject) was made available so the infusion took only 15 minutes instead of the several-hour protocol that occurs with iron polymaltose administration. The study protocol enabled the rapid identification and treatment of IDA. Use of the Masimo probe required some finesses, was more sensitive in males than females and was a good overall screening tool to identify patients with IDA, allowing same-day iron replacement and reducing the number of hospital visits.41

Taking stock

An audit of 100 consecutive major elective surgical cases at the LGH was undertaken in 2015 and compared with 100 comparable cases from 2010 (Figure 5). The rates of preoperative anaemia are similar between the two cohorts; the most commonly identified patients were those presenting for hip or knee arthroplasty and gastrointestinal cancer resection (44 per cent and 42 per cent respectively of all identified cases of preoperative anaemia). Fewer of the major orthopaedic patients were anaemic (23 per cent), compared to patients with gastrointestinal malignancies (40 per cent). In 2015, 76 per cent of patients presenting for major elective surgery had iron studies preoperatively – this can be improved upon as a relatively new practice. Of all anaemic patients identified in 2015, 14 had co-existing iron deficiency; of these 14 patients, nine received a preoperative iron infusion. There were four cases of preoperative anaemia where ferritin levels exceeded 300µg/L. It is of note that in 2015, a further 11 patients with preoperative haemoglobin in the “low end” of the normal range had iron studies suggestive of iron deficiency (ferritin 30–50µg/L with low transferrin saturation). None of these patients received preoperative iron therapy. It is unclear whether these patients with preoperative iron therapy due to their impending blood loss – this remains an area of research.

Blood transfusion occurred in six patients in 2015, compared with 13 in 2010. The decrease in transfusion rate may arguably be due to a decrease in transfusion threshold, iron therapy or both.
Figure 5. Audit of LGH anaemia rates, iron infusion and blood transfusion practice 2010 and 2015

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative anaemia prevalence</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Preoperative iron studies requested</td>
<td>2%</td>
<td>76%</td>
</tr>
<tr>
<td>Blood transfusion rate</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Iron infusion administered in setting of IDA</td>
<td>N/A</td>
<td>9/14</td>
</tr>
</tbody>
</table>

Where to from here?

Preoperative identification and treatment of IDA as part of a blood conservation strategy is a relatively new concept in anaesthetic practice. If done well, it is of benefit to patients undergoing major elective surgery. Even now, the widely applauded process of patient blood management instigated statewide in Western Australia seems a little difficult to replicate.

In their analysis of the Western Australian success, Farmer et al. acknowledged that changing medical practice in a sustainable manner is challenging. Cultural change takes time to implement and requires consistent practice and communication from those driving the change. They refer to a three-stage, eight-step model published originally by Kotter, and inform that over 50 per cent of organisations will fail in the earliest stage: “Defrosting a hardened status quo”. For example despite the success of the Masimo probe as a screening tool it is not currently being used in the preoperative assessment unit at the LGH.

Streamlining for success – better operative planning

The LGH Department of Anaesthesia is planning the best way forward. Recently published guidelines have encouraged a sustained change with regard to PBM and haematinic optimisation. The role of transfusion nurse will be expanded to incorporate all perioperative PBM coordination. That will include the ongoing task of directing perioperative haematinic optimisation, and linking with various hospital departments; including haematology, anaesthesia, surgery, emergency medicine and intensive care. There will also be more emphasis on contact with general practitioners, such that patients listed for major elective surgery are screened (and where necessary, investigated and treated) for iron deficiency in the community in order to avoid surgical delays from late diagnosis.

The LGH Department of Anaesthesia is currently encouraging major elective surgical patients to be seen by an anaesthetist at least four weeks in before their surgical date, so that haematinic therapy can be timely, effective and convenient.

We plan to reintroduce point-of-care testing in the preoperative assessment unit using the Masimo. Patients from remote areas with low haemoglobin readings with this device will be prepared for a same-day iron carboxymaltose infusion, pending their formal haemoglobin and iron study results. In order to retain clinic efficiency, local patients will have a return visit coordinated after results of iron studies are known.

Checking of preoperative blood tests will become automated by the introduction of computer-based, pathology-server linked, anaesthetic assessment chart software. It will automatically populate preoperative results directly into patients’ anaesthetic files and abnormal results will automatically be flagged for intervention.

We have reviewed our clinical guideline for interpreting preoperative iron studies. Specifically, this guideline will incorporate transferrin saturation results to improve the diagnosis and treatment rate of iron deficiency (Figure 6).

Our plan for urgent cancer surgery patients includes mandatory full blood count and iron studies at the time the surgeon books the procedure. Results are directed to the anaesthetic clinic for timely subsequent management.

It has taken several years to implement, but since May 2015 the LGH stocks and administers intravenous iron carboxymaltose in the day procedure unit. Previously it was not stocked due to its expense. However, the LGH departments of Anaesthesia and Haematology convinced hospital management that, despite being a more expensive product, the 15-minute administration time is where the real cost saving is to be realised. It also allows identification and treatment of IDA on the day of clinic appointment, thus avoiding expensive repeat visits.

We must all acknowledge that criteria for surgical readiness have changed. IDA is common, easily identifiable and readily treatable. If IDA is left untreated, major elective surgical patients are exposed to unnecessary risk. Inadequately treated IDA subsequently represents a contraindication to major elective surgery.

Figure 6. Diagnostic flowchart for preoperative anaemia

Preoperative blood tests: full blood count, iron studies, CRP and renal function

- Anemia
  - Male Hb<130g/L
  - Female Hb<120g/L

Any unexpected finding of anaemia must be relayed to the patient’s general practitioner

- Ferritin <30mcg/L
  - Possible iron deficiency
  - Assess TSAT

- Ferritin 30-100 mcg/L
  - Possible iron deficiency anaemia
  - Consider clinical context and other causes

- Ferritin >100 mcg/L
  - Unlikely iron deficiency

CRP (C-reactive protein), TSAT (Transferrin saturation)
Perioperative nutrition

RA’EESA DOOLA, BHELTHSCI (NUTRITION & DIETETICS)
Senior dietitian at Mater Health Services, honorary associate lecturer at Mater Research Institute, The University of Queensland, Brisbane.
Ms Ra’eesa Doola is a senior dietitian with extensive clinical experience in the areas of perioperative and critical care nutrition. She is undertaking a PhD through the School of Medicine at the University of Queensland with a focus on glycaemic control in the high-risk perioperative and critically ill patient.

DAVID J STURGESS, MBBS, PHD, PGDIPCU, FRACGP, FANZCA, FCICM
Specialist in anaesthesia, Royal Brisbane and Women’s Hospital, Brisbane; deputy director of Adult ICU, Mater Health Services, South Brisbane.
Dr David Sturgess shares his clinical time between clinical anaesthesia and intensive care medicine. He has a keen interest in perioperative medicine research and practice.

ALWYN TODD, PHD, PGDIPDIET, BSC
Senior research dietitian at Mater Health Services, honorary senior lecturer at Mater Research Institute, The University of Queensland, Brisbane.
Dr Alwyn Todd is a senior dietitian with clinical research experience spanning Australia, New Zealand and the UK. Her research interests are primarily in the area of nutrition and metabolic health.

INTRODUCTION
Optimisation of nutrition during the perioperative period is increasingly recognised for its potential contribution to improving clinical outcomes. This review aims to collate evidence relating to perioperative nutrition in the hope it will guide implementation of evidence-based nutrition practices in this patient population.

PERIOPERATIVE METABOLISM
Surgical insult initiates a cascade of metabolic events affecting aspects of the endocrine, immunological and haematological systems. The injured site triggers a response to the hypothalamus via the nervous system. In turn, the hypothalamus releases hormonal secretions such as growth hormone releasing hormone (GHRH) and corticotrophin-releasing hormone (CRH) to exert an influence over the pituitary gland. GHRH and CRH stimulate the pituitary gland to produce increased amounts of growth hormone (GH) and anterior pituitary corticotrophins hormone (ACTH). ACTH specifically leads to the adrenal gland increasing its production of cortisol (Figure 1).

Figure 1. The post-operative metabolic response

1. Surgical insult initiates the postoperative metabolic response by sending signals to the hypothalamus via the nervous system.
2. The hypothalamus releases growth hormone-releasing hormone (GHRH) and corticotrophin-releasing hormone (CRH) to exert an influence over the pituitary gland.
3. The pituitary gland increases growth hormone (GH) and anterior pituitary corticotrophins hormones (ACTH) production.

Usual negative feedback mechanism ineffective post operatively
Cortisol is a hormone that significantly impacts on a patient’s metabolic processes by promoting gluconeogenesis, which subsequently leads to an increase in blood sugar levels. Growth hormone is responsible for the regulation of protein catabolism, influencing the rate of lipolysis and inhibiting the effects of insulin in order to stimulate protein synthesis. The inhibition of insulin in response to GH further contributes to raising blood sugar levels. Coupled together, the hyperglycaemic effect is notable and impacts on a patient’s wound healing and recovery4. Furthermore, the usual negative feedback mechanism responsible for the regulation of cortisol is rendered relatively ineffective post-operatively, leading to ongoing production of this hormone and a marked increase in stress. While this provides an overall picture of the metabolic response to surgery, both hyperglycaemia and muscle catabolism have been shown to influence outcomes14. Thus, the metabolic processes should be explored in greater depth.

Insulin and glucagon are the key hormones responsible for regulating glucose entering the bloodstream. Insulin is produced by the pancreas and released in response to an increase in blood glucose levels. It facilitates the movement of glucose into muscles and adipose tissue and promotes the conversion of excess amounts of glucose into glycogen and triglycerides7. Insulin also has a protective effect on muscle stores as it mitigates protein catabolism and lipolysis. During surgery, the anaesthesia administered to a patient has been noted to interfere with the secretion of insulin, an effect that may be related to the inhibition of β cell secretions7. Furthermore, cells seemingly become immune to the effects of insulin creating “insulin resistance” during the post-operative period. Glucagon, while promoting glycojenolysis, has been found to minimally contribute to hyperglycaemia post surgically1. Subsequently, post-operative hyperglycaemia is a common occurrence. Kiran and colleagues undertook a large study comprising of approximately 16,400 post-operative blood glucose readings in 2667 non-diabetic, colorectal patients5. It was found that approximately 67 per cent of patients experienced hyperglycaemia following surgery. Given the high percentage of patients likely to experience hyperglycaemia post-operatively, appropriate management is imperative. Poorly controlled hyperglycaemia can lead to delayed wound healing and adverse outcomes such as infection, sepsis and mortality.

Muscle catabolism is the other significant metabolic process of concern. Catabolism of muscle stores is related to cortisol production, which becomes elevated perioperatively triggered by the stress response mentioned previously. The end products of muscle breakdown are amino acids, which are metabolised into other energy substrates such as glucose, fatty acids and ketone bodies1. This process takes place in patients undergoing major surgery, however, catabolism of muscle stores and subsequent muscle wasting occurs to a much greater extent in patients who are receiving suboptimal energy and protein2. Carbohydrate stored in the body as glycogen in the liver is rapidly depleted when a patient is in starvation. It is for this reason that starvation is shown to be a key determinant of outcomes. A shift occurs to a shift in energy source, where muscle stores are broken down as part of our body’s natural adaptive process to meet the energy demands of vital organs such as the brain and erythrocytes3. These metabolic processes are the triggering factors that necessitate due consideration be given to the nutrition a perioperative patient receives.}

### Table 1. Malnutrition-screening tool (MST)

<table>
<thead>
<tr>
<th>Question</th>
<th>No</th>
<th>Unsure</th>
<th>Yes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you lost weight recently without trying?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you been eating poorly because of a decreased appetite?</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>If yes, how much weight (kilograms) have you lost?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>1</td>
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<tr>
<td>6-10</td>
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<tr>
<td>11-15</td>
<td>3</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&gt;15</td>
<td>4</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Unsure</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Obese patients at baseline, prior to a large weight loss, often have poor muscle stores, which may be related to poor quality nutrient intake and lack of physical activity. Inadequate muscle stores have been linked to suboptimal outcomes; therefore loss of this mass should be mitigated where possible. Muscle stores often form the primary fuel for wound healing and immune defence post-operatively. There is a gap in evidence, which warrants further investigation, as to whether the benefits of preoperative weight loss by means of a VLCD regime is greater than the risk of loss of soft tissue mass preoperatively. This risk needs to be assessed in terms of post-operative outcomes, focusing on high-risk groups such as those undergoing major gastrointestinal or gynae-oncological surgery.

**PERIOPERATIVE NUTRITIONAL MANAGEMENT**

A number of nutritional approaches have been studied or advocated in the perioperative context. Based on prominence in the published literature, elements that will be discussed further include parenteral nutrition (PN), immuno-nutrition, enhanced recovery after surgery (ERAS) and glycaemic control.

Parenteral nutrition in the perioperative patient

Perioperative nutrition is usually in the form of oral or enteral nutrition, however in some instances parenteral nutrition may be warranted. The American Society of Parenteral and Enteral Nutrition (ASPEN) recommend consideration of parenteral nutrition in malnourished patients undergoing gastrointestinal surgery. Specifically they recommend parenteral nutrition be commenced preoperatively for five to seven days continuing into the post-operative period should the patient be unable to tolerate adequate enteral nutrition9,10. However, there has been much debate surrounding parental nutrition and its role in the perioperative and/or critically ill patient. The strongest deterrent for most physicians is the perceived increased risk of infection. This concern is primarily based on data from older studies11,12,13, where adequate glycemic control was not a priority, strict aseptic techniques for preparation of parenteral nutrition was not the norm and the available lipid formulations were high in polyunsaturated fats, which have the potential to be pro-inflammatory14. Some more recent large randomised controlled trials reflect these same adverse outcomes, while others show no increase in infection rates, length of stay or mortality. While the studies are predominantly in the ICU setting, the results may be considered applicable to perioperative patients that require parenteral nutrition. To explain these differences in outcomes, the study design and patient cohort need to be considered.

Cesar and colleagues showed an increased risk of infection, increased proportion of patients requiring mechanical ventilation for greater than two days, an increased mean duration of renal replacement therapy and an increased cost to the healthcare in patients receiving early supplemental parenteral nutrition in the EPaNIC study25. There are a few factors that could have potentially influenced this outcome. Firstly, patients randomised to the intervention arm may or may not have had a clinical indication for parenteral nutrition. A patient who has a functioning gut should ideally persist with enteral nutrition preferentially over parenteral nutrition26 and, as such, this aspect of the study makes generalisation of the findings difficult to apply to patients who clinically require parenteral nutrition. Secondly, patients in the intervention arm received a large glucose load within the first 24-48 hours thereby contributing to a hyperglycaemic state. While there is no definitive evidence to suggest poor outcomes with the introduction of early glucose, evidence does exist that hyperglycaemia on admission and within the first 24 hours is associated with a higher risk of mortality17,18. A study by this issue is that despite being key evidence for the decision to start PN in instances where nutrition was deemed insufficient, patients on supplemental parenteral nutrition never received >1g per kilogram of body weight of protein, and inadequate protein has been shown to impact on mortality outcomes19,20. Results from the EPaNIC trial are in direct conflict with those of the more recently published Early Parenteral Nutrition trial by Doig and colleagues21. This study took an approach more akin to normal clinical practice and recruited patients who had relative contraindications to receiving enteral nutrition. Patients were randomised to standard care versus early parenteral nutrition. Results showed no difference in rates of infection between groups, no difference in length of ICU or hospital stay, and no difference in mortality. With a large sample size (n=1372) this study was sufficiently powered to detect such differences if they were to exist. Interestingly, this study did find a significant result for one additional outcome, a reduction in duration of mechanical ventilation for patients in the intervention arm. The results of the study by Doig and colleagues are supported by the findings of the CALORIES trial, which also found no significant difference in rate of infection or mortality22. The CALORIES trial is a large, randomised controlled trial, which compared the enteral to the parenteral route in an effort to optimise nutrition delivery to patients admitted unexpectedly into the ICU. Its key findings included no difference in mortality or infectious complications between the enteral and parenteral group23. The comparison between these studies are summarised in Table 2.

<table>
<thead>
<tr>
<th>Design</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Limitations/confounding factors</th>
<th>Key conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesar, et al (2011)25</td>
<td>Randomised controlled trial (n=4640). Patients recruited and consented if they scored &gt;3 on the NRS tool.</td>
<td>Compared early initiation of parenteral nutrition with late initiation to supplement insufficient enteral nutrition.</td>
<td>The intervention arm (early PN) showed:</td>
<td>• Large glucose load within the first 24-48 hours in intervention arm.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Risk of infection.</td>
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<td></td>
<td></td>
<td></td>
<td>• Number of patients requiring mechanical ventilation &gt;2 days.</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Duration of renal replacement therapy.</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Cost to healthcare.</td>
<td></td>
</tr>
<tr>
<td>Doig et al (2013)26</td>
<td>Randomised controlled trial (n=1372). Recruited patients who had relative contraindications to receiving enteral nutrition. Patients were randomised to standard care versus early parenteral nutrition.</td>
<td>In length of mechanical ventilation.</td>
<td>No difference between groups for:</td>
<td>• Premixed PN – low dose protein to energy ratio.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mortality.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Infectious complications.</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>• Length of stay.</td>
<td></td>
</tr>
</tbody>
</table>

Harvey et al (2014)27 | Randomised controlled trial (n=2400). Assigned patients who could be fed through either the parenteral or the enteral route to a delivery route initiated within 36 hours after admission and continued for up to five days. | No difference between groups for: | | • The target delivery of 25 kcal/kg/d was not reached in a majority of patients in each study group. |

PN = parenteral nutrition.

In the light of the fact that there appears to be no increased risk of infection in patients commenced on parenteral nutrition when clinically indicated, it should ultimately be left to the clinical judgement of the treating healthcare professional as to whether there will be any benefit in commencing parenteral nutrition. Potentially, early parenteral nutrition (within seven days) should be reserved for patients with a BMI <25 or >35kg/m² as it appears that patients in these groups tend to have lower muscle mass and subsequently benefit from early, aggressive nutrition28.
Enhanced recovery after surgery (ERAS)

The ERAS study group, encompassing leaders in surgical care, was formed in 2001 with the aim of implementing best practice by means of multimodal surgical care. Their first publication was 10 years ago when a consensus document for protocols in patients undergoing colorectal surgery was published. As the evidence grew, a society was formed in 2010. Since the initial guidelines, the ERAS Society has endeavoured to validate the ERAS protocol in various surgical patient populations. The ERAS Society, in conjunction with ESPEN, has published consensus guidelines for the management of patients undergoing gastrointestinal surgery, radical cystectomy, pancreatic-duodenectomy, elective colorectal surgery and pelvic surgery. The ERAS protocol accounts for various aspects of care in the pre, intra and post-operative phases of surgery, including anaesthesia, nutrition, mobility and fluid control.

The ERAS protocol discourages use of mechanical bowel preparation, advocates for adequate glycaemic control (<12mmol/L at a ward level), a reduction in fasting duration to six hours for solids and two hours for clear fluids, carbohydrate loading two hours preoperatively with a 12.5 per cent carbohydrate solution comprised of predominantly maltodextrin and an early introduction of enteral nutrition including the use of oral nutrition supplements for at least the first four days post-operatively to assist patients in meeting a greater percentage of their requirements. Prior to the release of these guidelines, the standard preoperative fasting period was usually between eight to 12 hours. Since glycoxy stores are depleted within 24 hours of starvation, patients fasting for lengthy periods of time often mobilise lean tissue mass early in the post-operative phase. Muscle wasting, if persistent, is associated with adverse outcomes such as an increased risk of acquired infections, muscle weakness and an increased length of stay. Implementation of the nutritional components of the ERAS protocol has led to improved glycaemic control, lower levels of insulin resistance, more rapid return of bowel function and a reduced length of stay (Figure 2). Certain patient groups form an exception to ERAS recommendations; these include diabetic patients and patients with delayed gastric emptying. Carbohydrate loading in diabetic patients is counterintuitive due to the expected hyperglycaemic effect it has and therefore should be avoided for this patient population. Patients with delayed gastric emptying are at an increased risk of aspiration on administration of anaesthesia. Studies have shown improvements in short-term clinical outcomes such as a reduction in post-operative infections and shorter lengths of hospital stay. The largest nutritional governing body in Europe, the European Society of Parenteral and Enteral Nutrition (ESPEN), endorses the recommendation of immune-modulating formulae use in elective upper GI surgical patients. However, this may be the case, controversy regarding the efficacy of perioperative immuno-nutrition when compared to preoperative immuno-nutrition continues to exist. Studies have found that preoperative administration of immuno-nutrition provides a similar beneficial effect when compared to perioperative use of these products. The use of preoperative supplements alone could potentially mean a cost saving and, as such, further research is required into the benefits and need for perioperative immuno-nutrition. Clinicians should note that the Canadian Critical Care Clinical Practice Guidelines recommend against use of arginine-enriched formulations in critically ill patients as these have been associated with increased mortality based on the results of a few studies. Since larger, more robust studies have not been carried out to definitively confirm these findings, it is best to err on the side of caution should patients become critically ill during the perioperative period thereby mitigating the risk posed to them.

Glycaemic control

While certain aspects of the ERAS protocol are relatively low risk based on available evidence, other aspects of the protocol warrant clinical consideration on a case-by-case basis. Adequate glycaemic control and post-operative nutritional supplements are low risk and should routinely be implemented with minimal clinical concern. Preoperative carbohydrate loading in the majority of patients undergoing major abdominal surgery should be recommended with the exception of patients with diabetes and those who have delayed gastric emptying. Duration of fasting from solids preoperatively and the type of bowel preparation used is likely to continue to be determined on a case-to-case basis by the treating surgeon due to the associated risks.

Glycaemic control

Post-operative insulin resistance and hyperglycaemia is commonplace in surgical patients as the insult sustained during surgery initiates a cascade of metabolic events conducive to this state. Hyperglycaemia is well known for its association with adverse outcomes in post-operative patients such as delayed wound healing, increased rates of infection, sepsis and mortality. While adequate preoperative glycaemic control potentially impacts on these outcomes; limited data is available and therefore no conclusive recommendations can be made. Van De Berge and colleagues generated much discussion when data from her study conducted in a surgical ICU depicting the strong mortality benefit that intensive insulin therapy had was published. Following this, further studies were undertaken and, in particular, one large randomised controlled trial found that intensive insulin therapy was associated with an increase in hypoglycaemic episodes and subsequently increased mortality. Since then it has been widely agreed that a more conventional approach to glycaemic control would be taken with a target of <12mmol/L and, ideally, where possible, <10mmol/L. Implementation of appropriate insulin therapy, along with elements of the ERAS protocol that assist with blunting the post-surgical hyperglycaemic response, is likely to lead to improved patient outcomes.
POST-OPERATIVE ENTERAL INTAKE

Post-operative enteral nutrition, especially following major elective surgery, may be delayed due to the surgical prejudice surrounding accepted feeding practices in the post-operative patient. More specifically, there is much controversy surrounding the use of enteral nutrition in gastrointestinal surgery. Enteral feeding in this patient population was, and sometimes still is, considered to be high risk, with concerns specifically related to the breakdown of the anastomosis and subsequent leakage into the peritoneal cavity. Historically, post-operative nutrition was delayed until a patient passed flatus or a bowel motion, thereby putting them at an increased risk of malnutrition and delayed post-operative recovery. There are at least three recent (2001 onwards) meta-analyses surrounding feeding initiation within 48 hours of surgery, none of which reported an increased incidence of anastomotic leak. In fact, the largest meta-analysis (n = 1240 patients) spanned more than 30 years, focused on gastrointestinal resection surgery and showed that patients receiving nutrition proximal to their anastomoses had a statistically significant reduction in morbidity. Furthermore, no adverse effects were noted. Despite this strong body of evidence, hospitals around the world have been slow to implement a change in practice and the delay in feeding patients remains related to common models of multidisciplinary team involvement in patient care. This will contribute to an increase in adoption of early enteral feeding post-operatively.

COLLABORATIVE APPROACH TO PERIOPERATIVE NUTRITION

It has been suggested by Martindale and colleagues that patients undergoing elective surgical procedures ideally receive a “prehabilitation” period, which includes early nutrition assessment preoperatively to identify at-risk patients, an exercise physiologist to establish adequate physical activity in order to attenuate any muscle wasting, assessment and optimisation of glycemic control and a smoking cessation program 30 days prior to surgery. From a nutrition perspective, identifying patients at risk will include patients who are either undernourished or obese. The undernourished patients will ideally receive five to seven days of nutrition optimisation pre-surgically. Immuno-enhanced formulas in this preoperative period of known benefit for patients undernourished for malignancy and should be considered as part of routine clinical practice. However, more studies measuring the benefits of perioperative immuno-nutrition need to be undertaken prior to implementing the post-operative immuno-nutrition component.

Although additional studies also are needed to address the treatment of the obese patient pre-surgically. At present, data surrounding the adverse effects of obesity on post-surgical outcomes has been extrapolated to formulate management strategies preoperatively. Patients may benefit from intensive weight loss programs with a concurrent exercise program to minimise muscle wasting pre-surgically, but this benefit in patients undergoing surgery for malignancy is yet to be shown in any randomised controlled trials. Patients requiring specialised nutrition support post-operatively, such as those undergoing gastrointestinal surgery, should be triaged on enteral nutrition where viable. Use of parenteral nutrition should be limited to patients who can not be managed via the enteral route. Due to the associated risks of parenteral nutrition, it seems prudent that it should be held off for at least five to seven days in well-nourished patients, but may be provided sooner for malnourished patients with poor intake. Early administration of parenteral nutrition may also be considered in the critically ill surgical patient to facilitate an earlier wean off invasive ventilation. In light of the complicated nature of nutrition support in patients undergoing surgical procedures, a multidisciplinary approach, including dietician referral, is recommended to optimise patient outcomes.  

REFERENCES

Modern metal implant toxicity and anaesthesia

ADRIAN LANGLEY, BSC(HONS), MBBS, FANZCA

Specialist anaesthetist, Queen Elizabeth II Jubilee Hospital, Brisbane, Australia.

Dr Adrian Langley is a specialist anaesthetist and is currently finishing his intensive care fellowship qualification and undertaking a diploma in palliative care medicine. He has a particular interest in heavy metal and micronutrient metabolism in critically ill patients.

CHARLES T DAMERON, BS, PHD

Biochemist, bioinorganic chemist and lecturer, Saint Francis University, Loretto, US.

Dr Charles T Dameron graduated from Texas A & M University with a PhD in biochemistry with a focus on copper metabolism. Following his interest in metals, he moved to the University of Utah, Department of Biochemistry, where he worked as a NH Hematology Fellow to study metalloregulation of genes in yeast. In 1993 he became a senior research fellow at the University of Queensland's National Research Centre for Environmental Toxicology where he continued his studies on metalloregulation and metal toxicity. In 2001 he moved to Duquesne University, Pittsburgh, US to become an associate professor of biochemistry in the Department of Chemistry and Biochemistry. Dr Dameron is committed to biochemistry education, but devotes his spare time to developing and passing on woodworking skills.

INTRODUCTION

The use of metals in therapeutic procedures dates back several centuries. Corrosion and lack of tensile strength restricted the application and development of early implants. The introduction of stainless steel in the 1920s led to an increasing number of implantable metallic devices for medical use. These devices are becoming more common for therapeutic and diagnostic purposes. Wear, corrosion and failure can lead to the release of metal ions, which may result in local and systemic effects. Although several metals, including iron, zinc, copper, manganese, iodine, chromium, selenium, molybdenum and cobalt, are essential to life, in higher concentrations these and many non-essential metals are toxic9. Metal toxicity from implantable devices can cause a range of clinical symptoms and organ impairment. The safety of metal-on-metal implants has been the subject of recent debate and media attention5. This review will provide a brief history of metals in medicine, outline the toxicity of metals used in modern prostheses and suggest an approach for pre-operative assessment of patients with new organ impairment and known metallic implant.

HISTORICAL USES OF METALS IN MEDICINE

Metals have been used in medicine for thousands of years. Metallic silver was known to the Chaldeans as early as 4000BC. Together with gold and copper, these metals were the antimicrobials of the ancient world. The Phoenicians, Greeks, Romans, Egyptians and others used silver to preserve food and water. Silver nitrate was used to treat surgical wounds, skin ulcers and compound fractures. Silver sutures were used to treat vesico-vaginal fistulas in the 1800s6. Te (tellurium) and Mg (magnesium) oxides as well as Cu (copper) and Hg (mercury) salts have been used to treat diseases such as leprosy, tuberculosis, gonorrhoea and syphilis. Hg(l) chloride was traditionally used in the 16th century as a diuretic and laxative throughout Europe1. The metalloid, arsenic, well known as a poison, was prescribed for a range of ailments, such as rheumatism, malaria, tuberculosis and diabetes. Although the toxicity of these medicines caused them to be largely abandoned for therapeutic use in Western society they may still be found in traditional Chinese, Tibetan and Ayurvedic medicines3,5.

Some of the earliest uses of metal implants were by the Romans, Chinese and Aztecs, who used gold in dentistry more than 2000 years ago. Europeans fashioned replacement teeth out of iron from around 200 AD. Ancient Incas used silver or gold plates to repair cranial defects5. In the early 1800s, experiments were undertaken to examine the suitability of implant materials testing silver, gold, lead and platinum in animals. In 1866, metal plates were used for the first time for internal fixation of a fracture. Early implants were often problematic because of corrosion, lack of tensile strength, surgical technique and infection. The discovery of stainless steel in 1924 allowed metals to be used in the body routinely, at a reasonable cost and with greatly increased reliability. A cobalt (Co) metal alloy was introduced in 1936 and became one of the most popular metal alloys in orthopaedic surgery for many years. Titanium (Ti), titanium alloys, stainless steel and cobalt-chromium (Cr) alloys form the majority of modern metallic implants introduced in 1936 and became one of the most popular metal alloys in orthopaedic surgery for many years. Titanium (Ti), titanium alloys, stainless steel and cobalt-chromium (Cr) alloys form the majority of modern metallic implants in what is a multi-billion dollar industry with millions of procedures performed each year9.

CORROSION OF METALS

Corrosion of metal implants is of great clinical concern. Structural failure or reduced implant integrity may result in increased local and systemic concentrations of metals leading to patient morbidity. These patients may present to the anaesthetic preadmission clinic for review. Corrosion is of particular concern in younger patients, who may be exposed to the systemic metal toxicity for longer periods of time. Any metallic implant within the body is subjected to electrochemical degradation. The combination of various ions in an aqueous environment, including sodium, chloride, calcium, magnesium, bicarbonate and plasma proteins, creates a thermodynamic force for oxidation reduction reactions. A protective oxide layer, surface modification techniques and materials provide some protection reducing the rate of corrosive attack10.
Modern metal implant toxicity and anaesthesia

Metals play an important role in the neurological structure and function. Metal dyshomeostasis has been implicated in the development or progression of neurodegenerative disorders such as cancer, autoimmune disorders, ageing, cataracts, rheumatoid arthritis, cardiovascular and neurodegenerative diseases19. Metals including aluminium, cadmium, cobalt, chromium, copper, iron, nickel, tin and vanadium may lead to chronic kidney disease or the development of chronic and degenerative diseases such as cancer, autoimmune disorders, ageing, cataracts, rheumatoid arthritis, cardiovascular and neurodegenerative diseases20. Neurological symptoms, including cognitive decline, memory difficulties, tremor, incoordination, polyneuropathy, vertigo, hearing loss and visual changes have been reported from cobalt and chromium toxicity post hip replacement21. These symptoms, including cognitive decline, memory difficulties, tremor, incoordination, polyneuropathy, vertigo, hearing loss and visual changes have been reported from cobalt and chromium toxicity post hip replacement21. These symptoms may be caused by the release of metal ions, which can induce oxidative stress, modify proteins or displace critical metals in metal dependent processes or structures22. Generation of reactive oxygen species (ROS) in excess of the host detoxification mechanisms may result in tissue damage, leading to the development of chronic and degenerative diseases such as cancer, autoimmune disorders, ageing, cataracts, rheumatoid arthritis, cardiovascular and neurodegenerative diseases23.

HAEMATOLOGICAL TOXICITY
Metal toxicity may have a variable effect on haematological parameters. Cobalt has an erythropoietic effect and has been used to treat anaemia and for blood doping in sport24. Chromium may compete with iron in binding to apo-transferrin causing anaemia25.

IMMUNOLOGICAL TOXICITY
Nickel, cobalt, chromium and titanium are capable of producing immunological responses through altered B and T cell function, modified cytokine release, haptenisation or direct immunotoxicity. Numerous case reports have linked immunological responses to adverse performance of metallic cardiovascular, orthopaedic, plastic surgical and dental implants. In vivo metal sensitivity may play a role in the failure of implants containing these metals26.

ENDOCRINE TOXICITY
Metals including cobalt, nickel, aluminium and vanadium are endocrine disruptors. Hypothyroidism results from inhibition of thyroxine iodinase by cobalt(III) ions27. Aluminium, cadmium, chromium, cobalt, copper, nickel, tin and vanadate also have been identified as metalloestrogens, compounds capable of binding to cellular oestrogen receptors and mimicking the actions of physical oestrogens. Their role in aberrant oestrogen signalling in the human breast requires further research28.

CARDIAC TOXICITY
Epidemiological evidence suggests metal contaminants may play a role in the development of atherosclerosis and its complications29. Cobalt accumulation within the myocardium may result in a cardiomyopathy and echocardiographic changes that suggest altered left ventricular relaxation and early filling30.

MUSCULOSKELETAL TOXICITY
Adverse local tissue reactions are locally destructive lesions resulting from inflammatory reactions, which may account for implant failure. Muscle atrophy, abductor tendon avulsion, pseudo tumour formation, peri-prosthetic collections and synovial thickening are reported soft tissue abnormalities suspected to result from the inflammatory response to metal wear debris in patients with metal-on-metal hip implants31.

CARCINOGENESIS AND DEVELOPMENTAL TOXICITY
There have been few studies of carcinogenicity of metal-on-metal hip resurfacing arthroplasty. There is no consistent evidence of an overall increase in cancer rates although non-statistically significant higher rates of haematopoietic malignancy, prostate cancer and melanoma have been noted. Transplacental passage of metal ions has been demonstrated without any observed teratogenic effect32.

Metals, modern implants and anaesthesia

Metals used in most modern surgical implants include stainless steel, titanium, titanium alloys and cobalt chromium alloys (Table 1). While there is no evidence that elevated serum levels of these metals directly influence either inhalation or intravenous anaesthesia, it is clear from hereditary metal disorders that the pharmacokinetics and pharmacodynamics of anaesthetic drugs can be significantly altered by end organ impairment33. Although classified as inert or biocompatible metals, there are increasing numbers of case reports of patients presenting for joint-revision surgery following either local or systemic toxicity from these implants. It is an emerging area of concern the anaesthetist should be aware of.

Dissemination of metal from implants leads to erosion and implant fracture, which may accelerate the release of metal ions resulting in the accumulation of metal in the soft tissue surrounding the implant, peri-prosthetic soft tissue destruction, osteolysis, pseudo tumours and infiltrates of lymphocytes and plasma cells34. Several forms of corrosion are recognised, including uniform, pitting, galvanic, fatigue and leaching. Titanium is a relatively inert metal with good biocompatibility. It has corrosion rates that are typically less than 0.02mm per year and well below the 0.13mm per year maximum corrosion rate commonly accepted for biomaterial design and application35. Different metals within alloys have different rates of corrosion in the same electrolyte solution. Selective leaching of one element may impair the structural integrity and performance of the implant36.

METAL TOXICITY
The toxicity of metals has been known for thousands of years. The early Greeks and Romans documented both the toxic and therapeutic effects of metals. Industrialisation has increased exposure to metals through new applications in medicine, industry and agriculture as well as environmental contamination. The clinical consequences of metal toxicity depend on the type of exposure (ingestion, inhalation, dermal absorption), the form of metal (elemental, salt, particulate, vapour, amalgam), the dose and the duration or frequency of exposure. Mechanisms of metal toxicity are diverse including: inhibition of enzymes, disruption of structure and or function of cellular processes, free-radical production, interaction with DNA leading to mutagenesis and carcinogenesis, covalent modifications of proteins or displacement of critical metals in metal dependent processes or structures37. Generation of reactive oxygen species (ROS) in excess of the host detoxification mechanisms may result in tissue damage, leading to the development of chronic and degenerative diseases such as cancer, autoimmune disorders, ageing, cataracts, rheumatoid arthritis, cardiovascular and neurodegenerative diseases19.

EXPOSURE TO METALS
Exposure to certain metals in both environmental and occupational settings has been reported to be carcinogenic. Nickel, vanadium, arsenic, cadmium, cobalt, chromium and copper have been identified as carcinogenic in both animal and human studies. Certain compounds including of cobalt, iron, lead, manganese, platinum, titanium and zinc have induced tumours in experimental animals, but the doses used and modes of administration differed from those of any known human exposure38. Metals can cause genotoxicity and carcinogenicity through multiple pathways or enhance a biological effect itself. Several mechanisms, in addition to ROS, have been identified including metal induced regulation of transcription factors, effects on signal transduction pathways, metal induced apoptosis, mutagenesis through DNA repair inhibition or alterations in cell cycle control39. The carcinogenic capability of metals depends mainly on factors such as oxidation states and chemical structures. Trivalent chromium Cr(III) is an essential metal while hexavalent chromium Cr(VI) compounds have been shown to exert genotoxicity in vivo and in vitro40.

NEUROTOXICITY OF METALS
Metals play an important role in the neurological structure and function. Metal dyshomeostasis has been implicated in the pathology of neurodegenerative diseases including Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington disease, Menkes, ornithine transcarbamylase deficiency and Parkinson’s disease41. Metals including aluminium, copper, lead, manganese, mercury and thallium are known nervous system toxins. Oxidative stress may be a significant factor in the development or progression of neurodegenerative disorders42. Neurological symptoms, including cognitive decline, memory difficulties, tremor, incoordination, polyneuropathy, vertigo, hearing loss and visual changes have been reported from cobalt and chromium toxicity post hip replacement43.

RESPIRATORY TOXICITY
Metal induced respiratory disease is largely caused by inhalation injury. Cobalt chloride can induce pulmonary hypertension through upregulation of HIF1α activator and increased muscularisation of the small pulmonary blood vessels44. Metallo-protein formation may result in immediate type (fSG-mediated) and cellular hypersensitivity induced asthma and chronic bronchitis. Several metals have been linked to granulomatous lung disease including titanium, aluminium and copper. Gold lung presents as hypersensitivity pneumonitis in rheumatoid arthritis patients treated with gold salts45.

GASTROINTESTINAL TOXICITY
Gastrointestinal metal-associated toxicity usually arises from the ingestion of food, minerals supplements or hereditary storage diseases such as haemochromatosis and Wilson’s disease. Elevated titanium, chromium and cobalt levels have been found in the liver and spleen of patients with failed hip or knee prostheses46. Titanium alloy particles can cause granulomatous hepatitis and hepatosplenomegaly47.

RENAL TOXICITY
The kidneys are particularly sensitive to metal-induced toxicity. Accumulation of metals in the proximal tubule may induce a Fanconi syndrome characterised by a decreased glomerular filtration rate (GFR), increase in urinary flow rate, proteinuria, glycosuria, aminoaciduria and the loss of phosphate and bicarbonate ions48. Chronic exposure to lead, cadmium, mercury, antimony, chromium, gold and platinum may lead to chronic kidney disease or the development of end stage renal failure49.
Modern metal implant toxicity and anaesthesia

Levels of titanium have been found within synovial fluid, serum and urine of patients after total hip and knee procedures. Titanium particles and ions can induce osteolytic cytokines and inhibit osteoblast collagen expression in vitro. Raised serum titanium levels are still one of the most used alloys in implants ranging from cardiovascular to otorhinology. Iron, chromium and nickel are among the most widely used for biomedical applications. Although regarded as a relatively inert metal, accumulation of titanium is still one of the most used alloys in implants ranging from cardiovascular to otorhinology. Iron, chromium and nickel release have been reported from stainless steel arch bars used for maxillomandibular fixation, however the released amounts were significantly below the average dietary intake. There is little data available on metal release from prosthetic stainless steel implants. Nickel is a common contact allergen but, based on the low release rates of nickel, sensitisation caused by stainless steel is unlikely. Nickel-free implants have been developed. Serum and urine levels of chromium and nickel have been found to be elevated in patients with scoliosis who had undergone spinal instrumentation.

STAINLESS STEEL
Stainless steel was discovered in 1904 and used in surgical applications began in 1926. Stainless steel is an alloy of iron, carbon and other elements. A minimum of 12 per cent chromium is added to make the steel “stainless” and prevent corrosive attack by the formation of a stable and passive oxide film. Medical-grade stainless steel (316L) is an alloy containing 16 per cent chromium, 10 per cent nickel and 2 per cent molybdenum. Stainless steel is still one of the most used alloys in implants ranging from cardiovascular to orthotolohy. Iron, chromium and nickel release have been reported from stainless steel arch bars used for maxillomandibular fixation, however the released amounts were significantly below the average dietary intake. Chromium (III) is low toxicity. Chromium(VI) readily crosses cell membranes to cause toxicity.

TITANIUM
Titanium is a high-strength, highly corrosion resistant, low allergic potential metal commonly used in stainless steels as a stabilising element. Pure titanium and the alloy titanium-aluminium-vanadium (Ti-6Al-4V) are among the most widely used for biomedical applications. Although regarded as a relatively inert metal, accumulation of titanium and alpha particles may induce osteolytic cytokines and inhibit osteoblast collagen expression in vitro. Raised serum levels of titanium have been found within synovial fluid, serum and urine of patients after total hip and knee arthroplasty and following instrumented spinal arthrodesis.

<table>
<thead>
<tr>
<th>Implant</th>
<th>Example</th>
<th>Type of metal</th>
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<tbody>
<tr>
<td>Neurological</td>
<td>Neuronomodulation device</td>
<td>TI, Ti6Al4V</td>
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<tr>
<td></td>
<td>Recording electrodes</td>
<td>Pt, W, P1r, 316L SS</td>
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<tr>
<td></td>
<td>Cochlear implant</td>
<td>Pt</td>
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<td>Coils</td>
<td>Pt</td>
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<tr>
<td>Cardiovascular</td>
<td>Stents</td>
<td>316L SS, CoCr, CoCrPtTi, P1Cr, Ti6Al4V, TiNi, P1W, P1r</td>
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<tr>
<td></td>
<td>Artificial valve</td>
<td>316L SS, Ti6Al4V, CoCrMo</td>
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<td>Pacemaker, ICD</td>
<td>P1r, Ti, 316L SS, P1t, Ti6Al4V</td>
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<tr>
<td>Orthopaedic</td>
<td>Bone fixation (plate, screw pin)</td>
<td>316L SS, Ti6Al4V</td>
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<td>Artificial joints</td>
<td>CoCrMo, Ti6Al4V, Ti6Al6Nb</td>
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<td>Spinal rods</td>
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<td>316L SS, CoCrMo, TiMo</td>
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<td>Orthodontic brackets</td>
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<td>Filings</td>
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<td>Restorations</td>
<td>Au-PT-Pt-Ag; Au-PT-Cu-Zn</td>
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<td>Craniofacial</td>
<td>Plate and screw</td>
<td>316L SS, CoCrMo, Ti, Ti6Al4V</td>
</tr>
<tr>
<td></td>
<td>Cranial plates</td>
<td>316L SS, Ti, Ti6Al4V</td>
</tr>
<tr>
<td></td>
<td>Orbit reconstruction</td>
<td>CoCrMo, Ti, Ti6Al4V</td>
</tr>
<tr>
<td>Otorhinology</td>
<td>Artificial ear drum</td>
<td>316L SS</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>Intrauterine devices</td>
<td>Cu, CuAg (Nova T380)</td>
</tr>
</tbody>
</table>

Metal | Biological effects
--- | ---
Aluminium | Dialysis encephalopathy and dementia, emotional lability, putative role in neurodegenerative diseases, inhibition of bone remodelling, inhibition of osteoblast and osteoclast activities, hypochromic microcytic anaemia, increased risk ischaemic heart disease.
Cobalt | Polycythemia, dermatitis, hypertriglyceridaemia, hypoacoagulability, cardiomyopathy, goiter, hypothyroidism, headache, anxiety, peripheral neuropathy, optic nerve atrophy, tinnitus, deafness, tremor, diminished co-ordination, slow cognition, seizure.
Chromium | Skin ulceration, acute irritative dermatitis, allergic eczematous dermatitis, renal tubular lesions, hepatocellular necrosis, gastritis, enteritis, asthma, lung cancer, septal ulceration and perforation, fetal abnormalities in animal studies, teeth discoloration.
Nickel | Contact allergy, eczema, skin erythema, allergic asthma, carcinogenesis.
Platinum | Conjunctivitis, urticaria, dermatitis, eczema.
Tantalum | Allergy.
Titanium | Yellow nail syndrome (YNS).
Vanadium | Greensh-black tone discoloration, polynuropathy, ototoxicity.

* Metallic platinum is relatively inert. Toxicity from complex platinum salts; (YNS): triad of nail changes, lymphoedema and respiratory tract involvement;
* Chromium (III) low toxicity. Chromium(VI) readily crosses cell membranes to cause toxicity.

CHROMIUM
There is evidence to suggest that chromium was used by the ancient Egyptians and Qin dynasty in sword production. Chromium (III) appears to be essential for glucose metabolism. Hexavalent Cr(VI) is largely responsible for acute and chronic toxic effects. Chromium is added to alloys to impart corrosion resistance. Accelerated wear of metal-on-metal implants leads to higher levels of chromium in the blood. There is currently no accepted level of chromium in the blood associated with adverse health. The Therapeutic Goods Administration (TGA) recommends that patients with hip pain and metal-on-metal implants have chromium levels measured at least annually and approximately every three months thereafter where metal ions levels continue to increase. Levels higher than 135 nmol/L 18 months after implantation can indicate the implant is beginning to fail. Soft tissue damage around the joint may occur if the implant is not revised.

PLATINUM
Medical applications for platinum include anti-cancer drugs, the construction of dental equipment such as crowns, bridges, pins, fillings, and implanted biomedical devices, such as pacemakers and catheters. Its electrical conductivity and ability to fabricate extremely small and complex shapes has seen its use in neuromodulator devices, implantable cardioverter-defibrillators (ICDs), coils and catheters for the treatment of brain aneurysms. The main health effect platinum compounds, excluding the neurotoxicity of the chemotherapeutic agents cisplatinum, carboplatin and oxaliplatin, is sensitisation. Soluble platinum salts induce allergic reactions in which both the respiratory tract and the skin are involved. There is limited human or experimental data on the toxicity or carcinogenicity of platinum compounds.

NICKEL
Nickel is a highly toxic metal and is known to cause systemic, immunologic, neurologic, reproductive, developmental and carcinogenic effects. The most common adverse reaction is allergic skin reactions. Nickel concentration has been observed to be elevated from two to six weeks post hip arthroplasty with cobalt-chromium-nickel prosthesis.
Modern metal implant toxicity and anaesthesia

ALUMINUM
Aluminium is a suspected neurotoxin and also has been implicated in the pathogenesis of dialysis encephalopathy, osteodystrophy, anaemia and inhibition of bone remodelling. Animal studies also have reported altered cognitive function. Aluminium is added to titanium alloys to improve strength and ductility. Aluminised levels have been found to be elevated in a failed knee arthroplasty from metal-on-metal contact of a Ti-6Al-4V alloy prosthesis and in patients following scoliosis repair.[1,3]

VANADIUM
Vanadium (V) is present in almost all living organisms but its necessity in cellular function is yet to be established. Hip replacements were initially made from stainless steel but are now mostly contain titanium alloy, the most commonly available being Ti-6Al-4V. Vanadium may be cytotoxic in vivo and produces gastrointestinal distress, fatigue, cardiac palpitation, renal injury and metabolic alterations in experimental animals. Vanadium-free titanium alloys have been developed including Ti-15Mo-5Zr-3Al for cemented and Ti-6Al-2Nb-1Ta-0.8Mo for non-cemented hips.[2] Raised vanadium levels have been found in serum, urine and urine of patients implanted with the titanium alloy Ti-6Al-4V.[3] Vanadyl metallosis caused polyneuropathy, ototoxicity, and tongue discoloration in a patient with a ceramic on ceramic hip arthroprosthesis containing a fenamal titanium alloy component.[4]

NEWER ALLOYS
Concern over biocompatibility and corrosion resistance has lead to the development of new titanium alloys incorporing zirconium (Zr), niobium (Nb), tantalum (Ta), palladium (Pd) and indium (In).[5] Elevated niobium levels have been detected from Ti-Al-Nb alloys used for scoliosis repair in paediatric patients.[6] Tantalum metallosis has been reported following a failed hip arthroplasty. There is little data on the long-term toxic effects of niobium or tantalum[7].

DIAGNOSIS AND TREATMENT OF METALLOSIS INDUCED METAL TOXICITY
Metallosis has been defined as aspecic fibrosis, local necrosis or loosening of the prosthesis secondary to metallic corrosion and release of wear debris. It has been reported with a wide range of metallic implants including stainless steel, titanium and cobalt-chromium alloys but may also occur with metal on polyethylene joint replacements.[8,9] Diagnosis depends upon clinical history, examination and investigations. Symptoms and signs of metallosis may include pain, grey discolouration of the tissues surrounding the joint, increasing noise from the replacement, a sense of joint instability and effusion although implant loosening, peri-prosthetic fracture, osteonecrosis, infection, tendinitis, impingement and referred pain may cause similar symptoms.

Investigations including serum metal levels, hip aspiration and imaging may be useful. Rising serum cobalt and chromium levels may be an early indicator of implant failure. Cobalt levels in hair, blood and urine can be often elevated in patients with metal-on-metal hip replacements. The diagnosis may be confirmed by the aspiration of dark grey or black synovial fluid.[10] Radiological findings may include misalignment and loss of joint space, suggesting wear or fracture of the prosthesis liner, amorphous densities in the peri-prosthetic tissues and hyperdense rounded images with a higher contour (metal deposits).[11] Effective treatment involves joint revision surgery to remove metal debris and bone graft areas of osteolysis. Elevated blood levels of cobalt and chromium can persist for at least a year following revision, especially in patients with high levels of exposure[12].

SUMMARY
Metals have a long history of use in medicine. The discovery of new alloys and improvement in metalurgy has expanded both the therapeutic and diagnostic indications for metal-containing implants. Concerns regarding systemic and local metal ion toxicity, most notably metal-on-metal hip replacements containing cobalt and chromium, have resulted in regulatory bodies including the US Food and Drug Administration (FDA), UK Medicines and Health Care products and Therapeutic Goods Administration (HMRA) and Therapeutic Goods (TGA) publishing clinical algorithms to detect potential implant failure and metal toxicity. There is currently no consensus statement outlining the relationship between symptoms, peak metal ion levels or the length of exposure. For other metal implants and newer alloys, little toxicity data exists.

Important pre-operative consideration for the anaesthetist when assessing a patient for surgery who has new neurological, cardiac, thyroid, renal or haematological impairment should include a thorough history, particularly noting the presence of metal implants. If clinical history and examination are insufficient to explain the patient's symptoms and they have a metal prosthesis, then an attempt should be made to identify the type, components and duration of implant insertion. For patients with older devices, known to contain cobalt or chromium, or have clinical features of metallosis, then consideration should be given to a toxicological evaluation to exclude metal toxicity as an underlying cause of the organ impairment.

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Anaphylactic shock under anaesthesia: A reappraisal of the pathophysiology and management

PETER R PLATT, MBBS, FANZCA
Director of the Anaesthetic Allergy Clinic, Sir Charles Gairdner Hospital, Nedlands, Western Australia.
Dr Platt has been the lead physician in managing the Anaesthetic Allergy Clinic since 1998.

PAUL SADLEIR, MBBS, FANZCA
Consultant anaesthetist, Anaesthetic Allergy Clinic, Sir Charles Gairdner Hospital, Nedlands, Western Australia.
Dr Sadleir is a staff anaesthetist at Sir Charles Gairdner Hospital with a special interest in cardiac anaesthesia and research on perioperative anaphylaxis.

RUSSELL CLARKE, MBBS, FANZCA
Consultant anaesthetist, Anaesthetic Allergy Clinic, Sir Charles Gairdner Hospital, Nedlands, Western Australia.
Dr Clarke is a staff anaesthetist at Sir Charles Gairdner Hospital. He maintains the anaphylaxis database and contributes to research projects on anaphylaxis.

INTRODUCTION
Almost every day in Australia and New Zealand there will be a case of anaphylaxis during surgery that challenges the attending anaesthetist. By following current management guidelines (http://www.anzaag.com/Mgmt%20Resources.aspx) most will respond to treatment and surgery will be completed. However, there are others that require an escalation in treatment, including CPR, large doses of adrenaline, abandonment of surgery and continuing care in an intensive care environment. Sadly, some of these patients do not survive. It is the treatment of these very sick patients that perhaps raises the most controversy. It is not clear why the cardiovascular depression in some patients is unresponsive to large doses of adrenaline, but various authors express enthusiasm for other alpha agonists or vasopressin, as well as novel agents such as sugammadex in rocuronium allergy. All the information about the proposed benefit of these treatments is based on a few case reports that, in general, are subject to criticism because they lack scientific rigour.

This is an opinion piece that hopefully challenges some of our understanding of the pathophysiology, haemodynamic changes and management of severe anaphylaxis.

PATHOPHYSIOLOGY OF ANAPHYLAXIS
Cross-linking of the high affinity receptor
The syndrome of anaphylaxis can be triggered by a number of different mechanisms. During anaesthesia, the most common – and that which causes the most severe reaction – is mediated by the antibody immunoglobulin E (IgE). Mast cells and basophils are responsible for the release of the chemical mediators, such as histamine, that are responsible for the physiological changes seen during anaphylaxis. Mast cells reside in the tissues and basophils in the circulation. They both express high affinity receptors (FcεRI) on their surfaces. Because of easier isolation, basophils have been studied more intensively. The number of FcεRI varies between 29,000-680,000 per cell in different individuals. A correspondingly variable amount of IgE is bound with a very high affinity (Kd = 10^-9 – 10^-10 M) to the FcεRI. The production of receptors by the cell and the stability of the complex are enhanced by an increased concentration of IgE in the circulation. Pholcodine-containing cough suppressants have been shown to dramatically increase the serum IgE levels when experimentally imbibed by patients who have been selected because of previous anaphylactic reactions to neuromuscular blocking agents. This increase in antibodies is most notable for those that recognise substituted ammonia groups present in pholcodine, morphine and suxamethonium, but also to unrelated items such as inhaled aero-allergens. With increasing IgE levels, there is a corresponding increase in the number of FcεRI/allergen complexes into lipid rafts in the cell membrane, resulting in mediator release from the mast cell or basophil.

A minimum number of cross-linking events, between 100 and 1000, are required for any degree of release, and the lifetime of the cluster is also important. Studies have shown a 30-fold range of sensitivity (number of IgE molecules for 50 per cent of the maximum IgE mediated response) between basophils from different individuals. The optimal release of any mediator in granular form, such as histamine, from an individual cell by a specific allergen is dependent on the amount of specific antibody bound to the FcεRI, the concentration of antigen and the degree of affinity of the IgE for the antigen. This variability in mediator release is evidenced by the severity of the clinical presentation expressed as the grade of anaphylaxis and measured by the mast cell tryptase released into the circulation.
Anaphylactic shock under anaesthesia: A reappraisal of the pathophysiology and management

There are a number of unusual characteristics of anaphylaxis caused by neuromuscular-blocking drugs (NMBDs). It is uncommon for small molecular-weight drugs, less than 10,000 daltons, to be antigenic unless bound to a protein, the process of hapten formation. This is not the case with NMBDs, which are relatively small (rocuronium has a molecular weight of 610 daltons) and in which the substituted ammonia groups may be to the complementary antigenic sites. Most anaphylactic events precipitated by a NMBD occur on first exposure, suggesting environmental exposure and sensitisation to substituted ammonia groups in commonly used chemicals such as pholcodine, or those used by hairdressers.

The requirement for a drug to have a blocking effect at the neuromuscular junction requires a chemical structure with two substituted ammonia groups separated at a distance from 1 to 1.45nm. It is this bistable structure that makes the drug bind adjacent FcɛRII antibodies.

Because the antibodies in the sensitised individual have not been specifically raised to a single NMBD, merely recognising the substituted ammonia groups, one would expect all muscle relaxants to behave similarly; however, there is a spectrum of affinity within the members of the group. We therefore see a spectrum of cross-sensitivity that is difficult to predict. One cannot conclude that a benzylisoquinoline and a rocuronium have a re-occurring effect. A patient who had a reaction caused by a steroidal muscle relaxant and another, would result in a sensitisation state. A number of mechanisms have been proposed to explain how the drug will lead to the return of the sensitised state. A number of mechanisms have been proposed to explain how the drug will lead to the return of the sensitised state. The physiological responses from the complex interaction of these multiple mediators with their individual receptors

and preventing further cellular interactions. This results in acute desensitisation of the mast cell to the antigen. After desensitisation of the activated antigen-antibody-FcɛRI complex occurs, removing them from the cell surface and preventing further cellular interactions. This results in acute desensitisation of the mast cell to the antigen. After desensitisation of the activated complex, some of the FcɛRI are bound to regulatory proteins called ubiquitins, a necessary step before degradation by lysosomal pathways. Not all FcɛRI are degraded and some are returned to the cell surface after removal of antigen/antibody complex by “sorting” and “recycling” endosomes.

While there is in-vitro evidence that disengagement of an antigen from the FcɛRI can terminate downstream intracellular signalling, it now is clear that mediator release or the physiopathological response that follows, from the mast cell, can be attenuated by the discontinuation of the causative allergen, although this is a common recommendation. In the case of disengagement of rocuronium by sugammadex, for any possibility of prevention of anaphylactic reaction if an allergic individual could have an aminosteroid or sugammadex in an intravenous fluid (PAF) and the eicosanoids – PGD2, LTC4 and LTB4 that can each have physiological consequences, such as bronchospasm and local or generalised angioedema. Enhanced gene expression leads to the production of the third mediator, the cytokines and chemokines, which are responsible for cell signalling and chemotaxis. The physiological consequences of these multiple interactions are the release of mediator release of phospholipases A2 – such as platelet-activating factor (PAF) and the eicosanoids – PGD2, LTC4 and LTB4 that can each have physiological consequences, such as bronchospasm and local or generalised angioedema. Enhanced gene expression leads to the production of the third mediator, the cytokines and chemokines, which are responsible for cell signalling and chemotaxis.

Histamine is probably the most important mediator of the anaphylactic response. The role of histamine in anaphylaxis is supported by the beneficial effects of antihistaminic drugs in anaphylactic reactions, and the increase in plasma histamine levels in accordance with the severity and duration of the reaction. Histamine in dogs causes generalised arteriolar vasodilatation and sequestration of blood in the limbs, but most importantly constriction of the hepatic venous bed leading to massive splanchnic pooling of blood – the principle cause of death in anaphylaxis in these animals.

In rats, histamine causes a dose-dependent dilatation of the systemic blood vessels and muscular vessels. In man, resting plasma histamine levels in one study were 0.62 ± 0.52 ng/ml and after infusion of histamine to achieve blood levels around 2.5 ng/ml, there was a significant flush and headache, and a 30 per cent increase in heart rate and pulse pressure. Lorenz investigated the role of histamine in anaphylaxis by negative intravascular signals that find their way into the intracellular signalling pathways of the mast cell. From a description of the mediator release, it is evident that histamine, causing an increase in blood pressure, is a consistent rise to a mean of 3.5ng/ml was found associated with an immediate tachycardia and even further doses of rocuronium would be unlikely to induce further hypotension.

19. Lorenz investigated the role of histamine in anaphylaxis by negative intravascular signals that find their way into the intracellular signalling pathways of the mast cell. From a description of the mediator release, it is evident that histamine, causing an increase in blood pressure, is a consistent rise to a mean of 3.5ng/ml was found associated with an immediate tachycardia and in turn increases both capillary permeability and blood pressure was associated with almost complete failure of venous return to the venous reservoir, which, to prevent critical depletion, required the addition of 360ml to maintain an adequate output from the cardiopulmonary bypass pump. This case demonstrates that hypotension occurs not only as a result of a fall in systemic vascular resistance, but also because of failure of venous return due to both interstitial loss and sequestration of blood in the peripheral venous systems. It also demonstrates that vasopressors, essential to increase systemic vascular resistance, will be ineffective on their own unless cardiac output is maintained by volume replacement.

In conclusion, the resolution of the tachycardia occurred in less than 30 minutes, but took over 90 minutes in the most severe reaction.

More recently, Clarke et al. shed some light on the circulatory changes in man in reporting a case of anaphylaxis triggered by a clinical setting, in which the patient had experienced a severe anaphylactic episode caused by rocuronium, it is theoretically less risky to readminister rocuronium after a change to an upright posture in 10 of 38 anaphylactic shock deaths that occurred outside hospital. He described a mechanism based on lack of venous return to explain this phenomenon. He went on to express the importance of the recumbent patient, with legs raised, in first aid of shocked patients and explained why adrenaline can be counterproductive in these patients. The benefit of posture has also been echoed by Brown in the emergency medicine setting, as has the benefit of the pneumatic anti-shock garment, or MAST suit.

The importance of venous capacitance has largely been forgotten or ignored in discussions of the circulatory changes during anaphylaxis shock; however, this relationship between changes in capacitance and blood pressure is well described. The veins are not merely conduits to carry blood back to the heart, but by their compliant nature can contain variable volumes of blood. Sympathetic stimulus will lead to a reduction of venous compliance, an increase in mean circulatory pressure and mobilisation of blood with an increase in venous return, right ventricular end diastolic pressure and blood pressure is increased, in effect, when the veins constrict, the heart expands and vice versa.
Failure of venous return. Figure 2A shows a hydraulic model of the normal circulation with the capacitance of the venous reservoir represented by movement of the piston is the principal variable on the venous side of the system through a resistance (systemic vascular resistance) to the venous reservoir. The variable capacitance of a high-pressure, low-compliance arterial reservoir. Blood flows back to the heart from the high pressure arterial system by gravity, increasing venous return and cardiac filling. The position of the piston determines venous capacitance. Outward movement of the screw represents the condition during anaphylaxis, in which a large increase in capacitance occurs with a consequent reduction in venous return to the heart (Modified from Gow with permission of the American Physiological Society).

The relationship between capacitance and right atrial pressure is elegantly and simply demonstrated by Gow’s mechanical screw analogue shown in Figure 1(1). In anaphylactic shock a massive increase in capacitance leads to failure of venous return. Figure 2A shows a hydraulic model of the normal circulation with the capacitance of the venous system alterable by a piston. In times of increased demand such as the onset of exercise sympathetic stimulation leads to a decrease in compliance and maintenance of venous return and cardiac filling. During severe anaphylaxis, as in Figure 2B, dilatation of the venous system occurs, demonstrated as a marked fall in the piston, leading to pooling in the peripheral circulation and failure of venous return. This effect is enhanced by the loss of volume from the intravascular to the interstitial compartment.

Figure 2A. A hydraulic model of the normal circulation modified from Tyberg, Jv 25.

The heart is represented by a pump that moves blood from a low-pressure, high-compliance venous reservoir to a high-pressure, low-compliance arterial reservoir. Blood flows back to the heart from the high pressure arterial system through a resistance (systemic vascular resistance) to the venous reservoir. The variable capacitance of the venous reservoir represented by movement of the piston is the principal variable on the venous side of the circulation, determining the volume of blood available for cardiac filling.

Figure 2B. Representation of a severe allergic reaction. Systemic arteries and veins dilate.

The downward movement of the piston represents the dramatic increase in capacitance of the highly compliant venous system. Blood is sequestered in portal and systemic veins, critically reducing cardiac filling. Volume is also lost from the circulation into the interstitial space. Systemic arterial dilatation causes a fall in systemic vascular resistance which, combined with the severely compromised cardiac output, leads to severe hypotension.

THE TREATMENT OF ANAPHYLAXIS

The management of anaphylaxis is represented pictorially in Figure 2C. Endogenous catecholamine release at the onset of anaphylaxis is massive(14). The use of echocardiography during anaphylaxis characteristically shows a hyperdynamic but empty heart(11,12). This would suggest that, in most cases, there is not a primary pump problem, although in rare circumstances acute coronary syndromes have been described that include stress cardiomyopathy (Takotsubo and reverse Takotsubo syndrome), which may more commonly be caused by the adrenaline used for treatment rather than endogenous catecholamines, or allergic myocardial infarction (Kounis syndrome). The inotropic and chronotropic effects of adrenaline – endogenous and exogenous – on the heart will have little beneficial effect on cardiac output, and thus blood pressure, if the heart is empty and until venous return is restored.

Adrenaline is a potent alpha-agonist in large doses, possibly offset by a beta2 agonist effect of vasodilatation in skeletal muscle. What overall effect this has on resistance and blood volume in skeletal muscle affected by neuromuscular blocking drugs and the mediators of anaphylaxis is unknown. The use of alpha agonists such as metaraminol, methoxamine(26) or vasopressin(29) has been recommended in anaphylactic shock that is unresponsive to adrenaline and fluid replacement. Although the mechanism of the beneficial effect is unclear, it is proposed that the principle effect is on the peripheral arterial circulation, increasing systemic vascular resistance and diastolic pressure. An attractive alternative explanation is a reduction in venous capacitance with a resultant increase in cardiac filling, but there is little evidence that vasopressin or alpha-agonists have a significant effect on venous smooth muscle.

Although fluid replacement is recognised as essential, and often successful without other intervention, it is not always immediately possible because of inadequate venous access. Often small-bore central venous lines are inserted in preference to large-bore peripheral cannulae, and the focus of treatment is usually adrenaline. In a rat model, adrenaline alone was shown to be less effective than with concurrent volume replacement, and colloids was more effective than normal or hypertonic saline(22). Although the use of the Trendelenberg position has not found favour in other forms of shock, in the distributive shock seen in anaphylaxis it would aid in venous return, as would the simple measure of elevating the lower limbs. The early use of transoesophageal echocardiography, if available, is useful in determining the contractility and filling of the heart.

Sugammadex will reverse muscle relaxation and increase muscle tone, which will compress intramuscular and intra-abdominal vessels, increasing venous return and translocating blood into the heart. The recommendation to minimise all anaesthetic drugs during shock may lead to patient arousal and movement exaggerating this effect. This is analogous to the onset of exercise, when muscle activity and a concomitant sympathetically mediated decrease in venous compliance increase venous return by as much as 500ml(31). It has been suggested that early administration of sugammadex in large doses is more likely to be beneficial by minimising the immunological cascade(32). In a skin model of anaphylaxis in individuals sensitised to rocuronium, an equivalent to 240mg.kg(-1) was ineffective in modifying the flare and wheal response to rocuronium(32). Administering a large dose of sugammadex presumes that the diagnosis of anaphylaxis is correct and that rocuronium is the trigger, which is not always the case. There are cases in which sugammadex has been reported to be of benefit when the anaphylaxis has subsequently been proven to have been caused by an antibiotic.
If this improvement can be substantiated, it would rule out an immunological mechanism. With conventional treatment, anaphylaxis is often rapidly curtailed and the surgical procedure completed. Administration of sugammadex may preclude this option. If the sugammadex is ineffective and the haemodynamic disturbance unresponsive to treatment, a dilemma can arise if further muscle relaxation is required.

Figure 2C. Adrenaline and volume replacement are the mainstays of treatment of hypotension.

Systemic vascular resistance and both cardiac contractility and rate are increased. This will have no beneficial effect unless volume replacement and decreased venous capacitance, represented by upward movement of the piston, have improved venous return and cardiac filling.

CONCLUSION
The importance of venous capacitance and its regulatory role on circulatory haemodynamics are important concepts to understand in the management of severe anaphylaxis. Increased focus on this aspect of treatment may improve the outcome in the most severe cases that are unresponsive to adrenaline. If there is one area for improvement in the management of anaphylaxis in the operating theatre, it would be the more aggressive use of volume, which would be simplified by immediate insertion of large-bore peripheral or central cannulae in preference to a conventional central line. We also propose that in the unlikely event that there is any beneficial effect of sugammadex on the circulation in intraoperative anaphylaxis, it is not an immunological but a circulatory response secondary to improved cardiac filling.

ACKNOWLEDGMENT
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REFERENCES
Pulmonary hypertension: An overview for the “non-cardiac” anaesthetist

IAN SMITH, MBBS, FANZCA
Staff specialist, The Prince Charles Hospital, Brisbane.
Dr Ian Smith is a full-time cardiothoracic anaesthetist at The Prince Charles Hospital in Brisbane with main interests in cardiothoracic transplantation, mechanical support and bad right hearts.

INTRODUCTION
For many anaesthetists, providing safe anaesthesia for patients with known pulmonary hypertension (PH) is a daunting prospect. Mortality is very high with observational reviews quoting 10-15 per cent1-4. Perioperative morbidity approaches 40 per cent; this includes arrhythmias, respiratory and right ventricular (RV) failure3.

This review is aimed at the generalist anaesthetist who may see these patients infrequently and those preparing for the final examination. The aims are to improve the understanding of the aetiology, classification and pathophysiology of pulmonary hypertension, the therapies available, and the principals of providing safe anaesthesia.

PULMONARY HYPERTENSION
Pulmonary hypertension (PH) is defined according to mean pulmonary artery pressure (mPAP) at rest as assessed by right heart catheterisation (RHC)5. The resistance to flow through the pulmonary vascular bed is most simply defined using Ohm’s law. The pressure drop across the system divided by flow equals the resistance. This is an oversimplification but is adequate for most clinical scenarios.

RHC is the gold standard for assessment but is an invasive procedure. It provides information on right heart and pulmonary artery pressures, cardiac output and index, and pulmonary artery occlusion pressure (as a surrogate for left ventricular end diastolic pressure).

It must be noted, just as in left heart failure, that a failing right heart may be unable to generate high pressures. Hence, presence of a low pulmonary artery pressure does not guarantee a normal right heart and pulmonary vasculature, it may be a sign of severely declining function and the function of the right heart must be taken into consideration with the pressures.

Table 1. Normal and abnormal values

| PH pulmonary hypertension, RAP right atrial pressure, mPAP mean pulmonary artery pressure, PAPs/d pulmonary artery pressure systolic/diastolic, LAP left atrial pressure, CI cardiac index L/min/m², PVR pulmonary vascular resistance dynes/sec/cm², All pressures mmHg. |
|---|---|---|---|
| Normal | Mild PH | Moderate PH | Severe PH |
| RAP  | 2-5 | | |
| mPAP | 12-15 | 25-40 | 40-55 | >55 |
| PAPs/d | 25/7 | >2/3 systemic systolic | |
| LAP | 6-10 | 10-15 | >15 |
| CI | >2.2 | | |
| PVR | <250 | | |

Transthoracic echocardiographic criteria
Transthoracic echocardiography (TTE) criteria provide a non-invasive assessment of right and left heart function, valve function and morphology. From Doppler interrogation of the velocity of any tricuspid regurgitation jet, a modified Bernoulli equation can be used to estimate right ventricular systolic pressure (RVSP) (not mean pressure, systolic). RVSP = right atrial pressure + (tricuspid regurgitation jet velocity)² x 4.
Pulmonary hypertension: An overview for the “non-cardiac” anaesthetist

Recent years have seen a significant increase in awareness of pulmonary hypertension (PH), with an improved understanding of its pathophysiology and treatment. This has led to improved perioperative management for patients with PH. PH is defined as a sustained increase in mean pulmonary artery pressure (PAP) of >25 mmHg at rest or during exercise, and is a complex disease that affects patients of all ages.

### Pathophysiology

Pulmonary artery pressure and resistance are regulated by several mechanisms, including myogenic, neurogenic, and humoral factors. The primary mechanisms include:

- **Myogenic mechanisms:** These are intrinsic to the smooth muscle of the pulmonary vasculature and are responsible for the basal tone of the pulmonary arteries.
- **Neurogenic mechanisms:** These are influenced by the autonomic nervous system, with the sympathetic nervous system dominating the vessels of the lung.
- **Humoral mechanisms:** These include the release of vasoactive substances such as endothelin, thromboxane A2, and nitric oxide.

### Classification of Pulmonary Hypertension

Pulmonary hypertension is classified into five main categories, according to the World Health Organization (WHO):

1. **Idiopathic pulmonary arterial hypertension (IPAH)**
2. **Hereditary PAH**
3. **Pulmonary hypertension associated with HIV infection**
4. **Pulmonary hypertension associated with portal hypertension**
5. **Pulmonary hypertension associated with congenital heart disease**

Each of these categories has distinct clinical and therapeutic implications.

### Echocardiographic Features

Echocardiography is a critical tool in the diagnosis and management of PH. Key echocardiographic features include:

- **High right atrial pressure:** This is often the first sign of PH.
- **Elevated right ventricular pressure:** This is typically seen with chronic PH.
- **Right ventricular hypertrophy:** This is a common finding in PH.

### Monitoring during Anaesthesia

During anaesthesia, patients with PH require careful monitoring to prevent complications. Key areas of concern include:

- **Hydrostatic and myogenic effects:** These can be exacerbated by changes in blood volume and perfusion.
- **Respiratory effects:** Changes in cardiac output and pulmonary blood flow can affect PH.

### Anaesthetic Considerations

- **Vasopressors:** Consideration of vasopressor support during anaesthesia.
- **Intra-aortic balloon counterpulsation (IABP):** May be useful in managing right ventricular dysfunction.
- **Transcatheter pulmonary valve implantation (TPVI):** A newer technique for patients with severe PH.

### Conclusion

Pulmonary hypertension is a complex disease that requires a multidisciplinary approach to management. Anaesthetists should be aware of the potential complications and should work closely with cardiologists and pulmonologists to ensure optimal perioperative care for these patients.
PRE-OPERATIVE EVALUATION

In idiopathic or familial PH, presentation may be non-specific. Symptomatic patients may complain of dyspnoea on exertion or chest pain, due to right heart ischaemia. Syncope may occur but is often a late sign heralding a severe situation. Rarely, patients may have hoarseness from left main pulmonary artery enlagement and left recurrant laryngeal nerve stretch. In types two to five, other symptoms may be apparent from the primary condition causing the PH. Haemoptysis is uncommon.

The patient should be examined from a multi-system approach looking at primary and secondary effects. They may be hypotensive, partly from low cardiac output, but also as a consequence of medical therapy. Pulse oximetry may show hypoxia, this may worsen with exercise due to low output, V/Q mismatching or intracardiac shunts. The jugular venous pulse may be elevated and rise abnormally with inspiration. As the RV dilates, TR may cause a prominent V wave. The praecordium may demonstrate an RV heave and a loud second heart sound with increased splitting. Signs of congenital heart disease should be sought, cyanosis, clubbing and previous cardiothoracic surgery. Hepatomegaly, ascites and peripheral oedema are signs of hepatic congestion. Some patients may have had a pacemaker or automated implanted cardiac defibrillator (AICD). They may have long-term central venous catheters for prostacyclin delivery.

Echocardiography is a highly sensitive tool for the diagnosis of PH. It provides information on causes (such as CHD and left-sided heart disease) and on the heart's response to elevated pulmonary pressures. An RV that is compensating for increased afterload may generate a mean PAP of 60mmHg, however with failure this falls and should not be mistaken as a less severe situation, the pressure should be interpreted in the context of RV function and trends. Imaging of RV function will help in this distinction. The complex mechanics of the RV make echo assessment less robust than LV assessment. Tricuspid annular plane systolic excursion (TAPSE) measures the distance the tricuspid annulus moves during systole; >15mm is considered normal; TAPSE decreases as RV function declines, <18mm being associated with worsening outcomes in the context of PH. Pressure overload will cause flattening of the IVS throughout the cardiac cycle, becoming concave to the left when severe. The tricuspid regurgitation jet velocity is indicative of pulmonary pressures. TTE will also describe the size, dilatation and function of the RV.

Cardiac MRI is excellent for RV assessment; it has the ability to calculate accurate volumes and ejection/ regurgitant fractions. It remains a highly specialised study and requires skill in interpretation. It will not be discussed further here. Presence of an AICD contraindicates MRI scanning.

Pulmonary function tests may demonstrate underlying intrinsic lung disease, restrictive or obstructive patterns may be seen.

The six-minute walk test is a useful non-invasive test that correlates well with maximal oxygen uptake (VO2max). A distance walked less than 600 metres correlates with a VO2max of 15ml/kg/min and less than 300 metres is associated with increased morbidity and mortality.

Blood sampling may demonstrate polycythaemia in those with hypoxaemia, hypocapnoea and compensatory changes. Hypoxaemia may be present due to intrinsic lung disease and left-sided heart disease (for example, mitral regurgitation) causing pulmonary venous pressure elevation and increased alveolar water. The low cardiac output due to RV failure can cause death to the body. This is reduced oxygen delivery to the body. This contributes to systemic desaturation and hypoxaemia. Should the patient have an intracardiac right to left shunt such as an ASD, this will also cause desaturation. Sampling before sedation can be a useful indicator of where the chronically ill patient “lives” and what targets are reasonable intra and post-operatively.

A number of factors have been associated with worse outcomes in pulmonary hypertension. These are summarised in Table 4.

Table 4. Prognostic variables in pulmonary hypertension

<table>
<thead>
<tr>
<th>Determinants of Risk</th>
<th>Lower risk/good prognosis</th>
<th>Higher risk/worse prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs RV failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>WHO PH functional class</td>
<td>I or II</td>
<td>IV</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>&gt;500m</td>
<td>&lt;300m</td>
</tr>
<tr>
<td>VO2max</td>
<td>&gt;15ml/kg/min</td>
<td>&lt;12ml/kg/min</td>
</tr>
<tr>
<td>Echo assessment</td>
<td>Minimal RV dysfunction, TAPSE &gt;20mm</td>
<td>Pericardial effusion, RV dilation/ dysfunction, RA enlargement, TAPSE &lt;15mm</td>
</tr>
<tr>
<td>RHC</td>
<td>RAP&lt;8mmHg, CI&lt;2.5 L/min/m²</td>
<td>RAP&gt;15mmHg, CI&gt;2.0 L/min/m²</td>
</tr>
<tr>
<td>BNP</td>
<td>Minimal change</td>
<td>Significant elevation</td>
</tr>
</tbody>
</table>

Pulmonary hypertension: An overview for the “non-cardiac” anaesthetist

RV right ventricle, 6MWT six-minute walk test, VO2max derived from cardiopulmonary exercise testing, RA right atrium, RAP right atrial pressure, TAPSE tricuspid annular plane systolic excursion, BNP brain natriuretic peptide. WHO PH functional class – class 1 asymptomatic, class II dyspnoea chest pain or near syncope with ordinary physical activity, class III marked limitation in activity with chest pain, dyspnoea or near syncope at rest, class IV all symptoms present at rest and worsen with any activity. Adapted from Galie et al. Eur Heart J. 2009 30: 2493-337.

Pharmacotherapeutic considerations

Patients may be receiving treatment for the cause of PH, such as anti-retrovirals, steroids and immunosuppressives. The patient may be anticoagulated due to a thrombophilic state, atrial fibrillation, presence of a caval filter or low cardiac output. Emergency surgery may require use of prothrombin complex concentrates, which can rapidly reverse warfarin without the large volumes required of fresh frozen plasma that may overload the RV. Thrombolytics are used to reduce renal and hepatic congestion, but excessive use may reduce RV and LV preload. Patients may be on continuous home-oxygen therapy.

Once patients are established functional class II or worse, depending on their WHO PH classification, they are managed with advanced agents aimed at reducing PVR. These include anticoagulants (ERAs), phosphodiesterase type 5 inhibitors (PDE5i), prostacyclin analogues and soluble guanylate cyclase stimulators (sGCs). None should be interrupted in the perioperative period.

Prostacyclin is continuously delivered by PICC due to a very short half life. Brief interruption can lead to profound rises in PVR and death.

ANAESTHETIC AND PROCEDURAL MANAGEMENT

A basic premise that fits many cardio pulmonary diseases requiring anaesthesia is “keep them where they live”, meaning that safe haemodynamic and metabolic targets are those present in the awake, non-sedated patient. Whatever technique is chosen, two golden rules should be followed: maintain RV coronary perfusion (use arterial line and pressor) and avoid/predict rises in PVR.

Spinal anaesthesia

This may cause rapid and sometimes unpredictable changes in SVR and preload and cause dangerously unstable haemodynamics so is not recommended.

Epidural anaesthesia

Slowly titrated block level in those with intact coagulation remains a very useful and safe tool, but invasive pressure monitoring is suggested.

Limb and plexus blocks

Barriers to the continuance of anticoagulation and anti platelet use, limb or plexus blocks may prove excellent techniques where appropriate. The effects of diaphragmatic paralysis though should be considered, as it may be tolerated very poorly in those with a low cardiac respiratory reserve.

Procedural sedation

Monitored sedation may pose higher risk than general anaesthesia. Sedative agents can cause reduced minute ventilation and airway obstruction leading to hypercapnoea, hypoxia and respiratory acidos. Cardiovascular effects of sedative drugs can be variable and include bradycardia and hypotension, both undesirable. Agitation, disorientation and restlessness can be hard to control. Unplanned conversion to general anaesthesia may increase instability and reduce the control over the patient’s physiology.

General anaesthesia

Where general anaesthesia is necessary, key points include: Avoid sympathetic surges – adequate sympathetic nervous system blunting for laryngoscopy/intubation/ extubation but maintain SVR and coronary perfusion pressure. Preventing shivering. Judicious use of forced air warmers from the pre-op bay to recovery, warn the operating room prior to patient entry. Avoid hypoxia. Avoid hypercapnoea, adequate bag mask ventilation and minute ventilation. When beginning positive pressure ventilation, the impairment to venous return may cause severe hypotension. Adequate pain relief in the post-operative period to avoid inadequate respiration and splinting. Venous thromboembolism prophylaxis.

Monitoring should always include invasive arterial pressure monitoring. If long procedures or fluid shifts are anticipated, or major body-cavity surgery is planned, a central venous catheter (CVC) is useful. This may be necessary pre-induction to allow inotropes or pressor to be infused during the high-risk period of induction. Anxiety should also be managed, it may raise sympathetic tone. ACD deactivation and application of external defibrillator pads may be required.
Pulmonary hypertension: An overview for the “non-cardiac” anaesthetist

In some cases, continuous trans-oesophageal echocardiography may be beneficial. Pulmonary artery catheters (PAC) are less commonly used since several studies failed to validate their utility and demonstrated increased complications. However, in this patient group they provide valuable information to those familiar with their use and interpretation. The presence of arrhythmias with PAC usage is higher in the PH population and the arrhythmias will be poorly tolerated. The presence of severe TR will make cardiac output measurement inaccurate.30

Induction agents should be carefully considered. Propofol is very effective in preventing a pressor response to laryngoscopy, but may cause systemic hypertension leading to a downward spike due to failed right coronary perfusion.

Where available, etomidate potentially offers a favourable haemodynamic profile. However, it may be preferable to avoid its use and to rely upon the adrenal access in the critically ill.18

Ketamine provides excellent haemodynamic stability at induction doses of 2-3mg/kg without impairing SVR or changing PVR though conflicting studies have caused confusion regarding the effects of ketamine on pulmonary pressures.31 The classic cardiac induction, heavy on fentanyl and midazolam, gives good haemodynamic stability with little effect on PVR, SVR or cardiac contractility. It significantly reduces sympathetic nervous system tone for up to 20 minutes. The patient may be relying upon, and is not suited to rapid emergence requiring prolonged ventilation.

The circulation time of drugs will be slow, when titrating drugs to a response, small doses with time to achieve effect is the key.

Adequate muscle relaxation prevents coughing or straining with intubation, otherwise large fluctuations in venous return result that are poorly tolerated. Using agents that do not cause histamine release (and the resulting bronchospasm and vasoconstriction) is suggested. Full reversal prior to extubation is also important, to prevent hypoxia, hypercarbia and anxiety.

Nitrous oxide should be avoided as it directly raises PVR.32 Analgesic techniques should consider the risks of post-operative respiratory depression and hypercapnoea. Vasoactive agents can be considered as pressors, positive inotropes and those that may reduce pulmonary vascular effects, most are mixed. Specific pressors are phenylephrine, metaraminol, noradrenaline and vasopressin, ideally they should only raise SVR and not PVR. Vasopressin is thought to offer more systemic than pulmonary bias.33 Mifeprine has effective inotropic properties and should preferably be infused with vasopressin (over noradrenaline) to maintain SVR.34 Levosimendan has a long half-life and may contribute to hypotension so is not suited to intraoperative use.

Nitric oxide (iNO) is an inhaled gas delivered via the breathing circuit in compatible anaesthetic machines, via an intensivist or by a tightly fitting face mask. Its extremely short half-life means it must not be interrupted (for example, bagging or transfer), interruption may cause rebound PH severe hypoxaemia and death.

Surgical approach

It is important that surgery for PH patients is well planned, involving a multidisciplinary approach where pulmonary physicians, anaesthesiologists, intensive care physicians and surgeons collectively form a plan. Ideally the case should be done during normal working hours early in the week when full clinical resources are available.

In the case of abdominal procedures, laparoscopic approaches are often favourable due to better post-operative recovery. The surgery should be performed proficiently with low insufflation pressures (for example, 10-12cmH2O). Pneumoperitoneum immediately raises intra-thoracic pressures, raises PVR and impairs venous return. Carbon dioxide is the primary cause of raising PaCO2, and requiring a rise in minute ventilation. This may exacerbate raised intra-thoracic pressures and impaired venous return. Laparoscopic surgery may require reverse or Trendelenburg positioning for surgical access, both of which may worsen respiratory mechanics and haemodynamics.

Obstetric patients

Should a patient with severe PH present for delivery, a multidisciplinary approach in a tertiary-level care unit is required and should be planned early. Maternal mortality risk around 30% and is most common in the month post delivery.35 Published case series describe both vaginal delivery and Caesarean section in the context of maternal pulmonary hypertension. The overall trend appears to favour vaginal delivery. This may be related to less maternal coagulation disturbance and lower infection risk. Episiotomy is a contraindication for any Caesarean section to reduce maternal mortality than general anaesthesia likely due to greater haemodynamic stability. Invasive arterial and central venous pressure monitoring are required. Commonly active third-stage management includes agents such as oxytocin. Slow, low-volume infusion rather than bolus and large-volume (1000mL) infusion is safest. Carboprost (PGF2α) causes intense pulmonary vasoconstriction so is absolutely contraindicated. After delivery, auto-transfusion from uterine contraction can cause cardiovascular failure due to rapid in line pressure. Most deaths in the PH group occur between two and 30 days post partum, vigilance must continue with ICU level care for 72 hours. Early reintroduction of thromboembolic prophylaxis should be done when safe. Non interruption of PH medical therapy is mandatory.

POST-OPERATIVE PLACEMENT

Despite perfect pre and intra-operative care, these patients can die unpredictably in the post-operative period. They require high level post-operative monitoring for 48-72 hours. They should have invasive arterial pressure monitoring and continuous pulse oximetry. If patient-controlled analgesia is used, extra vigilance is needed to detect any respiratory depression. Patients should have intensive care unit (ICU) or high dependency beds booked preoperatively. Close monitoring is ideal during epidural discontinuation and transition to enteral or IV analgesia.

THE ACUTE PULMONARY HYPERTENSION CRISIS

This may occur at any time during the patient’s course of care. Failure to recognise and treat may result in death. Presentation may include distress, dyspnoea and progressive signs of a low cardiac output state, hypotension, tachycardia, hypoxaemia and end organ hypoperfusion. Signs include rapid CVP/JVP, systemic hypotension and features of low cardiac output, such as a falling urine output. The patient may rapidly develop a metabolic acidosis with elevated lactate, but has the ability to increase respiratory compensation causing rapid progression. Management should aim to lower PVR, maintain SVR and restore cardiac output and remove triggers. Triggers may include hypercapnoea from excess opiates, or intense sympathetic vasoconstriction from poorly managed pain. Sometimes no trigger will be identified. Opiates such as morphine and anaesthetics may help break the cycle. However, inotropes, ventilation and anaesthesia may have a role in the patient with PH. In cases of severe crisis, unresponsive to maximal medical therapy in patients considered retrievable with a reversible cause, peripheral veno-arterial extra corporeal membranous oxygenation should be considered.

CONCLUSION

Patients with severe PH are rare, but may present for elective or emergency surgery. They remain an extremely high-risk group of patients to anaesthetise with increased mortality and morbidity. Transfer to a cardiac unit should be considered depending on local expertise and urgency. An understanding of the patient’s physiology is mandated to provide optimal anaesthesia. The period of risk doesn’t end with placement of the surgical dressing. A crisis may happen unpredictably in the two to three days post-operatively despite perfect intra-operative care. Multidisciplinary teams should plan and co-ordinate care and post-operative intensive care is strongly advised.

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REFERENCES


Goal-directed transthoracic echocardiography – a translational education program

ALICIA DENNIS, MBBS, PhD, PGDPECHO, FANZCA

Staff specialist anaesthetist, Director of Anaesthesia Research, Royal Women’s Hospital Parkville, Australia. Associate Professor Alicia Dennis is a full-time staff specialist anaesthetist and Director of Anaesthesia Research at the Royal Women’s Hospital, Melbourne, Australia. Her research program examines haemodynamics in women with preeclampsia and has provided insights into the mechanisms of the development of hypertension. The use of transthoracic echocardiography in these research studies has led to the development of a translational echocardiography education program in obstetric anaesthesia and obstetric critical illness and she has developed a teaching and educational program in this area.

INTRODUCTION

Transthoracic echocardiography is used in many areas of medicine as a clinical, diagnostic and research device. It is non-invasive, safe and acceptable to patients. The ability of transthoracic echocardiography to provide volumetric and flow data – as well as to visually show the two and three-dimensional graphics of the heart – means that it is a powerful tool. Not only is it a useful device in the clinical setting, it also has a role in education, enabling teaching of cardiac physiology and pathophysiology and the modernisation of the curriculum for all those learning the function and structure of the human body.

Many groups have recognised these advantages, including emergency physicians and intensive care clinicians. Cardiac anaesthetists have a long-established structured educational and quality assurance program for transoesophageal echocardiography that has been incorporated into most hospitals providing cardiac anaesthesia. The use of transthoracic echocardiography, as opposed to transoesophageal echocardiography, by anaesthetists is increasing; however, there are few departments in Australia or internationally that have established a sustainable educational program that incorporates quality assurance and outcome measurements for transthoracic echocardiography teaching and training into their everyday practice. The purpose of this article is to outline an educational program that may fulfil the requirements for a sustainable program in transthoracic echocardiography, enabling integration of this important diagnostic tool into everyday clinical practice – a translational education program.

TRANSTHORACIC ECHOCARDIOGRAPHY

Transthoracic echocardiography has undergone significant advances in the past decade, with machine size reducing and portability increasing. Coupled with this is the absence, in some health services, of 24-hour echocardiography services to attend clinical emergencies. This has meant that anaesthetists have started to upskill in the area of echocardiography to assist with the management of critically ill patients. There have also been steady improvements in image quality and reproduction, meaning that instantly available scanning and point-of-patient-care devices are being increasing used. This enables clinicians to answer clinical questions at the point of care and measure the responses to interventions. Importantly, regarding accuracy of the data supplied by echocardiography, in skilled hands it has been shown to be accurate for estimating pulmonary artery pressure, left atrial pressure and left ventricular pressure. In addition, echocardiography has been compared with thermomodulation, electromagnetic and roller pump methods of determining cardiac output and found to be accurate.

Regarding the clinical applicability of echocardiography, many international groups have published recommendations and there are published guidelines on how to perform measurements and calculations, so that uniformity, precision and accuracy are maintained. In addition, there are also guidelines on how to maintain device safety, the issues of bioeffects and cleaning and infection control.

TRANSTHORACIC ECHOCARDIOGRAPHY AND ANAESTHESIA AND CRITICAL ILLNESS

Many of our patients undergoing anaesthesia are healthy with no pre-existing medical problems and are having elective low-risk surgery of short duration. This group of patients is unlikely to benefit from the routine application of transthoracic echocardiography, including a pre-operative transthoracic echocardiography examination. However, the situation is vastly different if we consider a high-risk patient population, such as those with pre-existing cardiovascular disease, the elderly, the pregnant or extremely obese, or the high-risk surgery population – perhaps those undergoing cardiac, neurological, obstetric, cancer, or emergency surgery – or the high-risk anaesthetic population. Often, baseline cardiac function is unknown prior to surgery and we rely on our knowledge of the predictable physiological responses to our pharmacological interventions. In the area of acute emergencies and unpredictable responses to treatment interventions, transthoracic echocardiography may be of use. In these situations, diagnostic dilemmas may arise and we may be unsure of the patient’s volume status, their estimated left ventricular end-diastolic pressure, or their ejection fraction. Reducing diagnostic uncertainty is important and there is the need for improvements in clinical care and accurate diagnoses.

Transthoracic echocardiography can be used to correctly answer clinically relevant questions and enable correct interventions in a timely manner (Table 1). It could be predicted that if the correct diagnosis (versus the wrong diagnosis) was made, thereby enabling the correct interventions to be commenced (versus incorrect treatments), then over time on a population level there would be positive impacts on patient outcomes. This is particularly
important in the area of the evaluation of hypotension, shock or haemodynamic instability of uncertain or suspected cardiac aetiology, as this meets the highest level of appropriateness or Class 1 recommendation according to American, British and European guidelines.8-11 A pre-operative evaluation involving transthoracic echocardiography establishes baseline cardiac function and structure, and then serial intra-operative and postoperative scanning, may be of assistance in guiding resuscitation, fluid therapy, use of vasopressors and inotropes and in decisions related to location of postoperative care. The following is a typical example of a diagnostic dilemma that may occur during fluid resuscitation in a patient who has bled, but remains hypotensive:

A 32-year-old woman is experiencing a postpartum haemorrhage (blood loss 750 mL) and the informal bedside haemoglobin value is 9 g/dL, after 2000 mL of intravenous crystalloid. Vital signs: heart rate 120, sinus rhythm, blood pressure 80/42 mmHg, respiratory rate 30 breaths per minute, oxygen saturation 94% on room air; temperature 37.1°C. The formal haemoglobin measurement and bedside arterial blood gases are sent but pending.

### Clinical scenarios and clinical questions in critical illness.

**Critical illness and acute emergencies**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Clinical questions addressed with the use of echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major haemorrhage</td>
<td>What is the intravascular volume status? 1+ normal</td>
</tr>
<tr>
<td>Myocardial Ischaemia</td>
<td>Are there regional wall motion abnormalities?</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Is there left ventricular contractility? 1+ normal</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Is there right ventricular outflow tract obstruction?</td>
</tr>
<tr>
<td>Embolism – pulmonary (blood clot), amniotic fluid, air</td>
<td>What is the right ventricular size and contractility? 1+ normal</td>
</tr>
<tr>
<td>Critical hypertension</td>
<td>Is there pericardial tamponade?</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Is there pulseless electrical activity?</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td></td>
</tr>
<tr>
<td>Respiratory emergencies (asthma)</td>
<td></td>
</tr>
<tr>
<td>Endocrine emergencies</td>
<td></td>
</tr>
<tr>
<td>Extreme obesity</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td></td>
</tr>
</tbody>
</table>

1 = decreased, 1+ = increased. Adapted from reference 1.

### WHAT TREATMENT DO YOU COMMENCE?

In this case, the cause of the haemodynamic instability is unclear and a diagnostic dilemma exists. It could be hypovolaemia, or alternatively it could be reduced ejection fraction heart failure. One is faced with the options of

In this case, the cause of the haemodynamic instability is unclear and a diagnostic dilemma exists. It could be

There are many benefits of integrating simulation into education and the benefits of simulation in the specific area of echocardiography are emerging.18-23 Simulation has significant advantages, as it enhances clinical education, creates opportunities for deliberate practice of new skills and allows the student to be exposed to clinical scenarios that are rare or uncommon.18 In the area of anaesthesia where practising transthoracic echocardiography may be time consuming, the use of a simulator to obtain and maintain skills could be highly advantageous.

### EDUCATION IN TRANTHORACIC ECHOCARDIOGRAPHY

Formalised education in transthoracic echocardiography exists for cardiology and ultrasonography and some areas of critical-care medicine; however, training for other groups is less defined.12 There is a wide range of brief courses and training workshops that occur predominantly outside the hospital environment. These courses are excellent in giving the novice operator (or someone with no experience at all) exposure to transthoracic echocardiography and the ability to experience transthoracic echocardiography first-hand. They are, however, limited by the fact that ongoing training, experience and quality assurance may be limited if the people being trained do not integrate with a hospital-based program for ongoing training, supervision and credentialing.

This leads on to the recognition of two groups of training levels: the novice and the advanced or expert operator, and two groups of transthoracic echocardiography examination scans — the goal-directed transthoracic echocardiography scan and the comprehensive transthoracic echocardiography scan. The novice or basic-level operator can perform an emergency transthoracic echocardiography scan and recognise life-threatening clinical conditions such as hypotension caused by hypovolaemia, reduced ejection fraction, right ventricular failure or cardiac tamponade. However, the novice operator must appreciate the limitations of their skills and in doing so minimises a risk of transthoracic echocardiography — incorrect diagnosis from lack of training. The advanced or expert operator has the ability, after training in a stepwise fashion from basic to advanced skills and knowledge, to perform a full cardiac assessment.

Regarding transthoracic echocardiography examination scans, goal-directed transthoracic echocardiography is ideally suited to anaesthesia and critical care. Goal-directed transthoracic echocardiography is defined as an abbreviated or shortened transthoracic echocardiography examination performed at the point of patient care, designed to rule out the presence of major abnormalities as the cause of an acute physiological disturbance. It involves the acquisition, recording and storage of a reproducible, easy to obtain, clinically relevant minimum data set, by a trained operator, that can be used to make a clinical diagnosis and assist with treatment interventions.

Principles of goal-directed scans are:

- **Acceptable and applicable**
- **Bedside test**
- **Comfortable and concise examination** – limited views
- **Diagnosis and response to therapy** – contractility status and volume status
- **Embolic air, blood, amniotic fluid** — right heart function/relative size
- **Foetal heart rate assessment** (in the case of a pregnant woman)

In 2014 the Australian and New Zealand College of Anaesthetists (ANZCA) developed PS46, the guidelines for the training and practice of perioperative cardiac ultrasound in adults.24 For goal-directed echocardiography, the PS46 document recommends that at least 20 supervised transthoracic echocardiography studies, at least 20 additional unsupervised transthoracic echocardiography studies with full review by a supervisor, and at least 50 additional goal-directed transthoracic echocardiography studies (with review by supervisor as necessary), be performed. After basic training is achieved, maintenance of standards is achieved by participating in audit and peer review of cardiac ultrasound cases and the performance of at least 50 transthoracic echocardiography studies annually.

Included in PS46, transthoracic echocardiography education must have quality assurance. PS46 does not include the need to record outcome data; however, with the implementation of any new device or educational program, this too is essential. Regarding outcome assessment for educational programs, Kirkpatrick’s framework provides four levels of assessment for evaluating their impact:

- **Level 1** — Reaction — participant’s reaction to the intervention.
- **Level 2** — Learning — the degree to which the learning occurs as a result of the intervention.
- **Level 3** — Behavioural change — the transfer of learning to behaviour at work.
- **Level 4** — Organisational performance — the impact of learning on patient outcomes.
Ideally, educational programs satisfying these four areas of evaluation would result in a positive reaction by participants to the education program (Kirkpatrick level 1), improved learning by the participant (level 2), the transfer of skills and knowledge to the clinical environment by the participant (level 3) and an improvement in patient outcomes (level 4). Therefore it is within the framework of:

1. The new guidelines from ANZCA regarding the training and practice of perioperative cardiac ultrasound
2. The applicability of goal directed transthoracic echocardiography in anaesthesia and critical illness and
3. The role of simulation in enhancing education

that this example of an educational program is presented (Figure 1).

**A GOAL-DIRECTED TRANSTHORACIC ECHOCARDIOGRAPHY EDUCATIONAL PROGRAM**

An example of an educational program is shown in Figure 1. The program aims to educate a small number of senior anaesthesia trainees or fellows (five) and a larger number of anaesthetic consultants (15) in goal-directed echocardiography. The staff who participate in the educational program should work at least four sessions per week at the hospital and should be planning to continue working at that hospital for the time required for education in goal-directed transthoracic echocardiography (one year). Specifically, the program incorporates the recognition and management of acute emergencies including hypotensive heart failure, acute hypertensive heart failure and acute hypovolaemia. It does this by teaching the participants the knowledge and skills to determine ejection fraction, contractility, left ventricular end-diastolic pressures and left and right ventricular end-diastolic volumes using both simulator cases of normal and abnormal cardiac function and structure, and human cases of normal and abnormal cardiac function and structure.

**Evaluation of the program**

Evaluation is performed by applying Kirkpatrick’s framework, with evaluation occurring at four distinct time points:

- **Assessment 1** – prior to commencing the education program.
- **Assessment 2** – after the initial four-month training period.
- **Assessment 3** – after the subsequent four-month probationary training period.
- **Assessment 4** – after the final four-month independent training period.

**Organisational performance and the impact of learning on patient outcomes**

Level 4 outcomes are assessed for individual patients by review of logbook data as recorded by the participant. A standardised case-reporting form is used and all cases are stored on a database. Answers to the following questions are recorded:

- Did echocardiography result in the diagnosis of reduced ejection fraction?
- Did echocardiography result in a beneficial change of therapy?
- Was an incorrect therapy commenced as the result of incorrect echocardiography findings?
- Did echocardiography contribute to patient satisfaction at the time of its use?

Outcomes are also aggregated from the group of participants and used to record group patient outcomes. These include:

1. The number of patients in which goal-directed echocardiography resulted in the diagnosis of reduced ejection fraction.
2. The number of patients in which goal-directed echocardiography resulted in a beneficial change of therapy.
3. The number of patients who experienced complications of echocardiography, including incorrect therapy, as a result of incorrect echocardiography findings.
4. Patient’s satisfaction level (five-point Likert scale) – either with their involvement in the education program, or as a patient with the use of echocardiography.

**Hospital and department**

For a program to be successful, the anaesthetist department has to be interested in and committed to its implementation. As with the introduction of any new program, there needs to be a philosophy of discovery and learning, and teaching activities need to be encouraged and supported within the organisation. As internet learning is part of the curriculum, widespread modern internet connections, 24-hour library access and quiet workspaces to enable both virtual and real-life learning are necessary.

**Personnel**

The educational leader and curriculum developer for the educational program need to be decided upon for each department and be advanced or expert-level operators. The leader needs to have assistance to run hospital-based workshops and initial teaching – at least two additional trained people. Ideally, there should also be a person who can recruit patients for the human workshops and coordinate the review of participants’ echocardiography studies during the initial and probationary training period.

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**Figure 1. Educational program outline for a 12-month continuing program in echocardiography**

<table>
<thead>
<tr>
<th>Assessment 1</th>
<th>Pre-education</th>
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<tbody>
<tr>
<td>Pre-existing knowledge and skills questionnaire and scenario-based clinical management questionnaire†</td>
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<thead>
<tr>
<th>Initial training</th>
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<tr>
<td>Four months</td>
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<tr>
<td>Internet and textbook learning – Anaesthesia and Critical Illness Curriculum (tailored to department’s AOI)†</td>
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<tr>
<td>Workshops – four-hour duration – one machine: five trainees – 1 trainer: five trainees</td>
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<tr>
<td>Simulation studies – 25 cases (20 fully supervised); Human studies – five cases (five fully supervised)</td>
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<th>Assessment 2</th>
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<tbody>
<tr>
<td>Post initial education</td>
</tr>
<tr>
<td>Participant’s reaction to the initial training – questionnaire (Kirkpatrick Level 1 evaluation)</td>
</tr>
<tr>
<td>Degree to which learning occurs due to the initial training – questionnaire (Kirkpatrick Level 2 evaluation)</td>
</tr>
<tr>
<td>Acquired knowledge and skills test and scenario based clinical management test</td>
</tr>
<tr>
<td>Skills station assessment – setting up, performing and reporting a normal goal-directed TTE scan</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Probationary training</th>
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</thead>
<tbody>
<tr>
<td>Four months</td>
</tr>
<tr>
<td>Case studies (simulation and human) – 2 cases/week – 32 cases (20 fully reviewed) Logbook recording†</td>
</tr>
<tr>
<td>Attend departmental TTE clinical case quality assurance review meeting every two weeks</td>
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<tr>
<th>Assessment 3</th>
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<tbody>
<tr>
<td>Probationary training</td>
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<tr>
<td>The participant’s transfer of learning to behaviour at work (Kirkpatrick Level 3) – assessment of logbook (i.e., number of times TTE independently used), self-assessment questionnaire, feedback from staff</td>
</tr>
<tr>
<td>Acquired knowledge and skills test and scenario based clinical management test</td>
</tr>
<tr>
<td>Teaching station assessment – demonstrating the set-up, performance and reporting of a goal-directed TTE scan to a novice trainee</td>
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<th>Assessment 4</th>
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<tr>
<td>Post-independent training</td>
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<tr>
<td>Impact of learning on patient outcomes (Kirkpatrick Level 4)</td>
</tr>
<tr>
<td>Acquired knowledge and skills test and scenario based clinical management test</td>
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<tr>
<td>Teaching station assessment – demonstrating the set-up, performance and reporting of a goal-directed TTE scan to a novice trainee</td>
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<table>
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<tr>
<th>Completion of training and commencement of Maintenance of skills and knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attendance at yearly update and refresher course</td>
</tr>
<tr>
<td>Yearly review of logbook* – one case/week (50 per year) (simulation or human)</td>
</tr>
<tr>
<td>Attendance at departmental TTE clinical case quality assurance review meeting (six per year)</td>
</tr>
<tr>
<td>Self-nominated interested participants who have demonstrated aptitude and excellence on tests will be offered opportunity to teach in subsequent programs</td>
</tr>
</tbody>
</table>

| TTE = transthoracic echocardiography |
| AOI = area of interest |
| †similar to that presented in this article |
| *i.e. general and subspeciality anaesthesia |
| ‡standardised case reporting form and all cases stored on departmental database |
Equipment
At least one portable transthoracic echocardiography machine with data storage and review capability is necessary. Access to an echocardiography simulator would be advantageous to readily enable practice scanning and maintenance of skills.

Clinical review and quality assurance meetings
Clinical review meetings are necessary – similar to what occurs in departments with a transoesophageal echocardiography service – with presentation of all scans performed during the previous selected time period (two weeks), with opportunities for review, discussion and highlighting of key issues.

Time and access to in-real-life learning
The person implementing the educational program needs dedicated teaching time (one session per week) to run workshops, and supervise transthoracic echocardiography scanning as well as conduct and coordinate the departmental transthoracic echocardiography clinical case, quality assurance review meetings. In order to enable the smooth integration of transthoracic echocardiography into clinical practice, the department should allocate at least one elective theatre list as a transthoracic echocardiography scanning list where, after obtaining consent, all patients on that list undergo transthoracic echocardiography scanning prior to their surgery.

SUMMARY
Transthoracic echocardiography has significant advantages and does have a place in anaesthesia and critical illness. Workshops and short training programs external to hospitals offer people a chance to learn what transthoracic echocardiography is all about and obtain basic views and initial training. Unfortunately, few, if any hospital-based anaesthesia departments, offer a sustainable program of transthoracic echocardiography education with which these people can build upon their knowledge and skills. This means that these skills are not maintained and there is little quality assurance or maintenance of standards.

The time has come to develop formal hospital-based educational programs, such as the one outlined here, that incorporates quality assurance and outcome measurements, so that the skills and knowledge acquired by learning transthoracic echocardiography can be translated into clinical practice and improved in patient outcomes. We, as anaesthetists, have an opportunity to be leaders in this translational education. It is only through the hard work and commitment of anaesthetic departments and financial support to obtain equipment and staff, that the dream of widespread implementation of transthoracic echocardiography in medicine will become a reality.

REFERENCES
11. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohn M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012 Aug;14(8):803–869.
Pain management for trauma: Time to embrace regional anaesthesia?

IAN O FLEMING, MBBS, FANZCA, FRCA, BSC, DIP MEDED, EDRA
Anaesthetist, Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Western Australia.
Dr Ian O Fleming's specialist interests include regional anaesthesia and anaesthesia for high-risk patients. Ian also has a major commitment to medical education. Personal interests are soccer, cycling and golf.

BILL WILLIAMS, MBBS, BSC, FANZCA, FRCA
Anaesthetist, Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Western Australia.
Dr Williams is an airway and pain-medicine specialist. Outside work, his pursuits include soccer and playing the guitar.

INTRODUCTION
Debate persists regarding best-practice pain management for patients sustaining traumatic injuries. In the developed world, trauma (meaning “wound”) is the leading cause of death in the first four decades of life, and the fourth-leading cause of death in all age groups. In recent decades, introduction of standardised protocols for early trauma management has dramatically improved survival rates. Of the survivors, a large proportion progress to chronic pain and functional disability. This represents a global healthcare problem that may, in part, be addressed by improving pain management.

Regional anaesthesia is established as an integral component of high-quality, evidence-based perioperative anaesthetic care. Safety, efficacy and versatility are greater than ever before. Enhanced recovery pathways for elective surgery use regional techniques extensively. This has spread into “high risk” specialties, such as thoracic and vascular surgery, and emergency care. Principal aims include avoidance of iatrogenic problems (for example, opioid-related side effects), minimising the stress response, and facilitation of early return to normal function. Using regional anaesthesia to achieve these objectives would appear to be highly desirable, irrespective of whether one was on a true enhanced recovery pathway or not. However, acceptance for the use of regional anaesthesia in treating trauma has been hindered by numerous barriers.

Pain as a symptom is almost ubiquitous following injury, and remains poorly treated. Isolated historical reports, representing low-level evidence and subject to reporting and publication bias, have fuelled an aversion to regional techniques in this population. Systemic opioids form the main analgesic strategy, exposing patients to suboptimal analgesia and a range of undesirable side effects.

The logic driving traditional resistance to the use of regional anaesthesia in trauma is under scrutiny. The weight of evidence is shifting, with favourable data attesting to the feasibility, efficacy and safety of regional interventions in managing victims of battlefield and natural disasters. Performed under extreme and challenging conditions, such demonstrable improvements represent an opportunity to refine pain management for civilian trauma.

In this review we will discuss the challenge of effective pain control following traumatic injury, mechanisms of transition from acute to chronic pain, controversies surrounding analgesic management in trauma, the advancing role of regional anaesthesia for trauma, and safety considerations for the use of regional anaesthesia following injury.

THE "STRESS" OF TRAUMA
"Stress response" is a term denoting the complex physiological response to tissue injury, involving activation of the neural, metabolic, endocrine, haematological and immunological systems. The magnitude of this catabolic state is commensurate with the extent of tissue damage. In evolutionary terms, adaptive changes such as hypercoagulability, immunosuppression, vasoconstriction and fluid retention may have conferred a survival advantage. In the context of modern medicine, it is unclear whether these changes actually benefit the individual, and attenuation of the stress response has become a meaningful treatment objective. Plausible advantages of avoiding “stress” include improvement of the myocardial oxygen supply/demand ratio, maintenance of gut and immune function, and reduced thromboembolism risk. A sympathetic blockade may improve regional blood flow and support survival of an injured extremity.

BACKGROUND
Conjecture in the surgical literature has apportioned blame to regional interventions in trauma patients for contributing to undesirable outcomes. Scepticism concerning the safety profile of regional anaesthesia and fear of litigation has led to an aversion to its performance. Specific issues include coagulopathy, potential secondary nerve injury and perceived delayed diagnosis of acute compartment syndrome (ACS). For decades, management has defaulted to general anaesthesia and systemic analgesia alone, despite multiple recognised drawbacks.
More recent data suggest risks concerning regional anaesthesia are probably overstated and may be negotiated.

Caveats and these are listed in Table 1.

Advantages

- Favourable data from military sources detailing benefits of regional anaesthesia for complex trauma.
- Improved reliability and safety, through developments in training and technology (for example, needle design and ultrasound).
- Low quality of evidence against the use of regional interventions.
- Publication of data disputing historical concerns over true attributable risk of regional interventions.
- Greater awareness of the importance of pain, with inadequate control associated with poor functional and psychological outcome.
- Limited efficacy of systemic analgesics, coupled with a predictable multisystem morbidity profile.
- Professional guidelines addressing balance of risk issues.
- Favourable data from military sources detailing benefits of regional anaesthesia for complex trauma.

Limitations

- Psychological outcome.
- Greater awareness of the importance of pain, with inadequate control associated with poor functional and psychological outcome.
- Improved reliability and safety, through developments in training and technology (for example, needle design and ultrasound).
- Low quality of evidence against the use of regional interventions.
- Publication of data disputing historical concerns over true attributable risk of regional interventions.
- Greater awareness of the importance of pain, with inadequate control associated with poor functional and psychological outcome.

Table 1. Advantages and limitations of regional anaesthesia for trauma

<table>
<thead>
<tr>
<th>Advantages</th>
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<tbody>
<tr>
<td>Superior pain control</td>
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<tr>
<td>Chronic pain protection</td>
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<tr>
<td>Avoidance of airway management (for example, difficult/failed intubation, bleeding, oedema, dental damage, cervical spine movement)</td>
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<tr>
<td>Stable haemodynamics</td>
</tr>
<tr>
<td>Satisfaction</td>
</tr>
<tr>
<td>Ease of transport</td>
</tr>
<tr>
<td>Facilitation of physiotherapy</td>
</tr>
<tr>
<td>Reduced nursing requirement</td>
</tr>
<tr>
<td>Attenuation of stress response</td>
</tr>
<tr>
<td>Reduced opioid dosage</td>
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<table>
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<tr>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Competition with resuscitation objectives</td>
</tr>
<tr>
<td>Acute compartment syndrome</td>
</tr>
<tr>
<td>Secondary nerve injury</td>
</tr>
<tr>
<td>Coagulopathy</td>
</tr>
<tr>
<td>Training, infrastructure, education, attitudes</td>
</tr>
<tr>
<td>Polytrauma</td>
</tr>
<tr>
<td>Positioning</td>
</tr>
<tr>
<td>Local Anaesthetic Systemic Toxicity (LAST) risk</td>
</tr>
<tr>
<td>Management mandating general anaesthesia (for example, sternotomy, craniotomy)</td>
</tr>
</tbody>
</table>

The unpredictable nature of trauma precludes primary preventative interventions. Following injury, “secondary prevention” relies on prompt pain control to prevent transition from “normal” acute pain to maladaptive neural sensitisation that serves no useful function. Initiation of suitable therapy is problematic. Early management of trauma follows ATLS® resuscitation protocols, with stabilisation through simultaneous assessment and management of injuries. Immediate focus is on preserving life. Analgesia is given lower priority status than resuscitation treatment objectives. Caregiver concern may also limit analgesia provision, for fear of compounding physiological derangement through side effects including respiratory depression, hypotension and claudication of consciousness. Consequently, the true incidence and significance of pain is notoriously under-recognised and undertreated in trauma victims.

Unrelieved acute pain is an independent risk factor for progression to chronic pain. Where nerve injury occurs, through trauma or definitive surgical repair, neuropathic sequelae are more likely. Not surprisingly, operations associated with significant nociceptive input and neural injury, such as thoracotomy and amputation, exhibit high incidences of chronic pain (8–65 per cent and 50–85 per cent respectively).

Often described separately, post-surgical and post-traumatic pain share similar underlying aetiologies and pathophysiological responses to tissue injury. Both account for a large proportion of patients attending chronic pain clinics. A survey of pain clinics in the United Kingdom identified trauma as the primary cause in 18.7 per cent of patients, and post-surgical pain in 22.5 per cent. Traumatic injury frequently mandates definitive surgical management; thus, precise boundaries can be indistinct between post-surgical and post-traumatic pain.

The World Health Organization (WHO) defines health as “a state of complete physical, social and mental well-being and not merely the absence of disease or infirmity”. Traditional opioid-based strategies for treating acute traumatic pain often fail to satisfactorily alleviate pain and restore a significant proportion of patients to a state of healthy functioning. Countries including the United States and Australia now face endemic social problems resulting from opioid dependence and misuse. The global socioeconomic health burden from trauma can be measured in terms of short-term healthcare costs, or indirectly through lost productivity, unemployment or further medical expenditure. The global financial cost in the United States has been estimated to be between $US560-635 billion annually. A strong association exists between chronic pain, financial dependence, psychiatric disease and substance abuse. Additionally, pain is a risk factor for other conditions such as thrombosis and respiratory tract infection. Breaking this pattern is a major healthcare priority.

Pain signalling has a complex neurophysiological basis involving neurotransmitters, receptors, secondary messengers and selective gene expression, coupled with significant psychological overlay. Following injury, pathophysiological changes occur at all levels between the site of injury, the peripheral nerves, spinal cord and brain. Peripherally, the spontaneous discharge rate of primary afferent nociceptors increases. Hyperexcitability is maintained by pro-inflammatory mediators that increase sensitivity to further stimuli (primary hyperalgesia) in damaged tissue. This may progress to secondary hyperalgesia, in which pain sensitivity occurs in surrounding undamaged tissues. Regeneration of damaged nerve endings may lead to neuroma formation, with an increase in ectopic activity. Central pain pathways changes occur at the level of the spinal cord, brainstem and cerebral cortex, including increased dorsal horn excitability, increased central microglial signalling and suppression of inhibitory synaptic transmission. Where these changes are maintained, the end result is persistent pain with diminished function.

Pain is a major treatment target and an important quality-of-life indicator. Effective analgesia influences the physiological and psychological response of trauma victims. Control of acute pain to prevent chronic pain development is an important, yet elusive, treatment objective.

Factors contributing to progression from acute to chronic pain are summarised in Figure 1.
Pain management for trauma: Time to embrace regional anaesthesia?

Background factors
- Genetic predisposition
- Female gender
- Young adults
- Psychological vulnerability

Surgical factors
- Type of procedure (e.g. thoracotomy, laparotomy)
- Approach (e.g. open vs laparoscopic)
- Nerve injury
- Surgical complication (e.g. infection, viscus rupture)
- Repeat surgery

Acute pain control (Protective)
- Regional Analgesia
- Systemic Analgesia
- Avoidance of breakthrough pain

Psychosocial environment
- Support
- Work
- Income
- Social class
- Psychological response

WHY REGIONAL FOR TRAUMA?
Urgent, effective pain control is a key clinical and humanitarian goal. Regional anaesthesia affords many features of an ideal analgesic agent, including superior analgesia, avoidance of general anaesthesia, ease of transport, reduced perioperative complications and improved functional outcomes. An opioid-sparing strategy reduces predictable multisystem side effects, including respiratory depression, sedation, delirium, pruritus, immunosuppression, ileus, nausea, urinary retention, tolerance and dependence. Minimising opioid dosage permits certain recovery goals to be met, including participation in physiotherapy and an earlier return to oral diet.

Regional anaesthesia is highly desirable for a range of traumatic injuries. Essentially opioid-free pathways support continuous catheter infusions for neck of femur fractures. Paravertebral and thoracic epidural blocks reduce respiratory morbidity and possibly mortality for multiple rib fractures. These are considered the gold standard for pain relief following thoracotomy. Abdominal wall blocks, such as rectus sheath and transversus abdominis plane, provide somatic analgesia to the anterior abdominal wall and may be used in neuraxial techniques that are unsuitable. Brachial plexus interventions, such as interscalene blocks for shoulder reductions, and axillary blocks for distal upper limb injuries, yield efficacies and cost savings for both emergency departments and theatres. Beneficial end points have included reduced nursing requirement, recovery-room bypass and earlier hospital discharge.

Some success, there are injuries – such as tibial shaft fractures – where resistance to regional techniques remains high. Default to general anaesthesia and systemic analgesia is frequent. There remains a need to properly appraise the true, rather than perceived, risk of regional anaesthesia in such patients.

In recent years, military medical sources have published extensively on the feasibility, appeal and safety of regional interventions following traumatic injury.

Military experience
Experience from conflict zones has long driven medical innovation. Damage control resuscitation, transfusion medicine and human factors training represent advances that have transitioned well into, and become best practice in, civilian trauma care. Impressive advances in pain management are also described.

Opioid-based analgesia for trauma dates to the American Civil War following the invention of the hypodermic needle. The term ‘Soldier’s Disease’ was subsequently coined, denoting the propensity for opioid dependence among war-wounded soldiers. It is perhaps surprising that a greater connection between inadequate pain control, opioid dependence and death was not made until the end of World War II.

The Vietnam War first demonstrated the feasibility of regional interventions for managing combat casualties. Recent conflicts have renewed interest in trauma pain management. Complex battlefield injury patterns trigger sudden massive nociceptive input, often coupled with evidence of neuropathic symptoms. High-energy blast injuries from suicide bombers and improvised explosive devices (IEDs), alongside technological developments in body armour, have resulted in extremity amputations becoming a distinguishing injury pattern. Despite the increasing lethality of weapons used, a survival rate of about 30 per cent is high, comparative to previous conflicts. The ability to survive injuries that hitherto were almost uniformly fatal is also attributable to medical advances including improved surgical and critical-care techniques, blood transfusion strategies and human factors training.

Military campaigns in Afghanistan and Iraq have tasked clinicians with difficult environments to accomplish optimal pain relief, transport and functional recovery for complex trauma. Anaesthetists have been accountable for safely accomplishing long-distance chains of aeronautical medical evacuation. Following major injury, the wounded are evacuated from base hospitals by military aircraft to hospitals in Europe and North America. Multiple surgical episodes are undertaken at points along the chain, involving initial damage-control surgery and later, restorative procedures. Victims face life-altering physical and psychological changes. Effective and sustained pain relief is essential to optimise outcome.

A striking development has been the emergence of regional techniques as the standard of care for a range of injuries. The greatest benefit appears to be conferred through peri-neural catheter techniques using protocols agreed between anaesthetists, surgeons and emergency physicians. An encouraging and growing body of evidence identifies regional interventions as making a key contribution in the management of combat casualties. Additionally, traditional objections to regional anaesthesia in trauma can be negotiated with appropriate training, infrastructure and interdisciplinary dialogue. This novel approach has challenged conventional attitudes and redefined best-practice anaesthetic management. In contrast, opioid-based therapy alone confers suboptimal analgesia, a multitude of adverse side effects and can result in failed provision of general anaesthesia and resuscitation. Where systemic analgesics are administered for acute severe pain, the British military has used a “reverse pain ladder”. This invents the classic WHO analgesic ladder. Strong analgesics initially form the mainstay of treatment, stepping down in strength and dose over time as recovery progresses. An additional modification is “step 4” for uncontrolled severe pain, involving intravenous ketamine, clonidine and/or lidocaine. Anti-neuropathic medication such as gabapentinoids and tricyclic antidepressants are started early where evolving neuropathic phenomena are suspected.

Anaesthetists can influence pain relief at all stages in the recovery pathway, from the point of injury through to rehabilitation. Demonstrable success on the battlefield suggests a potential for greater use of regional interventions in civilian environments. It is noteworthy that regional anaesthesia is conspicuous among medical advances in trauma, since this has yet to transition successfully to any great extent.

CAVEATS TO REGIONAL ANAESTHESIA

Major trauma
The use of general anaesthesia is widely applicable for emergency treatment following major trauma. Comparatively, regional anaesthesia use may be limited in a number of circumstances:

- Standard contraindications (for example, untreated coagulopathy or refusal).
- Injuries mandating general anaesthesia (for example, cranial) for surgical management.
- Inability to obtain reliable consent.
- Polytroantas.
- Safety issues from combative patients.
- Inability to position patient for procedure (for example, spinal cord injury).
- Lack of appropriate training, equipment and support.

Where feasible, combining general with regional anaesthesia may expedite recovery. Potential benefits in critical-care patients include reduced opioid side effects, easier patient evaluation during surgery, faster respiratory weaning, early tracheal extubation and greater participation in physiotherapy. Improvements in oxygenation and ventilation following thoracic epidural, paravertebral or intercostal nerve blockade is well described. This may avert the need for invasive ventilation following pulmonary contusion. Paravertebral blockade is also described as providing unilateral segmental analgesia for multiple fractured ribs, while preserving neurological assessment in patients with concomitant lumbar spinal trauma. However, the intensive-care environment poses numerous practical challenges, including positioning, staff familiarity, wrong route administration, distorted anatomy and lack of appropriate space. Multisystem dysfunction...
poses additional considerations such as coagulopathy, immune-compromise and safety concerns over regional interventions in sedated patients. Where feasible, peripheral techniques are subject to fewer limitations and are preferred to neuraxial approaches. Despite advantageous features, only limited and low-level evidence addresses regional interventions in the critical-care setting. Detailed individual risk-benefit appraisal is warranted.

Acute compartment syndrome

ACS is a limb-threatening condition. It is a common yet feared consequence of traumatic injury. Annual incidence is estimated as 7.3 per 100,000 for males and 0.7 per 100,000 for females. A critical pressure increase in a confined myofascial space leads to microvascular ischaemia of nerves and vessels traversing the affected compartments. Definitive treatment is emergency fasciotomy decompression. Delays in treatment are a source of morbidity, mortality and litigation. Poor functional outcome and successful litigation are particularly likely if time from onset to compartmental release exceeds 12 hours, though irreversible damage can occur within four to six hours. Clinical assessment is challenging, and should include objective compartmental pressure monitoring for at-risk patients.

Pain disproportionate to the clinical situation is a cardinal feature of ACS. Nerve blockade in this context is controversial, since it may delay diagnosis by eliminating pain as the herald symptom. The evidence opposing regional techniques as analgesic modalities following trauma is neither compelling nor consistent. Isolated case reports provide limited evidence against regional anaesthesia where ACS is a concern. Such reports detail co-existent contributory factors to delayed treatment, including misattribution of blame to the wrong nerve distribution, inadequate monitoring and delayed decision-making, despite obvious clinical signs. The true contribution of regional blockade to delayed diagnosis in these reports, if any, is debatable.

In orthopaedic literature, pain is an unreliable symptom, yielding poor sensitivity (19 per cent) and positive predictive value (14 per cent) for ACS. Following injury, any analgesic modality may conceivably mask evolving ACS. Patient-controlled opioids, peripheral nerve and central neuraxial blockade have all been implicated in case reports as contributing to delayed diagnosis. A systematic literature review by Mar et al. indicates there is no association between regional interventions and delayed detection of ACS. Rather, diagnosis may be assisted where breakthrough pain is reported in the presence of previously satisfactory perineural blockade. More recent reports support this, detailing breakthrough pain in a patient with an effective brachial plexus catheter as an indicator of developing ACS, facilitating prompt diagnosis and fasciotomy. A prospective national paediatric epidural audit also found no association with regional interventions and delayed ACS diagnosis. Of 10,663 epidurals, there were four incidents of ACS. None were masked by the epidural.

On logical, practical and humanitarian grounds, ACS risk does not preclude regional blockade. Prior discussion should occur with the responsible surgeon concerning the suitability of neural blockade. Strategies for safe practice in patients with ACS risk are described in Table 2.

### Table 2. Evidence-based factors influencing regional anaesthesia safety in patients with ACS risk

<table>
<thead>
<tr>
<th>Institutional factors</th>
<th>Pharmacological factors</th>
</tr>
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<tbody>
<tr>
<td>Vigilance</td>
<td>Avoid dense, long-acting regional blocks</td>
</tr>
<tr>
<td>Interdisciplinary communication</td>
<td>Peripheral nerve approaches where possible</td>
</tr>
<tr>
<td>Staff training</td>
<td>Boluses of short-acting local anaesthetic for operative ‘top-up’</td>
</tr>
<tr>
<td>Patient information</td>
<td>Benefit of adjuvant drugs is not established</td>
</tr>
<tr>
<td>Local protocols</td>
<td>For continuous perineural catheters:</td>
</tr>
<tr>
<td>High-quality documentation</td>
<td></td>
</tr>
<tr>
<td>Frequent clinical evaluation (including compartmental pressures)</td>
<td>Use minimal effective concentration of long-acting local anaesthetic agent.</td>
</tr>
<tr>
<td>“Sign in” and “Time out” procedures before proceeding with surgery</td>
<td>Patient-controlled function can increase reporting of breakthrough pain.</td>
</tr>
<tr>
<td>Attention to contributory causes of ACS (for example, circumferential casts, inadequate resuscitation, poor positioning)</td>
<td>Avoid motor block.</td>
</tr>
</tbody>
</table>

### Nerve injury

Neuropathy is a recognised complication of traumatic injury. Mechanisms for nerve injury include laceration, axial stretch, compression and vascular compromise. Neurological deficit may also be acquired or aggravated by iatrogenic causes, such as surgical fixation, poor positioning and regional anaesthesia interventions.

The “double crush” phenomenon, proposed by Upton and McComas in 1973, describes an association between cervical radiculopathy and carpal tunnel syndrome. A unifying explanation is that individual lesions in a nerve increase the risk of injury at a second location along the same nerve. Decades later, significance of the association between two apparently unrelated pathologies remains uncertain. However, concern over potential secondary nerve injury has led to a continued reluctance of practitioners to undertake regional interventions in patients with potential or confirmed neuropathy.

Individual risk assessment is crucial. Though additional risk may be conferred at the time of the block through needle trauma, a resulting sympathetic block and superior analgesia may contribute to improved function. Comprehensive neurological evaluation, with documentation of findings, is essential prior to block performance. Where perineural catheters are used, postoperative surgical assessment of function may be done before bolus administration of local anaesthetic. Recommended modifications to practice where potential nerve injury exists include using less potent local anaesthetic agents, reducing dose and avoiding vasoconstrictors. Contributory causes to neurological dysfunction should also be remedied, such as arterial hypotension, tight casts and poor positioning.

### Coagulopathy

Coagulation disturbance is common following injury. Acute coagulopathy of trauma is a complex process initiated by tissue trauma, hypoperfusion, hypothermia and acidemia. It is often compounded by large-volume autologous blood transfusion. Following definitive haemorrhage control, the balance of risk shifts towards thrombosis, and therapeutics aimed at prothrombotic administration is standard practice. Professional guidelines exist for regional anaesthesia practice in patients with abnormalities of coagulation, yet there is little available to guide management of such interventions, specifically in trauma patients. Point-of-care testing such as thromboelastometry provides prompt, objective data on coagulation status. This is used in addition to standard laboratory tests of haemostatic function. Though safe reference points for point-of-care tests are not covered by current published guidelines, they have become used extensively to guide the suitability of interventions. The likely sequence of coagulation status following injury must be considered to facilitate individualised provision of regional interventions. Where a complex risk-benefit balance exists, two consultants should agree the risk is justified.

The Camp Bastion Protocol is an approach to regional anaesthesia in subjects with suspected or confirmed coagulopathy of trauma. Implemented in May 2010 for combat victims in Afghanistan, significant bleeding-related complications have not been reported.

### Future direction

High-quality data from clinical trials in military or civilian trauma victims is hard to acquire. Most studies rely on observational data. Though challenging, acquisition of prospective data on regional interventions and functional outcome in trauma is a worthy research initiative. At an institutional level, a collaborative approach must complement appropriate training and infrastructure to ensure safe practice of regional anaesthesia in trauma patients.

### Summary

A strong association exists between traumatic injury, persistent pain and poor functional state. Pain control following trauma has historically been poor, and its significance under-recognised. Innovation from military campaigns has provided a growing evidence base supportive of regional interventions in patients whom historically such practice would have been considered irresponsible or contraindicated. Such experience of complex trauma has arguably redefined best-practice pain medicine. Effective multimodal analgesia strategies using an integrated, multidisciplinary approach has exemplified the value of effective, sustained pain control. Challenges remain in translating observed benefits into civilian care.
The role of regional anaesthesia in clavicle fracture surgery

JEREMY MILNE, MBBS (HONS)

Regional Fellow, Royal Perth Hospital, Western Australia.

Dr Jeremy Milne is a provisional Fellow at Royal Perth Hospital, Western Australia. He trained in Perth and maintains an interest in all aspects of anaesthesia including regional anaesthesia.

KRISHNA BODDU, MBBS, MD, DNB, FANZCA, MMED

Director, Regional Anaesthesia, Department of Anaesthesia & Pain Medicine, Royal Perth Hospital, University of Western Australia; University of Texas Health Sciences at Houston, Texas, US.

Professor Krishna Boddu is director of regional anaesthesia at Royal Perth Hospital and has special interest in ultrasound-guided regional anaesthesia and acute pain. In addition to his affiliation with University of Western Australia, Professor Boddu is adjunct professor of University of Texas Health Sciences at Houston, US and NTR Health University of India. He is a director of Global Medicine Ltd, which promotes global education on effective pain control, focusing on improving functionality of patients.

INTRODUCTION

The clavicle is a commonly injured bone in the human body accounting for 2.6 per cent to 4 per cent of all adult fractures with an annual incidence of 29 to 64 per 100,000 population per year. Fractures of the shaft account for between 69 to 82 per cent of all clavicle fractures while lateral end injuries are less common (21 per cent to 28 per cent) and medial end injuries are comparatively uncommon (2 per cent to 3 per cent). The typical patient is a young adult male involved in a sporting injury where force has been applied to the point of the shoulder, though there is a second smaller peak of incidence in elderly patients sustained during falls, which are more likely to be lateral or medial end fractures. Owing to the mechanism of injury, patients with clavicle fractures often have other injuries such as rib fractures or pneumothorax, which have anaesthetic implications.

TREATMENT OPTIONS

Treatment options of clavicular fractures can broadly be categorised as non-operative and operative treatments. Traditionally, acute mid-clavicular fractures have been treated conservatively with a sling or figure-of-eight bandage. However, owing to reports of improved functional outcomes and lower non-union rates with operative treatment, particularly for displaced clavicle fractures, the rate of surgical fixation for this injury is increasing.

The operative treatment options of clavicular fracture, which include plate or intramedullary fixation, achieve similar success rates in range of shoulder movement and bone union. Plate insertion requires extensive soft tissue dissection, which risks injury to the supraclavicular nerves and the plate may produce a prominence that the patient finds irritating. Conversely, intramedullary fixation is less invasive, requiring two small incisions, but is more technically challenging and has a higher rate of implant failure, particularly in rotationally or axially unstable fractures.

A recent Cochrane review of intramedullary fixation versus plate fixation for clavicle fracture surgery incorporated an analysis of pain between the two techniques. Four small studies compared intramedullary fixation with plate fixation in 160 people with acute collarbone fractures. The studies found little difference between intramedullary fixation and plate fixation with respect to pain. One study reported lower post-operative pain scores on days four and five post-operatively, but not on days one to three when a Knowles pin was used compared to plating for treating middle third clavicle fractures. Overall the authors concluded the available evidence is very limited and that further studies are justified.

INNERVATION OF THE CLAVICLE

The clavicle is unusual in the field of regional anaesthesia in that its innervation is poorly defined. It is widely accepted that supraclavicular nerve, a branch of the superficial cervical plexus, innervates the skin overlying the clavicle and shoulder, however the precise sensory innervation of the clavicle bone remains elusive. Among anatomy and regional anaesthesia textbooks, some attribute the innervation of the clavicle to the supraclavicular nerve originating from the superficial cervical plexus, while others state that the innervation arises from the brachial plexus via the following nerves alone or in combination: subclavian nerve, suprascapular nerve, long thoracic nerve.

From first principles, the innervation of the clavicle can be predicted by using Hilton’s law, which, as originally written in 1863 is: “The same trunks of nerves whose branches supply the groups of muscles moving a joint furnish also a distribution of nerves to the skin over the insertions of the same muscles; and – what at this moment more especially merits our attention – the interior of the joint receives its nerves from the same source.”

Hilton’s law was found to be reliable and applicable to all cranial and peripheral nerves when critically analysed in 2014. It can be paraphrased to “a joint is innervated by the same nerves that supply the muscles acting on the joint, which also supply the skin overlying the articular insertions of those muscles.” Thus it would be expected that the nerves to subclavius (subclavian nerve), pectoralis major, clavicular head (lateral pectoral nerve) and deltoid (axillary nerve) also contribute to clavicular articular innervation. These nerves arise from the upper brachial plexus (C5, A7).
Figure 1: Translated reproduction of Dejerine's Illustration (reproduced with permission Tran de QH, Tiypaprasetkul W and Gonzalez AP. Analgesia for clavicular fracture and surgery: a call for evidence. Regional Anesthesia & Pain Medicine. 2013. 38(6): 539-43).
Motor nerves to muscles derived from the pharyngeal arches are special visceral efferent fibres, which are not accompanied by sensory fibres. Muscles relevant to the clavicle are sternocleidomastoid and trapezius, which arise from the fifth pharyngeal arch and receive motor innervation from the accessory nerve. Local sensory nerves exist, which arise from the same spinal levels as the motor fibres (C2, 3 for sternocleidomastoid and C3, 4 for trapezius) via the transverse cervical and suprascapular nerves and most likely provide sensory innervation to the clavicle. The clavicular part of pectoralis major is supplied by lateral pectoral nerve (C5-7), which runs under subclavius along the deltopectoral triangle giving several branches that enter the clavicular part of pectoralis major between the coracoid process and the site of insertion of pectoralis major to the clavicle. The clavicular part of pectoralis major can be considered a separate anatomic entity to the rest of pectoralis major and is used as a myocutaneous flap to cover acromioclavicular defects, repair injuries caused by cervical tumours or recover motility in cases of facial paralysis. When the clavicular part is detached and reversed for flap surgery, branches of lateral clavicular nerve are seen penetrating the posterior surface, which may continue to the clavicle. This would be consistent with senior author Professor Boddu’s experience of successful clavicle fracture surgery under PEC blocks (infiltration of local anaesthetic between pectoralis major and minor).

A French neurologist named Joseph Dejerine first published that the clavicle may receive innervation from both the brachial and superficial cervical plexuses. He attributed the sensory innervation of the medial clavicle to the superficial cervical plexus via the transverse cervical and supraclavicular nerves and most likely provide sensory innervation to the clavicle. It is unknown how Dejerine reached his conclusions and he doesn’t reference others to substantiate his claims. Dejerine produced a useful diagram of sclerotomes (regions of bone innervated by a single pair of nerve roots) and the peripheral nerve supply of each bone (see Figure 2: Cutaneous innervation of the supraclavicular nerve.). The fact that brachial plexus injuries following clavicle surgery most commonly involve the suprascapular nerve suggests the suprascapular nerve may provide sensory innervation to the clavicle.

Adding further complexity is the fact that the ventral axial line of the upper limb (where the sensory innervation of the anterior chest wall jumps from C5 to T1) runs in close proximity to the clavicle region and could conceivably be crossed by an incision made to facilitate clavicle surgery. There is very little in the literature to provide evidence for the innervation of the clavicle and the use of regional techniques for clavicle fracture surgery (primarily case reports and case series) but what is available is summarised here.

Good regional analgesia for clavicle fracture has been described with the following techniques:

- Interscalene brachial plexus block using of high dose (200mg) bupivacaine in 22 patients with midshaft clavicle fractures.
- Superficial cervical plexus block in one patient with a midshaft clavicle fracture.
- Combined superficial cervical plexus block and C5 nerve root block in a total of three patients, one with a lateral clavicle fracture and two where the location of the fracture was not specified.

Other authors report inadequate analgesia/anaesthesia for clavicle fracture surgery using a single regional technique:

- King reported a patient with a lateral clavicle fracture who had excellent pre-operative analgesia after a superficial cervical plexus block, but after surgery the patient woke with severe pain in the lateral clavicle, which was effectively treated with an interscalene brachial plexus block.
- Santos reports a patient who had an interscalene brachial plexus block performed preoperatively. The block was deemed sufficient to attempt surgery under a purely regional technique but, when retractors were placed in the medial clavicle region, the patient experienced discomfort and required opioid analgesia/sedation to complete surgery.

Four authors have reported successful use of a pure regional technique for clavicle fracture surgery when both the superficial cervical and brachial (interscalene) plexuses were blocked:

- Avvaru, 30 patients, location of fracture not stated.
- Dillane, one patient, location of fracture not stated.
- Vandepitte, one patient with a midshaft fracture.

One or more foramina are usually present (98.1 per cent in one study) in the middle one third of the clavicle along its superior border, which transmit a nutrient artery and occasionally a medial fascicle of the suprascapular nerve en route to the anterior chest. It is possible that the variable occurrence of these transiting fibres could account for variability in pain experienced from clavicle fractures (with injury to these transiting fibres resulting in increased pain).

It would appear that a single regional technique cannot reliably be used to achieve surgical anaesthesia or perioperative analgesia for clavicle fracture surgery. Superficial cervical plexus block or isolated suprascapular nerve block in addition to a C5 nerve root block, either alone or as part of an interscalene block, may permit a regional-only technique for clavicle fracture surgery, with the medial clavicle likely innervated by the superficial cervical plexus and the lateral clavicle likely innervated by the brachial plexus. Some scepticism is warranted owing to the paucity of available evidence and inter-individual variability.
The brachial plexus is composed of the peripheral nerves of the upper extremity from the root level to the terminal branches. It is classically described as forming from the C5 through T1 nerve roots. The interscalene groove is the potential space between the anterior and middle scalene muscles. In the suprACLavicular region, the brachial plexus emerges from the interscalene groove and travels laterally and inferiorly beneath the clavicle. Of relevance to further discussion, the subclavian and suprACLavicular nerves arise from the superior trunk of the brachial plexus with C5 innervation, and the long thoracic nerve arises from the roots of C5, C6 and C7.

POSSIBLE REGIONAL TECHNIQUES

Superficial cervical plexus block using a high volume of local anaesthetic. A cadaveric study has shown 30ml methylene blue injected around the superficial cervical plexus actually penetrates through the superficial cervical fascia and reaches deeper structures, such as the deep cervical plexus and the brachial plexus.

- Interscalene brachial plexus block using a high volume of local anaesthetic aiming for spread to reach the supraClavicular nerve or superficial cervical plexus, accepting the likelihood of phrenic nerve blockade and the possibility of Horner’s syndrome, recurrent laryngeal nerve blockade as well as sensory and motor blockade of the upper limb.
- Interscalene block plus superficial cervical plexus block has been used successfully for surgical anaesthesia, but still risks phrenic nerve block.
- Interscalene block plus supraClavicular nerve block.
- C5 nerve root block plus superficial cervical plexus block, which would make phrenic nerve blockade unlikely.
- C5 nerve root block plus supraClavicular nerve block, the most targeted and precise option permitting very low doses of local anaesthetic.

C5 nerve root block is a risky procedure (risks include injection into the vertebral artery and intrathoracic injection through a dural sleeve), but it may have a role in patients with significant respiratory problems, who may benefit from avoiding an interscalene block and general anaesthesia.

Only one study comparing anaesthetic technique for clavicle fracture surgery could be located. This was a retrospective cohort study of 30 patients having clavicle fracture surgery. One group received an interscalene block plus a superficial cervical plexus block followed by general anaesthesia (eight patients). The other group received a general anaesthetic and local anaesthetic infiltration by the surgeon (22 patients). Outcomes analysed were opioid use and length of stay, both in recovery and in hospital. The only statistically significant difference was a modest reduction in recovery morphine use in the group that received regional anaesthesia.

DESCRIPTION OF REGIONAL TECHNIQUES

A technique for C5 nerve root block is included primarily for interest. Of key importance is identifying the C5 level. A reliable method of doing this is to use the C7 vertebra as a reference point. C7 is distinct from the other cervical vertebrae in that the transverse processes of the other cervical vertebrae have prominent anterior and posterior tubercles, while the C7 vertebra has a prominent posterior tubercle but a rudimentary, almost non-existent anterior tubercle (see Figure 3). The tubercles can be visualised on ultrasound with the probe in a transverse orientation across lateral neck and the patient in the lateral position. Once the C7 vertebra is identified, one can move the probe cephalad past the C6 vertebra with its sharp anterior tubercle (Chassaignac’s tubercle) to the C5 vertebra, where the anterior and posterior tubercles of transverse process form a characteristic two-humped camel sign with the nerve root nestled between the two humps (see Figure 4). To perform the block, one would enter the skin posterior to the ultrasound probe, needle in plane, angling anteriorly and advancing needle tip close to the nerve root between the two tubercles.

A superficial cervical plexus block is usually performed at the level of C4 (level of thyroid cartilage) with the needle advanced below the posterolateral edge of sternocleidomastoid, which is often underneath the external jugular vein.

Blockade of the supraClavicular nerve and interscalene brachial plexus can readily be achieved with a single needle insertion site. The supraClavicular nerve descends from the superficial cervical plexus over the belly of the middle scalene muscle, but deep to posterior border of sternocleidomastoid where it divides into two or three branches between the deep and superficial cervical fascia. A standard interscalene view of the brachial plexus is slightly more caudal than the superficial cervical plexus and a good place to pick up the supraClavicular nerve travelling between the deep and superficial cervical fascia because the other branches of the superficial cervical plexus have already diverged. With modest movements of the probe up and down the neck it is possible to appreciate the branches of supraClavicular nerve as small hypoechoic structures that can be targeted. If a nerve stimulator is used, paraesthesia may be elicited over the shoulder region. Only small volumes of local anaesthetic are required to block these nerves (1-2ml).
RISK OF NERVE INJURY FROM SURGERY

Injury to the supravcicular nerve as a consequence of surgery is high, and performing a superficial cervical plexus block or a supravcicular nerve block may implicate the anaesthetist as a potential cause of post-operative altered sensation in the distribution of the supravcicular nerve. Significantly, this can affect the breast and nipple area. In two small retrospective studies looking at the rate of post-operative numbness in the supravcicular nerve distribution following clavicle plating, the rate of numbness was found to be 55.3 per cent in one study[1] and 45.7 per cent in the other[2]. In the second study there was a significant difference in the rate of numbness depending on whether the surgeon used a horizontal or vertical incision (with a vertical incision being less likely to injure the supravcicular nerves). Thirteen of 21 patients (62 per cent) with a horizontal incision reported the presence of numbness. In comparison, only three of 14 patients (21 per cent) with a vertical incision reported numbness (p = 0.019)[2]. In the first study, two of 38 patients (5.2 per cent) reported being significantly bothered by their numbness and, in the second, five of 35 (14.2 per cent) reported being very or extremely bothered by their numbness at follow-up beyond 12 months.

There is a well-recognized association between fracture of the clavicle and injury to the brachial plexus, which usually occurs following supravcicular high-energy traction injuries[3]. Direct injury to the brachial plexus from clavicular bone fragments occurs less frequently, in the order of 1 per cent[4]. Cases of reported brachial plexus injury in this setting have a characteristic presentation of unmitting radicular pain, profound weakness and sensory loss in the immediate post-operative period[5]. Such a complication would be particularly devastating for the young active patients that typically undergo management of clavicle fractures.

A retrospective cohort study of all patients referred to the Peripheral Nerve Injury Unit at the Royal National Orthopaedic Hospital in the UK suggests delayed fixation is a risk factor for post-operative brachial plexus injury occurring. The study reviewed all patients referred with brachial plexus injury following fixation of clavicle fractures from September 2000 and September 2011. Patients with symptoms of brachial plexus injury prior to clavicle fixation were excluded. The cohort comprised 21 patients and all of them had a significant delay between the time of injury and the time of surgery with a mean of 19 days. It is thought the brachial plexus becomes tethered to the underside of the clavicle by the inflammatory process associated with callus formation and subsequent mobilisation of fracture fragments results in a traction injury to the plexus[6].

RISK OF NERVE INJURY FROM REGIONAL ANAESTHESIA

The risk of serious adverse events following superficial cervical plexus block seems low. A meta-analysis looking at complications following superficial or deep cervical plexus blockade for carotid endarterectomy found that of 2533 patients, there were no serious complications related to the block[7].

There is a case report of superficial cervical plexus neuropathy and chronic pain under the mandible after interscalene block[8]. In the first study, two of 38 patients (5.2 per cent) reported being significantly bothered by their numbness. In the second study there was a significant difference in the rate of numbness depending on whether the surgeon used a horizontal or vertical incision (with a vertical incision being less likely to injure the supravcicular nerves). Thirteen of 21 patients (62 per cent) with a horizontal incision reported the presence of numbness. In comparison, only three of 14 patients (21 per cent) with a vertical incision reported numbness (p = 0.019)[2].

Furthermore, a study of 273 patients undergoing elective shoulder/upper arm surgery with a single shot interscalene nerve block performed with nerve stimulation using a large volume of bupivacaine (40-50ml depending on weight) looked at sensation deficits of the superficial cervical plexus at 24 hours and 31 days[9]. All symptomatic patients recovered completely again by 31 days. Curiously, a proportion 21 of 273 (7.7 per cent, 95 per cent confidence interval 0.4-3 per cent) had superficial cervical plexus neuropathy and, at six months, all neuropathies had resolved. The transverse cervical and supraclavicular nerves were the most commonly affected. It seems logical if the superficial cervical plexus can be injured when attempting to perform an interscalene block, it is likely that the risk of superficial cervical plexus injury is higher when attempting to block the superficial cervical plexus itself.

The first brachial plexus block was reported in 1885 when William Halsted applied cocaine directly to a surgically exposed brachial plexus[10]. Needless to say, the morbidity associated with open exposure of the brachial plexus limited its widespread use. Despite refinements in technique, interscalene block is regarded as carrying the highest risk of transient neurological dysfunction of all peripheral nerve blocks. A meta-analysis of 4077 interscalene brachial plexus blocks performed in seven studies between 1999 and 2005 found an overall rate of neurological symptoms following interscalene block of 2.84 per 100 blocks (95 per cent confidence interval 1.3-5.98 per cent) with no permanent injuries[11]. Of note, only a minority of these studies used ultrasound to perform the blocks and the rate of neurological symptoms may be altered with ultrasound use.

CONCLUSION

It seems likely that the clavicle receives dual innervation from both the superficial cervical plexus (medial clavicle) and the brachial plexus (lateral clavicle) but the exact contribution of each plexus is yet to be defined. Multiple block combinations have shown the ability to provide surgical anaesthesia or perioperative analgesia for clavicle fracture surgery, but two blocks are probably required. A superficial cervical plexus block or supravcicular nerve block in addition to an interscalene block is likely to be adequate for a regional-only technique, if so desired. However, for the patient where avoiding the potential hazards of an interscalene block is important, other techniques, such as a C5 nerve root injection, may have role. The utility of pectoral nerve block for control of clavicular fracture pain warrants further evaluation. Further investigation to obtain a better understanding of the differences in analgesia requirements between the two operative techniques for clavicle fracture surgery (plate and intramedullary fixation) is warranted.

In summary, best practice for anaesthetic management of clavicle fracture surgery is yet to be defined. It will likely require a randomised-control trial with patients randomised to receive superficial cervical plexus block, interscalene block, or both, using low volumes of local anaesthetic, ultrasound guidance and performing the superficial cervical plexus block at the C4 level to avoid cross contamination of local anaesthetic between the two plexuses[12].

REFERENCES

17. Herring AA, Stone MB, Frenkel O, Chipman A, Nagdev AD. The ultrasound-guided superficial cervical plexus block at the C4 level to avoid cross contamination of local anaesthetic between the two plexuses[12].


Strategies to reduce emergence agitation in children

DAVID COSTI, BMBS(HONS), FANZCA

Staff specialist paediatric anaesthetist, Women’s and Children’s Hospital, Adelaide.

Dr David Costi is a full-time staff specialist paediatric anaesthetist with a number of research interests, including emergence agitation. He is an author of a Cochrane Systematic Review on this topic and also completed an emergence agitation randomised-controlled trial.

INCIpENCE AND DEFINITIONS

Emergence agitation (EA) is a very common issue after anaesthesia in children. The incidence of EA varies widely in individual randomised-controlled trials (RCTs) and depends on the definition used and the clinical setting studied. As an overall estimate of the extent of the problem, approximately one third of children will experience EA after sevoflurane anaesthesia. This figure is based on the 37 per cent incidence of EA in the 6281 children in the sevoflurane control arms of a recent Cochrane systematic review1.

The term “emergence delirium” (ED) is also commonly used, often interchangeably with EA. The term EA is preferred for this article as recent research suggests that a relatively low proportion of agitated children are genuinely delirious2,3. It is possible that ED is a subset of EA. Others have introduced the term “early post-operative negative behaviour” (e-PONB) encompassing EA, ED and pain, with separate definitions for EA and ED4.

There is no universal agreement on a definition of EA. At least 16 different scales have been used to assess EA but the most widely accepted scale at the present time is the Pediatric Anesthesia Emergence Delirium (PAED) scale. The PAED scale was first described6 in 2004 and is frequently referred to as the only “validated” scale. The PAED scale (Figure 1) consists of five items, each of which is scored zero to four, giving a maximum score of 20. The first three items, which are said to be more delirium specific, are reverse scored. The last two items are forward scored. The designers of the scale did not define a threshold PAED score for EA. Some EA studies simply compare PAED scores but most set an arbitrary threshold PAED score for presence or absence of EA. At least five thresholds have been used (≥10, >10, ≥12, >12, ≥16) with research supporting a threshold PAED score >123. Modifications of the PAED scale have also been described7. Due to the complexity of the PAED scale, researchers may also use a simple scale such as the Watcha scale (Figure 2)8. In the case of the Watcha scale, consolability is the difference between being classified as having EA (score ≥3) or not.

Figure 1. PAED scale

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Just a little</th>
<th>Quite a bit</th>
<th>Very much</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>The child makes eye contact with the caregiver</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>The child's actions are purposeful</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>The child is aware of his/her surroundings</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>The child is restless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>The child is inconsolable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 2. Watcha scale

<table>
<thead>
<tr>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calm, quiet</td>
</tr>
<tr>
<td>Crying, but can be consoled</td>
</tr>
<tr>
<td>Crying, cannot be consoled</td>
</tr>
<tr>
<td>Agitated and thrashing around</td>
</tr>
</tbody>
</table>

AETIOLOGY AND RISK FACTORS

There is no known unifying mechanism for EA, however risk factors have been well described. These include preschool aged group, pre-operative anxiety, certain temperaments (for example, poorly adaptable), ophthalmological and ear, nose and throat (ENT) procedures, sevoflurane or desflurane anaesthesia, and inadequate analgesia at the time of emergence. EA can certainly still occur in the absence of pain. This has been demonstrated in studies in the settings of MRI scans or surgical procedures with “effective” regional blocks (for example, caudal block with no haemodynamic response to surgical stimulation).

A wide variety of pharmacological agents that delay the emergence from sevoflurane anaesthesia also have been observed to reduce EA. This suggests that “sevoflurane washout” may be a possible unifying mechanism for their effectiveness. That is, by delaying emergence after cessation of sevoflurane, a child might emerge with a sevoflurane brain concentration of say 0.03-0.05 per cent rather than the more usual 0.1-0.2 per cent, but this is purely speculative. Additional analgesia may help explain the benefits demonstrated in some studies, particularly in the settings of...
painful procedures where an analgesic intervention has been studied but inadequate analgesia has been given to control group patients16.

**CONSEQUENCES OF EA**

EA is usually self-limiting with resolution within 15-30 minutes of emergence. However, the two main issues with emergence agitation are the suffering that may arise from analgesia withdrawal and the risk of rebound phenomena associated with the use of intravenous canule or other indwelling devices. EA can certainly result in unsatisfied and distressed parents, recovery-room staff and anaesthetists. One study has suggested an association between emergence agitation and new onset post-operative maladaptive behaviour after returning home from hospital11. However, these findings are questionable as the measure used for this research was not well validated and the study counted the children with negative behaviour, but did not consider those whose behaviour improved post-operatively. Nevertheless, the issues of self-injury and dissatisfaction are reason enough to consider strategies to reduce EA, especially in the high-risk pre-school population.

**INTERVENTIONS TO REDUCE EA**

Recent systematic reviews with meta-analyses provide an overview of effective interventions either compared to sevoflurane anaesthesia or as adjuncts to sevoflurane anaesthesia1,11,12,13. The largest of these is a Cochrane systematic review, which included 158 RCTs involving 14,045 children1. Although there are limitations with these reviews, in particular heterogeneity in the clinical settings studied and the definitions of EA, they do provide a useful overview to guide clinical practice. Effective and ineffective interventions are summarised in Table 1. The largest body of evidence exists for propofol, fentanyl, α₂-agonists (particularly dexmedetomidine) and halothane. Selected interventions are discussed in greater detail below.

### Table 1. Summary of effective and ineffective interventions for sevoflurane EA

<table>
<thead>
<tr>
<th>Effective</th>
<th>Ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>Desflurane</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Isoflurane</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Midazolam premedication</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Parental presence at emergence</td>
</tr>
<tr>
<td>Halothane</td>
<td>Gradual sevoflurane cessation</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Lower sevoflurane concentration during maintenance</td>
</tr>
<tr>
<td>IV Midazolam at end</td>
<td></td>
</tr>
<tr>
<td>Analgesia</td>
<td>Various sedatives</td>
</tr>
<tr>
<td>N2O washout</td>
<td></td>
</tr>
</tbody>
</table>

**PROPOFOL**

Propofol has been widely studied in many ways to reduce EA and can be effective as either total intravenous anaesthesia (TIVA), as infusion throughout maintenance, as transition at the end (1mg/kg), or as a bolus at the end (1mg/kg). Given our knowledge of the duration of action of propofol, it’s not surprising that studies of propofol used in the early stages of anaesthesia (for induction only, or as a 1mg/kg bolus shortly after induction) did not find a reduction in EA (Cochrane). Unfortunately the different propofol interventions have not been compared directly against each other in the same RCT. Meta-analysis of 14 studies found that propofol TIVA reduced the incidence of EA to about one third when compared with sevoflurane induction and maintenance1. Switching to propofol maintenance after sevoflurane induction may be more convenient if a gaseous induction is preferred, and is also effective in reducing EA1. Propofol administered as a 1mg/kg bolus at the end of sevoflurane anaesthesia has been successful in reducing EA in some RCTs but not in others, with meta-analyses showing a benefit, but not of the same magnitude as TIVA1,14. One of the 1mg/kg studies that found a benefit for propofol used an unusually high PAED score threshold of ≥16 for EA control group patients1,9.

Fentanyl

Recent meta-analysis shows that fentanyl is an effective adjunct to sevoflurane anaesthesia for reducing EA by a variety of routes, in particular by either intravenous (IV) or intranasal routes1. In contrast, an earlier systematic review with fewer included studies reported that intranasal fentanyl was effective but not IV fentanyl when subgroup analyses were performed11.

The nasal route has been successfully used in children undergoing insertion of grommets to prevent EA with the use of fentanyl 0.05mg/kg, suggesting an optimal dose of 2mcg/kg12. As well as this, EA in a child with no IV access, intranasal fentanyl is also an option for treating established EA in a child in which there is no IV access, including the scenario where a child has dislodged their IV cannula as a consequence of EA. Fentanyl 1mcg/kg IV at the end of sevoflurane anaesthesia reduced EA without increasing side effects11. Fentanyl has recently been directly compared against each other EA adjuncts (propofol bolus10, clonidine12) in two RCTs in the potentially pain-free settings of surgery with “effective” regional blocks. A comparison of IV fentanyl 1mcg/kg versus propofol 1mg/kg as placebo administered at the end of sevoflurane anaesthesia in children undergoing inguinal hernia surgery with caudal blocks found that fentanyl and propofol were equally effective in reducing EA, but there was more post-operative nausea and vomiting (PONV) with fentanyl12. Unfortunately there was no “fentanyl plus propofol” group allowing us to assess any additive or synergistic effects of these interventions. This is consistent with a recent meta-analysis of RCTs assessing multimodal approaches to EA prevention17. A comparison of IV fentanyl 2mcg/kg versus IV clonidine 2mcg/kg versus placebo administered at the start of sub-umbilical surgery in children with “effective” blocks found that only fentanyl reduced EA (but there was more PONV with fentanyl)15. In general terms these results, it is important to note that in these two studies, no prophylactic anti-emetics were administered, which is likely to be contrast to the actual clinical practice of many anaesthetists.

**CONSEQUENCES OF EA**

In individual RCTs, clonidine can be effective in reducing EA via several routes (oral, IV, caudal) and at a range of doses16. However, when looked at systematically, RCT evidence for effectiveness of clonidine appears limited to the reduction of recovery-room agitation with regional blocks (seven of the nine studies in Cochrane review meta-analysis) rather than ENT surgery1. In terms of IV clonidine, the majority of studies have used a dose of 2mcg/kg. Few studies have looked at lower doses, with mixed results. Clonidine 1.5mcg/kg IV was ineffective in reducing EA in children undergoing adenotonsillectomy16. The pilot study for this trial used 2mcg/kg but this dose resulted in sedation that delayed discharge11. An RCT comparing 1mcg/kg versus 2mcg/kg versus placebo in children undergoing inguinal hernia surgery with caudal blocks found both doses effective, but discharge was delayed with 2mcg/kg12. The RCT that studied clonidine 3mcg/kg reported sedation that delayed discharge and a significant reduction in blood pressure21. A recent prospective audit of clonidine use for adenotonsillectomy has been reported21. This audit did not standardise analgesia, EA adjuncts or clonidine dose (that is, everything was at the discretion of the treating anaesthetist). It found that clonidine did not reduce EA, and resulted in dose-dependent prolongation of emergence. There was an emergence half-time of 25 minutes with 2mcg/kg clonidine compared with 10.8 minutes without clonidine16. However, this audit had a very low rate of EA in the “no clonidine” patients (around 11 per cent) almost certainly due to effective use of propofol, fentanyl and other analgesics, which is often lacking in the control arms of RCTs20.

**DEXMEDETOMIDINE**

Dexmedetomidine has been extensively studied as an adjunct to propofol to reduce EA and the results are far more impressive than those obtained with clonidine. The large and consistent evidence in effective RCT trials is evident when comparing the forest plots for dexmedetomidine against those for clonidine in either the Cochrane systematic review1 or in another recent systematic review looking specifically at intraoperative α₂-agonists on post-operative behaviour in children10. Other reported benefits of intravenous dexmedetomidine include reduction in EA with or without regional blocks, reduction in EA with adenotonsillectomy, reduction in rescue analgesia, reduction in PONV and a minimal increase in emergence time (statistically significant, but not necessarily clinically significant)11-15. However, financial cost remains a significant hurdle to clinical use, limiting or preventing access in most workplaces. A significant increase in dexmedetomidine use is expected if and when it becomes more affordable, either administered intraoperatively or as intranasal premedication. In terms of IV dosing, numerous regimens have been studied, including IV doses of 0.15, 0.3, 0.5, 1mcg/kg given either in the early or late stages of anaesthesia, and IV infusions throughout anaesthesia12. Intraoperative administration of dexmedetomidine will vary depending on the surgical procedure and will be context-specific and depend on whether the effects of dexmedetomidine (for example, reduced heart rate and blood pressure, MAC-sparing, analgesia) are desired intraoperatively, or only for emergence. Dosage and timing of administration may influence emergence time and haemodynamics. A predictable drop in heart and blood pressure is reported in RCTs and is typically described as being not clinically significant (despite statistical significance), but this obviously depends on an individual patient’s comorbidities and the clinical scenario. Bolus administration of IV dexmedetomidine is recommended as a loading dose infused over 10 minutes, although one group of researchers has recently investigated the hemodynamic effects of bolus administration given as a rapid five-second bolus to healthy children11. One group has attempted to determine the optimal IV dose of dexmedetomidine for the prevention of EA after desflurane anaesthesia for tonsillectomy or adenotonsillectomy in children and concluded that the 95 per cent effective dose was 0.38mcg/kg13.
There are numerous studies now looking at dexmedetomidine (nasal or oral) for premedication with recent systematic reviews summarising the dexmedetomidine versus, midazolam trials[1,2]. Some of these premedication trials also investigated EA as an outcome measure. The systematic reviews conclude that dexmedetomidine performed either better than or equal to midazolam for induction outcomes (parental separation, mask acceptance, etc) and reduced the incidence of EA[3,3]. The intranasal route is more commonly studied than the oral route for dexmedetomidine. In terms of guiding intranasal dosage, a very recent RCT compared intranasal dexmedetomidine 1mcg/kg versus 2mcg/kg prior to induction and found given 45 minutes prior with no difference in EA, dose-dependent reduction in MACLMA in patients emerging time prolonged six and eight minutes respectively but no difference in time in PACU[4]. At our institution we recently introduced intranasal dexmedetomidine premedication in very selected cases (due to cost constraints) with the most commonly used dosage being 1.5mcg/kg given 45 minutes pre-induction. We are currently auditing our results.

OTHER VOLATILE AGENTS VERSUS SEVOFLURANE
Halothane has been extensively compared with sevoflurane in more than 30 RCTS and meta-analysis shows a halving of the rate of EA[5]. There is clearly no benefit for desflurane maintenance compared to sevoflurane in reducing EA with six studies meta-analysed[6] plus one further RCT[7] published after the search cut-off date in the Cochrane review. Meta-analysis of six RCTs comparing isoflurane and sevoflurane found no difference in EA with just one of the six individual isoflurane RCTs finding a benefit[8].

OTHER ADJUNCTS VERSUS SEVOFLURANE
Inhalational agents such as halothane, sevoflurane and desflurane, with their very different pharmacokinetics and pharmacodynamics, have been extensively studied. Many studies have found that inhalational agents, particularly halogenated volatile agents, are associated with higher rates of EA[9-11]. A meta-analysis of RCTs comparing sevoflurane and halothane (as well as desflurane in a few cases) showed that sevoflurane was associated with a significantly lower incidence of EA[12]. However, the clinical significance of this difference is uncertain, as the incidence of EA is generally low (about 10%) in controlled studies with optimal conditions, such as premedication with IV opioid and no IV access[13].

CONCLUSION – A GENERAL APPROACH FOR A CALM EMERGENCE
There are many pharmacological interventions that can reduce EA and improve the likelihood of the desirable calm emergence. Anaesthesiologists on a quest for a simple, universally effective, one-size fits all magic bullet to prevent EA with no adverse effects and no prolongation of emergence are likely to be disappointed. However, a context-specific, multimodal approach to EA prevention can result in reduced EA and greater satisfaction.

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Intraoperative awareness and general anaesthesia for caesarean delivery: A fresh look at an ongoing problem

PAUL COSENTINO, MBBS (HONS)
Senior registrar, Department of Anaesthesia and Pain Medicine, King Edward Memorial Hospital for Women, Western Australia.
Dr Paul Cosentino graduated from the University of Western Australia in 2006 and works as a provisional fellow at King Edward Memorial Hospital. He maintains an interest in all areas of anaesthesia including obstetrics and patient simulation.

IAN MADDOX, BSC, MBCHB, FANZCA
Specialist anaesthetist, King Edward Memorial Hospital for Women, Western Australia.
Dr Ian Maddox graduated from the Universities of St Andrews and Manchester in 1999, before moving to Australia in 2004 where he undertook anaesthetic training. He has interests in obstetric anaesthesia and analgesia, perioperative medicine and the history of medicine.

INTRODUCTION
The evolution of general anaesthesia for caesarean delivery has created a certain mystique among anaesthetists, obstetricians, midwives and mothers. Our past and current colleagues have strived by means of research, reviews, confidential enquiries and guidelines to facilitate performing this surgery in the safest way for the mother and baby.

To define safety is not as easy as it may seem. While one endeavours to employ good evidence in every medical decision, personal opinion is necessarily employed to weigh the importance of certain outcomes against competing ones. Frequently, little evidence is available, and experience and extrapolation from other settings are vital.

Sometimes by historical accident, or perhaps due to common cognitive biases, some evidence and opinion is given more weight than others and gains a momentum that is difficult to slow.

In this article, concentrating on awareness and pharmacology, we question some of the opinions and guidelines about providing general anaesthesia for a caesarean delivery, and present arguments and evidence for weighing the risks and benefits differently.

ACCIDENTAL AWARENESS DURING GENERAL ANAESTHESIA (AAGA) FOR CAESAREAN DELIVERY
Obstetric general anaesthesia has an unfortunate history with respect to accidental intra-operative awareness. In 1959, Hamer Hodges et al. described a technique for obstetric general anaesthesia involving thiopentone and suxamethonium followed by maintenance with nitrous oxide in oxygen. Ten years later, a series of patients anaesthetised with this technique were interviewed, 17 per cent of whom described unpleasant recall, and 6.7 per cent recounted recall with pain.

In the modern era, the situation is still less than perfect. The anaesthetic environment in obstetrics creates a perfect storm of risk factors for awareness: rapid sequence induction, higher incidence of airway difficulty, pharmacokinetic changes of pregnancy, and often urgency. An estimated rate of self-reported AAGA during caesarean delivery in the United Kingdom (UK) is one in 670, more than 10 times the average risk across all anaesthesia sub-specialties. This is comparable to an Australia-New Zealand prospective study estimating a risk of one in 382.

AAGA reported by the UK National Audit Project 5 (NAP5) refers to explicit recall of operative events during general anaesthesia. This is only one of many definitions of awareness. “Consciousness and memory are dissociable cognitive processes” and it is clear from isolated forearm technique (IFT) studies that response to even complex commands under relaxant anaesthesia occurs much more frequently than explicit recall of intraoperative events.

Tunstall first described the IFT in 1977 on obstetric patients. He documented four out of 12 mothers who moved their fingers in a “precise and direct response” to taped verbal instructions during surgery.

Aside from the increased probability of recall, this carries ethical and philosophical implications. Does providing amnesia without unconsciousness satisfy our responsibility to patients?

Determining the true rate of AAGA in the obstetric population is challenging and depends on the research methodology used. Prospective studies using the modified Brice interview detect a greater incidence of AAGA than other methods. Accidental awareness carries a significant risk of psychiatric morbidity including post-traumatic stress disorder (PTSD). Furthermore, lack of pain perception during awareness does not necessarily seem to be protective against PTSD. Avoidance behaviour features prominently in PTSD – the impact of this on reporting rates is not clear. In a 2007 series, 85 per cent of patients reported their AAGA to friends or relatives, but only 50 per cent reported it to hospital staff. In at least one well-chronicled account of definite awareness, the patient later recoiled from questioning and began denying any recall of intraoperative events to the investigators.

The spontaneous self-reporting of AAGA to NAPS may represent the tip of the iceberg.
INDUCTION AGENTS: HAS THIOPENTONE HAD ITS DAY? Recent high-profile publications have called into question the ongoing place of thiopentone in obstetric anaesthesia14-16. It can be argued that propofol is the preferred induction agent for caesarean delivery when maternal haemodynamic are not disturbed. There does not appear to be a clear advantage to either drug in terms of maternal or neonatal outcomes17. A Cochrane meta-analysis is underway to shed further light on this assumption. Proponents of thiopentone highlight its longer half-life as a post-marketing surveillance feature. There is, however, a growing list of human and institutional factors that are probably pushing the balance towards the use of propofol18.

Organisational factors Anaesthesia as a specialty arguably leads the medical profession in its exploration of human factors and risk management in reducing patient harm. The modern anaesthetic environment demands a close examination of factors that may have contributed to an adverse event. Advantages of propofol include: Greater familiarity for most modern anaesthetic trainees, less potential for drug errors and syringe swaps, reliable supply, no need for reconstitution and lower relative cost19. Syringe swaps are a recurring theme in accidental awareness, implicated in 14 per cent of cases of obstetric AAGA in NAPS. These events typically involve sterile water, antibiotic or local anaesthetic being given at induction instead of thiopentone19. Drug licensing remains a concern for many anaesthetists. In the UK, thiopentone is only licensed for use in pregnancy in doses up to 250mg.20 However, this restriction does not appear on the Australian therapeutic goods administration prescriber information. The dose recommended by the authors of NAPS is at least 5mg/kg. Propofol remains off-label in pregnancy. Many drugs used in obstetrics are unlicensed, but concerns about licensing alone should not preclude their use.

Pharmacological factors Desirable features of an induction agent include rapid predictable loss of consciousness, haemodynamic stability and resistance to hypotension. Thiopentone may marginally outperform propofol in this regard. Extrapolating these observations to meaningful patient outcomes is not without its challenges. The haemodynamic effects of induction agents in common use have been well characterised. At typical induction doses, propofol results in laryngoscopy and the cataractomilane surge more effectively than thiopentone, resulting in lower blood pressure and a greater incidence of hypotension21. Induction of anaesthesia in the septic or hypovolaemic patient creates specific challenges. Ketamine is associated with an improved haemodynamic profile22, reliable anaesthesia and acceptable indices of early neonatal wellbeing23. It is a reasonable choice in this setting. Excessively administered to haemodynamically compromised women were discussed in the most recent MBRRACE-UK report on maternal mortality. This contrasts somewhat with NAPS, which criticised the inadequate dosing of thiopentone. The authors of both publications questioned “whether thiopental should be used as the drug of choice for obstetric anaesthesia”24 and “whether thiopental should continue to have a place”25, although seemingly for different reasons. This serves to illustrate the particularly narrow therapeutic index for this drug.

Predictability is a highly desirable drug characteristic. It has been said that thiopentone is less variable than propofol, although we have not found convincing published support for this claim. Major documented similar variance in induction dose required for either agent when titrating to loss of larynx reflex26. The propofol plasma concentration to prevent movement to skin incision in 50 per cent of people (CP50) has a normalised standard deviation of around 15 per cent27, greater than the 10 per cent observed for the minimum alveolar concentration (MAC) of volatile agents. The intraoperative route (when compared to the inhalational route) exposes inter-individual pharmacokinetic differences that will further compound this variability.

Traditional rapid-sequence induction demands a rapid onset of anaesthesia. In non-pregnant patients, 4mg/kg thiopentone is one of the preferred induction doses, averaging 43 and 46 seconds respectively28. Return to consciousness is significantly longer for propofol, at 529 versus 330 seconds. Some patients receiving thiopentone are able to provide a positive IFT response at only 114 seconds post-induction29. One explanation for these observations is that thiopentone has intrinsically faster onset, so it is given in a relatively lower dose. However, equianæsic concentrations are about seven times higher for thiopentone, implying more profound amnesia for a given degree of sedation when propofol is used30. Importantly, this also suggests that propofol will be superior in ensuring greater amnesia following induction.

Intraoperative awareness and general anaesthesia for caesarean delivery: A fresh look at an ongoing problem Neonatal and maternal outcomes Key outcome measures, including neonatal wellbeing and maternal blood loss, are comparable when thiopentone or propofol are used for induction of general anaesthesia for caesarean delivery31. Thiopentone has been observed to produce higher Apgar and neurobehavioural scores32 although this was in the setting of relatively low doses of thiopentone and has been challenged in more recent studies33. At typical induction doses, neither thiopentone nor propofol demonstrate a sufficient plasma level to reliably prevent awareness by the time of skin incision and delivery during elective caesarean delivery34,35. Induction agents and the pharmacological changes in pregnancy Consideration of the pharmacokinetic changes of term pregnancy are prudent. The pregnant patient has a blood volume expansion of about 45 per cent. In physiological modelling of drug behaviour, this would represent a much larger initial volume of distribution. The increased cardiac output occurring in pregnancy can be expected to accommodate redistribution and early clearance of intravenous induction agents, the patient’s high blood flow being a reduced peak plasma concentration and a more rapid offset of effect. After a 2mg/kg bolus dose of propofol, plasma concentrations have been observed to be, on average, lower in pregnant compared to non-pregnant patients36. Target-controlled infusions (TCI) of propofol have been used in obstetric anaesthesia without modifications for pregnancy. However, it is clear that target bias exists in the algorithm for the obstetric population. The mean absolute prediction error of Marci TCI is about 35 per cent in both pregnant and non-pregnant patients37. It is worth considering the potential for the algorithm to underestimate the central compartment volume and central compartment clearance.

The MAC sparing effect of pregnancy for volatile anaesthetics may not be directly applicable to intravenous hypnotic agents. The weight-based dose of thiopentone to produce unconsciousness in early pregnancy appears to be 31 per cent lower than for non-pregnant women38. The mean plasma concentration of propofol required to produce unconsciousness during pregnancy seems to be relatively unchanged39-41.

VOLATILE ANAESTHETIC AGENTS After rapid-sequence induction of anaesthesia, the redistribution of the induction drug in the pregnant patient is rapid. When induction to delivery time is more than five minutes, the plasma concentrations of both propofol and thiopentone are significantly below those required for a high probability of unconsciousness42,43. To ensure anaesthesia is maintained, one should not rely on the propofol induction dose of intravenous agent. A sufficient effect-site concentration of volatile anaesthetic must be achieved.

Alveolar partial pressure and effect site concentration As anaesthetists, we have no direct measure of drug-induced inhibition of memory formation and we use indirect measures to estimate the probability of amnesia. It is fortuitous that the amnesic effects of volatile agents occur at subanaesthetic concentrations44. MAC awake is thus a useful surrogate for the probability of amnesia. Studies of MAC awake occur in the absence of noxious stimuli45. The effect of intense surgical stimulus on arousal and potentially on recall cannot be dismissed. Clearly there is a distinction between the concentration of anaesthetic agent required for a high probability of amnesia in unstimulated patients compared to patients undergoing surgery46. Can we extrapolate loss of recall for words, pictures or emotionally charged events to the loss of recall for a Pfannenstiel incision?47?

Measures of MAC assure sufficient time for the effect-site concentration or biophasic equilibrium to equilibrate with the alveolar concentration. Physiologically based pharmacodynamic models can be used to describe the biophase equilibration are 4.3 minutes for sevoflurane and isoflurane and 2.3 minutes for desflurane48. The time for biophasic equilibration with nitrous oxide is not well studied; however, we assume it to be rapid. This time delay is critical if the anesthesiologist is in the pursuit of achieving a desired effect-site concentration of volatile prior to skin incision. This premise seems to be neglected in published recommendations for obstetric general anaesthesia. Many modern guidelines still advocate minimal-inspired concentrations of volatile agent49,50, which is a practice we wish to challenge. The rate of rise of alveolar to inspired ratio (F/A/F) has been well characterised for inhalational anaesthetic agents in current use51. The increased cardiac output of pregnancy can be expected to delay the rise in alveolar partial pressure. Delivering an inspired concentration higher than one hopes to achieve in the alveoli (overpressuring) can attenuate the clinical effects of this change. In the presence of significant ventilation perfusion inequality (as may occur with airway closure in pregnancy), the alveolar partial pressure may be greater than the arterial partial pressure during wash in52. These changes, if not appreciated, can be expected to further delay the achievement of a sufficient brain partial-pressure of anaesthetic agent.

Isolated forearm studies repeatedly demonstrate unsettlingly high rates of positive responses when sub-MAC and near-MAC end-tidal concentrations of volatile agents are used during caesarean delivery53,54. In one study of obstetric patients, 97 per cent of patients responded with finger flexion to command during skin incision while awake and hydrated with 5% dextrose and 50 per cent nitrous oxide55.

We find the above considerations compelling reasons to express reservations to the volatilise the agent immediately after induction and prior to foetal delivery.
MAC reduction in pregnancy

Pregnancy decreases the MAC of volatile anaesthetic agents, although the magnitude of this reduction in humans is not well understood. The estimated MAC sparing effect for isoflurane in early human pregnancy is 28 per cent and, importantly, the narrow inter-individual variability appears preserved41. Reduction in MAC is presumed to apply to desflurane and sevoflurane, but to our knowledge this has only been observed in animals. Given that MAC-sparing drugs typically reduce MAC by a greater proportion than MAC awake, it can be assumed that the MAC sparing effect of pregnancy will reflect a similar magnitude of reduction in MAC awake or anaesthesia?

Anaesthetic agents and uterine atony

Potent volatile anaesthetic agents are known to impair myometrial contraction and confer risk for uterine atony. An impaired response to oxytocin becomes apparent around 0.75 MAC in vitro42. A Cochrane meta-analysis noted a greater fall in mean estimated blood loss (by 127%) at 32 weeks of pregnancy when anaesthesia was used compared to regional anaesthesia43. This did not translate into a greater need for blood transfusion in the study populations.

Nitrous oxide appears to preserve the ability of the uterus to contract, although this is implied to be from work done in 1969 on non-pregnant in vitro specimens of human myometrium44.

Impact on the foetus

Foetal exposure to anaesthetic agents prior to delivery is an unwanted but unavoidable consequence of general anaesthesia. Appropriate staff and facilities for support of the newborn must be at hand. In the truly compromised foetus the underlying pathology, and not the anaesthetic agents, is the greater concern. The modulating effects of anaesthetic agents on intrauterine oxygenation are unclear; however, maintenance of uterine perfusion pressure and oxygen delivery and avoidance of caval compression are priorities. A 2012 Cochrane review comparing general to regional anaesthesia for elective caesarean delivery reported no statistically significant difference in Apgar scores, cord blood gases, neurological adaptive scores or need for oxygen resuscitation in the neonate45. This supports the contention that “the effect on the foetus of anaesthetic agents . . . is innocuous and reversible”46 and should not preclude the provision of adequate anaesthesia to the mother.

NITROUS OXIDE

Nitrous oxide has been advocated for its disproportionately rapid wash-in (the concentration effect), its properties as a carrier gas (the second gas effect) and as a means of sparing the dose of potent volatile agents. Nitrous oxide is rapidly distributed to the tissues and has a high dissociation fraction on the use of higher fractions of inspired oxygen (FiO2). High FiO2 administered to the mother increases foetal oxygen content and partial pressure of oxygen46. Serum markers of free radical mediated oxidative stress are also increased in both the mother and neonate47. Additionally, nitrous oxide and ketamine have been shown to increase and prolong anaesthesia at the end of surgery48,49. It is likely that hyperoxia and ketamine will amplify free radical oxidative stress and could potentiate the adverse effects of nitrous oxide and ketamine, and, importantly, the narrow inter-individual variability appears preserved39. Reduction in MAC is presumed to apply to desflurane and sevoflurane, but to our knowledge this has only been observed in animals. Given that MAC-sparing drugs typically reduce MAC by a greater proportion than MAC awake, it can be assumed that the MAC sparing effect of pregnancy will reflect a similar magnitude of reduction in MAC awake or anaesthesia?

To our knowledge, the impact of pregnancy on the MAC of nitrous oxide in humans has not been studied. To assume that pregnancy is MAC sparing for nitrous oxide deserves thought, because of the distinctly different pharmacodynamic effects of this drug being compared to the halogenated volatile agents.

The ENIGMA trial brought into question the routine use of nitrous oxide and changed the anaesthetic landscape for a generation of training anaesthetists. No difference was observed between groups in the primary endpoint (duration of surgery); however, secondary endpoints of wound infection (including deep infection, atelectasis and severe nausea and vomiting (PONV) were increased in the nitrous oxide group compared to the 80 per cent oxygen group42. There may be some movement back toward the use of nitrous oxide since the publication of ENIGMA-II in 2014. This larger trial supported the observation of an increased incidence of PONV (15 per cent in the nitrous oxide group versus 11 per cent in the no nitrous oxide group), but demonstrated no increase in other adverse outcomes, including cardiorespiratory morbidity50.

A follow-up study of 640 ENIGMA patients observed a significant reduction in chronic post-surgical pain in the nitrous oxide group compared with a protective analgesic effect of the drug51. In an as-yet unpublished study exploring this, with chronic pain as the primary outcome, nitrous oxide had no effect52. Chronic post-surgical pain is known to occur after caesarean delivery, albeit usually with minimal impact on quality of life53. Encouraging study exploring this, with chronic pain as the primary outcome, nitrous oxide had no effect51. This probably means starting with an end tidal concentration of 40%, but should not be expected to contribute significantly to the provision of anaesthesia, nor should their analgesic effect be lessened the psychological impact on the patient if awareness occurs.

OPIOIDS

The MAC sparing effect of opioids is well documented, but how this translates to amnesia is not as clear. The reduction in MAC by co-administration of fentanyl is far greater than the reduction in MAC awake54. Fentanyl appears to have minimal effect on the cp50 (response to command) for propofol, but a profound reduction on cp550 for movement55. Administration of opioids, while MAC sparing, may not confer a proportionate advantage in maintaining amnesia as their MAC reduction may suggest.

It is assumed that a useful alternative to muscle relaxants to maintain controlled ventilation and satisfactory surgical conditions after foetal delivery. Paralysis is a major focus of psychological distress in victims of awareness, even in the absence of pain56. Neuroromuscular blocking drugs increase the risk of awareness57 and generate a focus for psychological trauma. Opioids have a robust role in obviating the need for muscle relaxants in the post-delivery period, but should not be expected to contribute significantly to the provision of amnesia, nor should their analgesic effect be less than expected to contribute significantly to the provision of amnesia, nor should their analgesic effect be less than expected to contribute significantly to the provision of amnesia, nor should their analgesic effect be less.
The neonatal effects of anaesthetic agents appear to be transient and reversible and should not preclude the provision of adequate anaesthesia to the mother. Likewise, minimising anaesthetic delivery is not a suitable substitute for adequate resuscitation in the hypovolaemic patient.

In this discussion we have questioned traditional published recommendations for general anaesthesia in obstetric obstetrics, which, even lately, advocate heavy paralysis and light anaesthesia. We favour an approach designed to minimise the risk of accidental awareness, which may be significantly underdiagnosed and carries serious consequences.

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Remifentanil patient-controlled analgesia (PCA) on the delivery suite – past, present and future

ANDREW MESSMER, FANZCA, ROYAL HOBART HOSPITAL

Dr Messmer is a staff anaesthetist at the Royal Hobart Hospital. He has been involved with the remifentanil PCA program there since its inception in 2007.

INTRODUCTION

Patient-controlled analgesia (PCA) is an established and efficacious delivery medium for post-operative pain relief, but its role in the management of pain in labour remains uncertain. Remifentanil is the most recent of numerous opioids to be trialled during labour using patient-controlled delivery and has been in use for over 15 years. Some centres report its use in more than 100 women per month without problems and numerous studies attest to high levels of maternal satisfaction with its use. Recently, however, case reports of serious morbidity associated with its use have led to questions over its suitability for use on the labour ward. This review explores the background and the use of remifentanil PCA on the delivery suite, the available evidence on whether it is an appropriate option to offer women in labour and future directions for its use.

HISTORICAL USE OF PCA IN LABOUR

The labour ward has had a prominent role in the development of patient-controlled analgesia as we know it today. In 1970, Scott published the first description of a PCA device in a paper, in which he presented findings on 56 women in labour who had received pethidine via a spring-loaded clamp that they would squeeze when in need of pain relief. Administration of a dilute solution of the pethidine would pass down the giving set as long as the clamp was held open. The women were instructed to release the clamp when pain relief was adequate. Eighty-nine per cent of women regarded the method as “good” or “very good”, and Scott believed “an enormous benefit was obtained merely if the mother had personal control of analgesic administration” (his italics).

In 1976, Evans presented a study of women in labour using a digitally controlled syringe pump containing pethidine, with which the prescriber could determine the bolus dose, rate of delivery and the lockout time. Interestingly, the patient was required to pass a test of simple reaction time in order to receive a bolus, with the intention that only those sufficiently alert would receive further analgesia – the test being that the patient was required to press the button twice within one second when making a demand. This apparatus evolved into the first commercially available PCA device, the “Cardiff Palliator”. However improvements in epidural technology and management during the 1970s and 1980s – primarily the advent of infusions and more compact epidural pumps – together with its high quality pain relief and lack of sedation, led to rapid increases in its popularity and the relative paucity of labour PCA development. Occasional reports of opioid PCA in labour – including fentanyl and tramadol – appeared, although it was consistently noted in these studies that analgesia was better and side effects were fewer (both maternal and neonatal) with epidural analgesia.

THE EMERGENCE OF REMIFENTANIL

This was the state of play when remifentanil PCA was first postulated as having a potential role in the delivery suite. Remifentanil was developed in the early 1990s and initially known as GI87084B. Its unique ester structure allowed it to be metabolised by blood and non-specific tissue esterases, resulting in an extremely rapid clearance of three litres per minute. In contrast to other opioids, its termination of effect was primarily due to metabolism rather than redistribution, resulting in an extremely short offset of effect, even for prolonged infusions. As noted in an early commentary, “remifentanil appears to be a very titratable opioid that will make it suitable for administration for either very brief periods, in which analgesia is required, or over prolonged periods, without the concern for prolonged recovery”.

The first reported use of remifentanil as a labour analgesic was by Brada in 1998, who used a remifentanil infusion to facilitate the siting of an epidural. The following year, Jones first described it in a PCA delivery system in a series of three patients, all with platelet counts too low to allow safe epidural analgesia. All three had a two-minute lockout and respective bolus doses of 75mcg, 35mcg and 40mcg, which provided effective analgesia with acceptable side effects. Appearances of the neonates appeared unaffected by the PCA, despite a cumulative time of 20 hours of use by the three patients. This latter finding was consistent with an earlier study by Kan, who had studied the neonatal effects of remifentanil infusion at caesarean section and found that placental transfer occurred readily, but was accompanied by rapid metabolism and/or redistribution by the foetus, resulting in an absence of adverse effects at the time of delivery. Other promising series were soon published but it was not long before concerns arose. Olufolabi conducted a study of anaesthetist-assisted remifentanil bolus analgesia in four parturients using a 0.25-0.5mg/kg bolus, but all subjects were eventually withdrawn from the study because of inadequate analgesia and significant opioid-related side effects. These early reports reflect the course of the literature thereafter, with promising studies and supportive commentaries interspersed with tempering case reports and editorial caution.
HOW GOOD IS REMIFENTANIL PCA?

When using maternal satisfaction as a measure of efficacy, remifentanil PCA ranks highly. For example, in studies where verbal descriptors were used to assess satisfaction, 94 per cent of users rated it good, very good or excellent, and 93 per cent rated it as very good or excellent when directly compared to the PCA delivery of epidural analgesia22,23,29. When directly compared to the PCA delivery of fentanyl PCA22, remifentanil PCA resulted in significantly higher maternal satisfaction. Satisfaction was found to be similar when compared to fentanyl PCA29 and in numerous studies comparing remifentanil PCA with epidural analgesia24,26,29,30. The most recent and largest of these remifentanil studies, comparing remifentanil PCA to epidural analgesia, was the UCSF multicentre study, in which maternal satisfaction was significantly higher in women receiving epidural analgesia30. In this multicentre study, in which maternal satisfaction was the primary outcome, 1414 women were randomised antenatally to receive epidural or remifentanil PCA analgesia if they were in labour. Ultimately, 447 women received a remifentanil PCA and 236 women an epidural. Although the result that satisfaction was significantly higher in the epidural group, it should be noted that there was a large amount of missing data (29% in the remifentanil group and 43% in the epidural group).

Despite high levels of maternal satisfaction, pain scores showed only modest reductions during remifentanil PCA delivery. When compared to epidural analgesia, it was found that satisfaction was significantly higher in women receiving epidural analgesia30. In this multicentre study, in which maternal satisfaction was the primary outcome, 1414 women were randomised antenatally to receive epidural or remifentanil PCA analgesia if they were in labour. Ultimately, 447 women received a remifentanil PCA and 236 women an epidural. Although the result that satisfaction was significantly higher in the epidural group, it should be noted that there was a large amount of missing data (29% in the remifentanil group and 43% in the epidural group).

When compared to remifentanil PCA and epidural analgesia, the pain scores were significantly lower when compared to fentanyl PCA22,23. When comparing remifentanil PCA to epidural analgesia, while reasonably low at 2-14 per cent (looking at studies with greater than 40 patients23,23,35,38), are considerably greater than the conversion rates from epidural to remifentanil PCA, which have been as low as 0.5 per cent27.

Hence, although giving only modest reductions in pain scores, the great majority of women are satisfied with remifentanil PCA. Pain relief is better and satisfaction higher when compared to when, compared to epidural analgesia, pain relief is poorer but satisfaction similar.

IS IT SAFE?

Although an analgesic regimen may be efficacious and acceptable to the recipient, it must also be safe. Historically, there have been concerns that if analgesic techniques are not properly managed there can be serious side effects. The incidence of respiratory depression is the incidence of failure of the analgesic technique. Conversion rates from remifentanil PCA to epidural analgesia, while reasonably low at 2-14 per cent (looking at studies with greater than 40 patients23,23,35,38), are considerably greater than the conversion rates from epidural to remifentanil PCA, which have been as low as 0.5 per cent27.

Hence, although giving only modest reductions in pain scores, the great majority of women are satisfied with remifentanil PCA. Pain relief is better and satisfaction higher when compared to when, compared to epidural analgesia, pain relief is poorer but satisfaction similar.

While this gives the reader an accurate picture of the central tendency and spread around the central value, it gives no information about the outliers at the lower range, which is what is of interest for identifying safety concerns. In some studies, the number of episodes of desaturation – for example, the number of times the oxygen saturation fell below 94 per cent – have been reported, but without additional details such as the depth or duration of the desaturation events20,21,24,47. In two other studies, no maternal oxygenation data was presented at all29,33. In studies where the range of oxygen saturations have been included, as low as 50 per cent have been reported40.

One study used capnography to monitor respiratory function during remifentanil PCA use45. Using an oral nasal canula, apnoea events (defined as a respiratory rate of zero for at least 20 seconds), with 14 of these events occurring during the first two hours of use. Maternal oxygen saturations fell to as low as 74 per cent during the apnoeic events described above, one woman was unresponsive and apnoeic oxygen was being delivered. When the oxygen saturation fell below 90 per cent. Although the above suggests that respiratory depression with remifentanil PCA may be occurring more frequently than some of the studies suggested, it is unclear whether this results in a dangerous level of oxygen saturation for women in labour. Significant maternal desaturation has been demonstrated during normal labour41,42 and in women who have received traditional opioid and nitrous oxide analgesia. Early pulse oximetry studies reported oxygen saturations as low as 60 per cent after intramuscular pethidine51 and as low as 75 per cent during nitrous oxide inhalation52. More recently, with increased awareness of the importance of adequate oxygenation during obstetric analgesia, in today’s delivery suites are still experiencing significant desaturations, similar to those found in the remifentanil studies of Blair and Stocki, but they are not being monitored to detect these events22,41. Inherent in this is the possibility that the respiratory parameters during labour42. Effective analgesia with only mild sedation (or no sedation at all if opioids are not used in the epidural solution) facilitates a relaxed breathing pattern and avoids the maternal hyper-hyperventilation cycle that can lead to desaturation. Epidurals have consistently been shown to improve maternal oxygen saturations and sedation scores when compared to remifentanil PCA24,26,29,30.

No woman has received naloxone, required airway support or ventilatory assistance during remifentanil PCA use in any of the published studies. In terms of mode of delivery, labour outcomes appear to be unaffected by remifentanil use. One case report of a newborn death due to asphyxia states that the use of remifentanil was responsible for the death. In several studies, detailed arterial blood gas analysis has been performed. In one study, 10 women had a blood gas analysis performed during remifentanil PCA delivery and the results were all within normal limits. No adverse effects were noted. In another study, 24 women had blood gas analysis performed during remifentanil PCA delivery and all results were within normal limits. No adverse effects were noted. In another study, 24 women had blood gas analysis performed during remifentanil PCA delivery and all results were within normal limits. No adverse effects were noted.

SERIOUS MORBIDITY

There have been three case reports of respiratory and/or cardiac arrest associated with remifentanil PCA44,45. One case report described a patient who died of asphyxia at the operating theatre, possibly due to a sedation overdose. Post-mortem examination of the patient’s record showed no adverse events during remifentanil PCA delivery. The patient had been given a bolus of 6 mcg/kg of remifentanil followed by a continuous infusion of 0.2 mcg/kg/min. The patient was found unresponsive and blue, apnoeic with a palpable carotid pulse. The patient was administered naloxone of 0.2 mg and recovered fully conscious in 15 minutes. The case report was also submitted to the Medicines and Healthcare products Regulatory Agency (MHRA). There have been three cases of respiratory and/or cardiac arrest associated with remifentanil PCA44,45. One case report described a patient who died of asphyxia at the operating theatre, possibly due to a sedation overdose. Post-mortem examination of the patient’s record showed no adverse events during remifentanil PCA delivery. The patient had been given a bolus of 6 mcg/kg of remifentanil followed by a continuous infusion of 0.2 mcg/kg/min. The patient was found unresponsive and blue, apnoeic with a palpable carotid pulse. The patient was administered naloxone of 0.2 mg and recovered fully conscious in 15 minutes. The case report was also submitted to the Medicines and Healthcare products Regulatory Agency (MHRA).

DOING AND DELIVERY

Fixed boluses, flexible boluses, with or without background infusions, and lockout times varying between one and five minutes have all been reported in making up remifentanil PCA delivery protocols. Numerous dosing studies have been performed53. Vohra and 16 women found that there was a fourfold variation in the individual dose required for effective analgesia26 and Blair found that adding a background infusion increased side effects but not efficacy43. The majority of studies have used a bolus of between 20-50mcg, a lockout of between one and two minutes and no background infusion. Respiratory depression and sedation are more frequent at higher doses26.
Remifentanil patient-controlled analgesia (PCA) on the delivery suite – past, present and future

NOVEL IDEAS

It was remifentanil’s rapid onset time of 30 to 60 seconds and lack of accumulation with long-term use (context-sensitive half-life of three to four minutes) that made it attractive as a labour analgesic. It was thought that analgesia might be provided for each contraction without accumulation. However, given that the average duration of a contraction is 70 seconds and the peak effect of remifentanil is at two and a half minutes it would appear that in many patients, maximum levels of effect would occur between contractions. This mismatch, resulting in significant remifentanil concentrations after the painful stimulus of the contraction had subsided, would result in the high sedation scores and respiratory depression as reported in some of the previously mentioned studies. Several attempts have been made to improve the correlation of maximal contraction pain and peak remifentanil effect. Volmanen, by observing the intervals between contractions, programmed a remifentanil PCA to deliver a bolus 140 seconds before the next expected contraction. When, however, compared to a control group in which there was conventional pressing of the PCA button at the start of the contraction, there was no improvement in pain relief and maternal oxygen saturations were similar. In another study, the timing, duration, spacing and intensity of contraction pains were recorded and there was an attempt to mathematically model remifentanil delivery to co-ordinate peak remifentanil concentration with peak contraction strength. However, because of the large variability of inter-contraction intervals, it was not possible to reduce the calculated mean remifentanil effect-site concentration in between contractions.

In a different approach, Jost asked women to press the PCA button continually until the peak of the contraction, with remifentanil being given at a reducing rate while the button was being pressed. There was no difference in satisfaction or maternal safety parameters when compared to a conventional delivery system. Perhaps the idea with the most promise is a vital signs-controlled, patient-assisted intravenous analgesia delivery system proposed by Sia. In a closed-loop interactive system the remifentanil bolus is titrated according to the number of demands stored on the oximeter) and follow-up of patients to ascertain satisfaction and concerns. Hence the decision as to the patient, regular audit of PCA charts (and ideally of pulse oximeters used where the oxygen saturation data is adequate resources must be available to ensure its safe delivery. These would include, but are not exclusive to, monitoring and care of the patient is entrusted to the midwives. It is clear that where remifentanil PCA is to be used, adequate resources must be available to ensure its safe delivery. These would include, but are not exclusive to, education of midwifery staff on the signs of increasing sedation and respiratory depression, clear and simple guidelines for management of increasing sedation and respiratory depression, continual presence of a midwife with the patient, regular audit of PCA charts (and ideally of pulse oximeters used where the oxygen saturation data is stored on the oximeter) and follow-up of patients to ascertain satisfaction and concerns. Hence the decision as to whether to offer remifentanil should be taken bearing the above in mind. Novel techniques of administration may improve safety while maintaining efficacy in the future.

CONCLUSION

Since the initial description of remifentanil PCA as a labour analgesic, numerous studies have attempted to clarify its efficacy, optimal delivery, safety and role. Many studies have been relatively small. From what information we have available, it is apparent that women like remifentanil as a form of pain relief during labour. It is relatively non-invasive, simple to initiate and affords the woman some degree of control over her contraction pains. It is a useful alternative for women in whom epidural analgesia is contraindicated or not possible, and attractive to women who are concerned about the nature and possible complications of epidurals. The analgesia offered is better and gives higher maternal satisfaction when compared to intramuscular pethidine. Data on the effects on newborns is reassuring. However, the analgesic effect of remifentanil PCA is inferior to that of an epidural and between one and seven in one in ten will find it inadequate to the point where they will elect to receive an epidural instead. The primary concern arising with its use is the significant degree of sedation and respiratory depression that occurs in a minority of women. Many delivery suites do not have anaesthetic personnel on the floor and as such, monitoring and care of the patient is entrusted to the midwives. It is clear that where remifentanil PCA is to be used, adequate resources must be available to ensure its safe delivery. These would include, but are not exclusive to, education of midwifery staff on the signs of increasing sedation and respiratory depression, clear and simple guidelines for management of increasing sedation and respiratory depression, continual presence of a midwife with the patient, regular audit of PCA charts (and ideally of pulse oximeters used where the oxygen saturation data is stored on the oximeter) and follow-up of patients to ascertain satisfaction and concerns. Hence the decision as to whether to offer remifentanil should be taken bearing the above in mind. Novel techniques of administration may improve safety while maintaining efficacy in the future.

REFERENCES

The combined oral contraceptive pill and perioperative venous thromboembolism risk

DAVID JANMAAT, BE (HONS), MBBS

Dr David Janmaat is completing FANZCA training with fellowships in airway, paediatric anaesthesia and retrieval medicine. He is proud to be a part of the team at Fiona Stanley Hospital and the Royal Flying Doctor Service in Western Australia.

BRIAN MORROW, FFARCSI, DIP ICM, FCICM, MA MED ETHICS & LAW (QUBELFAST)

Dr Brian Morrow has a background in anaesthesia and intensive care medicine. He is currently a consultant anaesthetist with Fiona Stanley Hospital and is the the Welfare Officer and ICU Liaison Officer.

BACKGROUND

The combined oral contraceptive pill (COCP) or “the pill” was introduced to Australia on January 1, 1961. In the same year a 40-year-old British nurse was the first patient to be diagnosed with a pulmonary embolus (PE) believed to be secondary to its use. The risk of venous thromboembolism (VTE) has been the subject of research and controversy over the subsequent decades as further generations of COCP have been developed.

The background rate of VTE in women of reproductive age is around four per 10,000 per year and it is accepted that this risk is two to three times higher in those taking the COCP1. VTE risks from COCP use are further increased within four months of commencing and returns to baseline within three months of cessation. VTE risk is even higher during the peri-partum period2 as illustrated in Table 11.

Table 1. VTE risk in the peri-partum period compared with COCP use

<table>
<thead>
<tr>
<th></th>
<th>Annual risk per 10,000 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE – no hormonal contraception and not pregnant</td>
<td>3 – 5</td>
</tr>
<tr>
<td>VTE – low dose COCP containing levonorgestrel or norethisterone (2nd generation)</td>
<td>5 – 8</td>
</tr>
<tr>
<td>VTE – low dose COCP containing newer progesterones (3rd generation)</td>
<td>9 – 12</td>
</tr>
<tr>
<td>VTE – antenatal</td>
<td>29</td>
</tr>
<tr>
<td>VTE – immediate postpartum</td>
<td>300 – 400</td>
</tr>
<tr>
<td>Death from VTE secondary to COCP</td>
<td>0.09</td>
</tr>
</tbody>
</table>

The sequelae of DVT may include significant leg pain with the potential to progress to a persistent pain condition and pulmonary embolus, which in rare cases may be fatal.

The increased risk of acute myocardial infarction and stroke reported are of a much smaller magnitude and will not be discussed further in this article. Post-menopausal hormone replacement therapy (HRT) involves an older age group and different hormonal doses and will not be discussed in this article.

ANAESTHESIA RELEVANCE

The use of the COCP is a modifiable risk factor for perioperative VTE. Like many patient risks managed by anaesthetists, this adverse event is low probability but with potentially serious outcomes, including death. It is well known that surgery increases VTE risk and the high-risk post-operative period for VTE events may be considered to extend to 12 weeks post-operatively6.

Given that more than one in five women in Australia aged 16-59 years old takes the COCP1, its perioperative management has relevance to many anaesthetists.

PATHOPHYSIOLOGY

VTE risk can be considered in terms of the interplay of haemodynamic changes, hypercoagulability and endothelial dysfunction; the so-called “Virchow’s triad”. This triad is relevant to perioperative COCP use and post-operative VTE risk with all of these factors being relevant to some degree.

The COCP contains oestrogen and progesterone. These hormones cause the suppression of follicle stimulating hormone (FSH) and luteinising hormone (LH) making tubal, cervical and endometrial conditions unfavourable for conception. Following COCP introduction, an increased rate of adverse VTE and cardiovascular events were noted. Oestrogen and progesterone doses have subsequently been modified in second and third-generation COCP formulations. For the purposes of this paper, the authors will use the generic term COCP.
The pathophysiology of this increased VTE risk is due to the effects of both oestrogen and progesterone having a procoagulant effect. Oestrogen increases the levels of clotting factors (VII, VIII, X, fibrinogen) and plasminogen, lowering antithrombin III and protein S levels, and altering activated protein C (APC) resistance. APC induces decreased factor V activity. With increased APC resistance, this inhibition is not in effect and the coagulation cascade proceeds. The net effect of combination pills is a procoagulant effect. Allied to this is the procoagulant effect of surgery with venous stasis (especially associated with the use of a tourniquet), increased acute phase proteins associated with stress response to surgery and endothelial changes either associated with the site of surgery or the use of a tourniquet.

The use of progesterone only pills (POPs) or the "mini-pill" does not appear to be associated with an increased risk of venous thromboembolism and will not be discussed further in this review.

CONSENT

While an extensive discussion of consent is beyond the scope of this paper the authors wish to highlight several considerations relevant to COCP use, VTE risk management and patient consent. Gebhard, a US lawyer, coined the term “informed consent” in 1957 built on three primary considerations. The patient should be:

1. Informed.
2. Competent (ability to: understand and retain information; assess rationally; to repeat and decide based on own values; communicate decision).

It is accepted that COCP use increases the perioperative risk of VTE but to quantify this risk is difficult and depends on other patient and surgical factors. Felcher et al showed that for patients undergoing foot and ankle surgery the rate of post-procedure VTE in patients taking COCP approximately doubled from the background rate of 3/1,000. It would seem that other anaesthesia risks, which are less likely and have less potential for morbidity, may still be communicated to patients, such as dental damage 2/10,000.

In prescribing the COCP, GPs typically justify the increased VTE risk of the COCP above baseline on the basis that the VTE risk is still very low and the risk in pregnancy is higher than that of the COCP. The authors contend it may not be appropriate to automatically extend this argument to perioperative COCP use. Patients taking the COCP may prefer to manage their contraception by alternative means for the perioperative period to decrease the increased VTE risk, including a switch the lower risk progesterone-only pill. This option should be offered to patients awaiting elective surgery.

There have been several pill scares regarding risk of VTE with some brands, which resulted in an increased number of pregnancies and therapeutic abortions after COCP use declined. Advice given to women on perioperative COCP use must also include these possible consequences of stopping the pill.

The extent to which patients are informed of risk and offered the opportunity to modify this risk in the perioperative period is further explored in the survey.

VTE RISK MANAGEMENT

The broad approach to VTE risk management in hospitals is as per the National Health and Medical Research Council (NHMRC) clinical practice guidelines for the Prevention of VTE in Patients Undergoing Elective Surgery. For surgical patients, this involves risk stratification based on individual patient VTE risk, bleeding risk factors and surgical factors.

Patient risk factors include previous VTE, increasing age, cardiac or respiratory failure, prolonged immobility, cancer, malignancy, varicose veins, obesity, smoking and inherited or acquired haematological abnormalities. Higher risk surgical procedures include abdominal, pelvic, thoracic or orthopaedic surgery. Major joint surgery and curative cancer surgery are identified as particularly high risk.

Treatment options include early mobilisation, non-pharmacological treatment, including compression stockings and pneumatic calf compression, and pharmacological treatments typically heparin or enoxaparin. In this NHMRC guideline, COCP is only mentioned as an individual patient risk factor to be considered.

There was extensive agreement (89 per cent) of respondents that VTE prophylaxis is a shared responsibility of surgeons and anaesthetists, although the remaining 11 per cent felt it was exclusively the surgeon's responsibility.

There was no difference in practice approach to managing perioperative COCP between surgeons and anaesthetists, although the remaining 11 per cent felt it was exclusively the surgeon's responsibility. The authors consider this illustrates the importance of having surgical colleges involved in the development and implementation of best practice guidelines on perioperative COCP management.

Surveys of practice

The South Metropolitan Health Service of Western Australia Human Research and Ethics Committee considered that ethics approval was not necessary due to the nature of the project so approval for the survey was sought and granted by the South Metropolitan Health Service Governance office.

A pilot survey was distributed to 12 consultant anaesthetists at Fremantle Hospital and Royal Perth Hospital with a response rate of eight (67 per cent). Minor changes to the survey format were made based on feedback from respondents.

The survey was distributed by the ANZCA Trials Group to 500 randomly selected Fellows of the College using Survey Monkey electronic survey distribution. The survey was voluntary, anonymous, confidential and IP addresses were not collected. Survey results were analysed using descriptive statistics.

Results

One hundred and twenty-two (122) surveys were completed, yielding a response rate of approximately 24 per cent. The demographics of the survey respondents were predominately (67 per cent) senior anaesthetists (>10 years of practice) mostly in full-time public practice. The results of the survey are presented in Appendix A.

Discussion

The low response rate of 24 per cent is consistent with response rates for previous surveys distributed by the ANZCA Trials Group. Given the data is from a survey and with a low response rate, rigorous conclusions about practice will not be made but simply used as a basis for discussion. To further investigate the practice of anaesthetists in terms of actual consent and perioperative practice would be a highly resource intensive project.

Given that 68 per cent of anaesthetists only “sometimes”, “rarely” or “never” routinely specifically ask COCP use, it seems a recognised VTE risk is not being routinely assessed as part of the patient history. In some preadmission settings, where a pharmacist reviews a patient prior to medical review, this information may be better elucidated.

Having identified COCP use (a risk factor for VTE) only 22 per cent of respondents would inquire into a history of venous thromboembolic disease. Other VTE risk factors such as smoking, obesity and patient history of clotting disorders were regularly identified. However, in the opinion of the authors, these factors are an important part of any anaesthesia preoperative assessment regardless of COCP use.

The majority (89 per cent) of respondents would use some form of non-pharmacological prophylaxis in an otherwise healthy woman taking the COCP having a laparoscopic cholecystectomy and 41 per cent would use pharmacological prophylaxis. Other techniques included maintaining hydration by minimising fasting times and use with intravenous fluid, although convincing evidence of the effectiveness of this is not found in the literature. Several respondents stated management of VTE prophylaxis was either specified by their institution or exclusively the responsibility of the surgeon.

Despite the presence of additional risk factors, including obesity, smoking, patient history or family history of VTE, a significant majority (67 per cent) of respondents would not cancel the patient to enable perioperative cessation of COCP.

Only 25 per cent of respondents were aware of best practice or hospital guidelines on the perioperative management of the COCP. Where known, these guidelines were typically followed. It would suggest that a best practice approach to managing perioperative COCP would be followed if anaesthetists were aware of such an approach. This represents an opportunity to improve patient care.

The increased risk of VTE from COCP use is communicated “usually” or “always” to the patient by only 21 per cent of respondents. Unfortunately it seems that patients are given suboptimal information about this potentially modifiable risk factor. Further, 88 per cent of respondents said they would “rarely” or “never” give a patient an opportunity to postpone surgery to cease the COCP perioperatively. The authors feel this does not provide sufficient autonomy to women to manage their contraception by other means during the perioperative period.

Contraindications to COCP use include VTE, stroke, coronary artery disease, structural heart disease, diabetes with complications, peripheral vascular disease, hypertension (blood pressure >160/100 mmHg), breast cancer, liver disease, headaches with focal neurological symptoms, major surgery or prolonged immobilisation, age greater than 35 years old or smoker greater than 20 per day and within the first 21 days post-partum.
The combined oral contraceptive pill and perioperative venous thromboembolism risk

Q2: If you encounter a patient on your list for laparoscopic cholecystectomy who is taking the COCP, which of the following risk factors for DVT/PE do you routinely inquire about? (You may select more than one of the options below.)

Q3: You meet a healthy, slim 38-year-old female non-smoker with no significant personal medical history or family history presenting for elective laparoscopic cholecystectomy. The only medication she takes is the COCP. You are due to operate/anaesthetise her on your list today.

On such a patient with regard to DVT/PE prophylaxis would you routinely use any of the following (please select as many options that you feel appropriate):

APPENDIX A: SURVEY RESULTS

Q1: Do you directly ask 14 to 50-year-old female patients whether they are taking the COCP?

REFERENCES


APPENDIX A: SURVEY RESULTS

Q1: Do you directly ask 14 to 50-year-old female patients whether they are taking the COCP?

- Always 12%
- Usually 20%
- Sometimes 22%
- Rarely 24%
- Never 22%
Q4: If the above patient was to have some combination of the following additional risk factors for DVT/PE listed below:
- Smoker.
- Body mass index (BMI) >40.
- Family history of DVT/PE/thrombophilia.
- Personal history of DVT/PE/thrombophilia.
Would the presence of some combination of these additional risk factors cause you to cancel surgery in order for her to cease the COCP perioperatively?

- Would cancel her solely on OCP use 2%
- 1 additional risk factor 0%
- 2 additional risk factors 3%
- 3 additional risk factors 6%
- All 4 additional risk factors 2%
- Would not cancel 87%

Q5: Are you aware of any best practice guidelines or hospital policy regarding COCP use and perioperative DVT/PE risk?

- Yes 25%
- No 75%

Q6: Do you consult and follow these guidelines when seeing a patient preoperatively on the COCP?

- Yes, consult and follow 5%
- Yes, follow (but not know the guidelines so do not consult 13%
- No, do not follow/consult 35%
- Not applicable 47%

Q7: Do you warn patients taking the COCP regarding an increased risk of perioperative DVT/PE associated with COCP use?

- Always 5%
- Usually 16%
- Sometimes 21%
- Rarely 26%
- Never 32%

Q8: Do you give patients the opportunity to postpone surgery should they wish to cease the OCP perioperatively?

- Always 3%
- Usually 6%
- Sometimes 3%
- Rarely 34%
- Never 53%

Q9: VTE prophylaxis is the responsibility of:

- Exclusively the anaesthetist 12%
- A shared responsibility for both the surgeon and anaesthetist 88%
Will my patient get stuck in ICU?

THOMAS J SHEPHERD, MBBS
Anaesthetic Registrar, Mater Hospital Brisbane.
Dr Tom Shepherd is an anaesthetic trainee at the Mater Hospital Brisbane. He is currently getting “stuck into” his dual anaesthetic and intensive care training.

DAVID J STURGESS, MBBS, PHD, PGDIPCU, FRACGP, FANZCA, FCICM
Specialist in anaesthesia, Royal Brisbane and Women’s Hospital, Brisbane, Australia.
Deputy Director of Adult ICU, Mater Health Services, South Brisbane, Australia.
Dr David Sturgess shares his clinical time between clinical anaesthesia and intensive care medicine. He has a keen interest in perioperative medicine research and practice.

CLAIRE MAXWELL, MBBS, BSC
Anaesthetic Registrar, Logan Hospital, Queensland.
Dr Claire Maxwell is an anaesthetic trainee on the Queensland rotation.

INTRODUCTION

It is generally acknowledged that intensive care medicine was born as an improvised response to the poliomyelitis epidemic of 1952. As part of a desperate attempt to save the life of a 12-year-old girl, Dr Björn Ibsen, a Danish anaesthesiologist, was invited out of the operating room to apply his skills. Since then, intensive care units have become a mainstream component of modern hospital systems, with an emphasis on improving survival of high-risk medical and surgical patients.

Despite an emphasis on reversible illness, the modern era of intensive care is confronted with the conundrum of patients that may survive surgery or critical illness but then require prolonged or indefinite organ support. Such patients might be considered “stuck” in ICU. This problem has become known as chronic critical illness. The term was coined by Girard and Raffin in 1985 with an article titled “The chronically critically ill: to save or let die?”. Patients who were previously considered ineligible for surgery are now candidates, but this is apparently contributing to a large and growing population of chronically critically ill patients. The ability to predict the development of postoperative chronic critical illness could guide discussion and decision making. High-risk patients, their families, friends and/or carers, as well as their clinicians, might shy away from operative management if it could be reliably known that lingering dependence on organ support would ensue. Also prediction of chronic critical illness could guide ICU resource management, as these patients generally spend significant time in ICU, require significant resources and are typically very slow to show improvements. The aim of this review is to assimilate research that has been published regarding chronic critical illness in order to characterise the prevailing issues, with a focus on the prospect of predicting high risk peri-operative patients.

DEFINITION OF CHRONIC CRITICAL ILLNESS

A binding definition of chronic critical illness remains elusive. The question of what exactly defines the condition has been a subject of debate internationally, with no real consistency in the literature to date. Although many papers have declared the need for a consensus definition, especially for data comparison and standardised research, the literature remains littered with different criteria.

A potential contributor to inconsistent definition is that investigators and clinicians are likely to approach the problem from a number of different viewpoints. Clinicians are inclined to recognise chronic critical illness from a pragmatic stance: the patient has survived acute critical illness or injury but has not yet recovered to the point of liberation from life sustaining therapies. Although this might translate adequately on the morning ward round, it is challenging to build into research, audit or health economic analysis.

From a research and audit perspective the definition for an illness or syndrome should:

• Have good sensitivity and specificity for the condition.
• Be easy to apply using data that is routinely present in the medical record.
• Be widely accepted by investigators, clinicians and administrators.

In attempting to apply a broadly relevant definition, it is important to appreciate that the transition from acute to chronic critical illness is gradual and there is no clear point of demarcation. Clinical thresholds that appear to hold most potential are the requirement for prolonged mechanical ventilation (PMV) or the insertion of a tracheostomy. Clearly, there is considerable overlap, but each threshold has arguments in favour or against (Table 1).
One hallmark of chronic critical illness is the requirement for PMV. In 2005 a consensus statement was published in the American Chest Journal, recommending the definition of PMV as greater than or equal to 21 days of mechanical ventilation, with at least six hours of mechanical ventilation per day5.

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In the 1990s, tracheostomy was usually inserted at approximately 10-12 days10, with the trend being towards earlier insertion. However, recent trials demonstrate a tendency toward later insertion in patients with chronic critical illness. Average insertion times of 16-17 days have been reported18. It is conceivable that this marks a shift from a selection bias. For example, tracheostomy might be considered earlier in younger, previously healthy patients with rib fractures following trauma, versus an elderly post-operative patient with a slow ventilatory wean due to chronic obstructive pulmonary disease (COPD) and heart failure. The outcomes of these patients would be expected to be very different due to comorbidities and functional reserve.

### Table 1. Comparison of tracheostomy insertion and prolonged mechanical ventilation as defining criteria for chronic critical illness

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mechanical ventilation duration</td>
<td>≥ 6 hours/day for ≥ 21 consecutive days</td>
</tr>
<tr>
<td>Pro</td>
<td>• Anticipation of prolonged mechanical ventilation = start of protracted course.</td>
</tr>
<tr>
<td></td>
<td>• Likely to survive for a reasonable amount of time.</td>
</tr>
<tr>
<td></td>
<td>• Family has consented (want ongoing invasive support).</td>
</tr>
<tr>
<td></td>
<td>• Procedure is clearly recognized from the clinical record.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>• Timing of tracheostomy not standardized:</td>
</tr>
<tr>
<td></td>
<td>– Differs between institutions.</td>
</tr>
<tr>
<td></td>
<td>– Differs between practitioners.</td>
</tr>
<tr>
<td></td>
<td>– Influenced by patient diagnosis and condition.</td>
</tr>
</tbody>
</table>

### Prolonged mechanical ventilation

A hallmark of chronic critical illness is the requirement for PMV. In 2005 a consensus statement was published in the American Chest Journal, recommending the definition of PMV as greater than or equal to 21 days of mechanical ventilation, with at least six hours of mechanical ventilation per day5.

The ideal definition of chronic critical illness should identify the time point that, once reached, signals a higher incidence of associated morbidities, excess mortality or increased resource utilisation. North American authors have favoured the definition of the chronic critical illness “syndrome” as being characterised as >21 days of mechanical ventilation (based on the definition of PMV) or tracheostomy insertion. However, considerable variation persists; for instance, very recent studies have used 14 days of mechanical ventilation as their definition11.

Other studies propose a combined definition, as mechanical ventilation for 7 days with a physician not expecting death or liberation from mechanical ventilation within 72 hours12. It should be noted that ENT surgical patients and patients with neuromuscular disease states such as muscular dystrophy are a specific subset of the population and are typically excluded. Clinician prediction of PMV has been shown to be poorly correlative to actual duration of ventilatory support, especially if greater than 14 days11. Thus it is difficult to argue for a definition that includes a clinical judgement that has shown to be poorly performed.

### Tracheostomy

Tracheostomy is an appealing threshold for defining chronic critical illness. It is a discrete time point that should be easily recorded or identified from the clinical record. It also indicates an acceptance by clinicians, and the individual providing consent, that prolonged ventilatory support is likely to be required and is indicated; the patient remains critically ill but end-of-life care is not planned or imminent. On the other hand, tracheostomy insertion times are variable with significant variance in times of insertion depending on individual clinician and institutional practices. Additional arguments include the possibility that timing of tracheostomy might influence outcome, and that patients that progress to chronic critical illness (according to other criteria) tend to be scheduled for tracheostomy after a longer period of mechanical ventilation.

In the 1990s, tracheostomy was usually inserted at approximately 10-12 days10, with the trend being towards earlier insertion. However, recent trials demonstrate a tendency toward later insertion in patients with chronic critical illness. Average insertion times of 16-17 days have been reported18. It is conceivable that this marks a shift from a selection bias. For example, tracheostomy might be considered earlier in younger, previously healthy patients with rib fractures following trauma, versus an elderly post-operative patient with a slow ventilatory wean due to chronic obstructive pulmonary disease (COPD) and heart failure. The outcomes of these patients would be expected to be very different due to comorbidities and functional reserve.

### THE CHRONIC CRITICAL ILLNESS SYNDROME

Beyond the persistence of respiratory failure requiring prolonged support, and regardless of definition, chronic critical illness appears to be characterised by a number of metabolic and pathologic associations11-13.

A plethora of endocrine changes are associated with chronic critical illness. These range from thyroid disturbance to adrenal insufficiency. Insulin resistance is common. Changes in growth hormone and vitamin D metabolism are also reported.

Gastrointestinal dysfunction is also common. Muscle wasting, metabolic derangement and malnutrition are common features of chronic critical illness. Infection can be recurrent. Impaired immune function is not unusual. Skin breakdown is also common. Development of pressure ulcers and issues with wound healing are often experienced.

Cognitive dysfunction (ICU delirium) and neuromuscular disorders (including critical care weakness), are frequently encountered in the chronically critically ill.

Conventional ICU management acknowledges many of these associations with prolonged management and endeavours to anticipate and avoid iatrogenesis14.

### EPIDEMIOLOGY

It is reported that 5-15% of ICU patients progress to develop chronic critical illness1. Typically these patients are characterised by advanced age, but despite multiple comorbidities, they have lived at home with good functional status before acute illness. Of patients fulfilling criteria for chronic critical illness, surgical patients (approximately 40%) are less common than survivors of medical illness requiring ongoing mechanical ventilation.

Certain surgical cohorts appear more likely to progress to chronic critical illness15. Based on analysis ventilator dependent post-operative patients in long term care facilities (N=1419; from 23 weaning centres across the USA)16, cardiac surgery (CABG 30%: heart valve 13.7%) had the highest representation. Other associations included gastro-intestinal surgery (non-neoplastic 15.5%; neoplastic 4.5%), neurosurgery (craniotomy 6.6%) and orthopaedic surgery (6.1%). Males and females were equally represented, and the median age was 71.8 years (range 18-97.7).

Overlap of admission characteristics might explain this. Patients not requiring PMV for greater than 24 hours had significantly higher incidence rates from each other and that these are influenced by the definitions applied with each study (Table 2).

Having already identified an over-representation of cardiac surgical patients, the literature suggests the possibility that this cohort behaves differently to conventional chronic critical illness. Post-operative cardiac patients are typically delivered to ICU intubated and sedated for maintenance of haemodynamic and respiratory stability. Analysis of this cohort suggests that mechanical ventilation beyond 24 hours identified outliers at risk of PMV, but that these patients generally had better outcomes than other patients with PMV11-18.
### Table 2. Comparison of a range of studies reporting chronic critical illness (CCI) and prolonged mechanical ventilation (PMV). Heterogeneity in definition, representation and significance are demonstrated.

<table>
<thead>
<tr>
<th>Study type</th>
<th>ICU type</th>
<th>Definition of PMV</th>
<th>Number enrolled</th>
<th>PMV %</th>
<th>Rate of tracheostomy</th>
<th>Mortality</th>
<th>Morbidity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective observational cohort study. Four years.</td>
<td>17 Beds. Public. Medical and surgical.</td>
<td>Greater than or equal to 14 days</td>
<td>347</td>
<td>–</td>
<td>76% @ average of 16.8 days after admission</td>
<td>44% in hospital mortality</td>
<td>Assessed via questionnaire</td>
<td>Significantly higher rates of patients post cardiac surgery compared to other admissions. 33% ICU mortality in patients ventilated ≤14 days. Long-term survival higher in post cardiac patients.</td>
</tr>
<tr>
<td>Prospective observational cohort study.</td>
<td>Private. 32 beds. Medical and surgical.</td>
<td>Greater than 20 days of ICU stay.</td>
<td>453 Adults</td>
<td>CCI = 11%</td>
<td>–</td>
<td>58% in hospital mortality</td>
<td>–</td>
<td>Pressure ulcers seen mostly after day 10.</td>
</tr>
<tr>
<td>Retrospective analysis of patients requiring MV in ICU.</td>
<td>Medical ICU only.</td>
<td>&gt;14 days</td>
<td>130 consecutive patients requiring MV support.</td>
<td>84% of this was due to PMV.</td>
<td>15% @ average of 11.5 days.</td>
<td>–</td>
<td>–</td>
<td>Showed similar morbidity and mortality post discharge in CCI and non-CCI patients. Low PMV rate 15% PMV admission from OT PMV patients consumed 42 % of ICU days.</td>
</tr>
<tr>
<td>Retrospective analysis over 18 months</td>
<td>Mixed medical and surgical. 34 beds.</td>
<td>&gt;14 days</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>48.8% hospital mortality</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

In the US, the issue of chronic critical illness is becoming a significant concern in health care expenditure (the following dollar amounts are reported in USD). The average hospital cost for a patient with >21 days of mechanical ventilation is approximately $423,596.\(^{17}\) The health economic implications persist even when different definitions of chronic critical illness are applied. Sources have showed that chronic critical illness patients (>14 days PMV) comprised 11% of patients and absorbed 40.6% of ICU resources with an average daily cost of $2,121 compared to non-chronic critical illness of $1347.\(^{27}\) Other studies using PMV as > 96 hours stated and average length of stay per patient cost between $158,000 and $198,000.\(^{22}\) Costs are starting to be appreciated in other cultures, with a Taiwanese study reporting that the increasing costs of chronic critical illness are not sustainable and alternative approaches need to be considered.\(^{28}\)

American predictions with population analysis suggesting an increase in PMV patients > 200% by 2020; yet this could be an exaggeration of the real problem as it defines PMV as > 96 hours.\(^{23}\) However, based on Australian data, it is hypothesised that the rates of PMV in ICU patients are significantly lower than described elsewhere.

### OUTCOMES

Regardless of definition, cohort studies of acute care hospitals document one-year survival between 30% to 50% for chronic critical illness patients.\(^{14}\) In the modern era, this is worse than most cancers.

With regard to one year mortality, outcomes are similar between medical and surgical ICU. The exception is trauma patients, who typically demonstrate much better survival. Long-term survival has not improved over the past 20 years.\(^{6}\)

If patients survive their hospital admission, morbidity and mortality remains high with a significantly increased rate of readmission to ICU in the future and high risk of another prolonged ICU stay.\(^{19,20}\) Survivors of critical illness are often left with physical and cognitive deficits. Chronic critical illness patients tend to be even more severely affected. Only 10% of patients with chronic critical illness are alive at home and functionally independent at one year. The overall impact upon quality of life is inconsistently reported.\(^{1,3}\) Some studies claim relatively good quality of life post discharge, while others report excess morbidity.\(^{14,15}\)

### PREDICTION OF AT RISK PATIENTS

The ability to predict patients at highest risk of requiring prolonged ICU management post-operatively is a laudable goal. Potential benefits could be realised by patients, clinicians and hospital administrators. However, reliable prediction remains impossible.

Previous studies have found using the critical illness severity scores such as the SOFA, SAPS3, ODIN, APACHE and IPS scores to determine for correlation with prediction of PMV on admission have shown no significant correlation to date.\(^{14,30,32}\)

One predictive scoring system has been created called the ProVent© score which assesses the one year mortality of patients with PMV according to age >50, Vasopressor use, thrombocytopenia and haemodialysis.\(^{11}\) This scoring system has been externally validated in a subsequent trials, but would not be suitable for pre-emptive surgical decision making.

At least three notable retrospective studies have been performed in this area in recent years.\(^{14,37,29}\) Unfortunately, consistency of definition is still lacking with two studies using mechanical ventilation > 14 days\(^{37,29}\) and the other ICU length of stay >20 days.\(^{14}\) These studies range in size from N=130 to N=2908. They are difficult to compare and found minimal collaborative data for predicting chronic critical illness.

### DISCUSSION

Chronic critical illness is an emerging issue with huge consequences for patients, family, caregivers and funding organisations. This issue has been receiving increasing interest internationally over the past decade, but scant data exists in the Australasian context. The lack of a consistently applied definition of chronic critical illness remains a significant barrier to research interpretation. External validity is also challenged by differences in case mix. The ICU’s involved are often single centre units, a mix of public or private units and varying combinations of surgical or medical units with relatively small recruitment numbers. It has been hypothesised that these rates of chronic critical illness are not as high in Australia compared to other countries but published data is lagging.

### REFERENCES


patients reported chronic pain – osteoarthritis and back pain provided close to 80 per cent of diagnoses. Almost non-pharmacological therapies. Of the opioid-based medications used, codeine 30mg combinations were prescribed the population, which may reflect unrealistic expectations of benefit of “painkillers”, along with difficulties in accessing becoming clearer. The Global Burden of Disease study 2010 provides the rankings for years lived with disability The general community burden of disease from low back pain, neck pain and other musculoskeletal disorders is AilMents AnD AGeinG newer agents (oxycodone, fentanyl, hydromorphone) in comparison with morphine may be encouraging unrecognised of MEDD labelling, has added to the potential for inadvertent misadventure. The relatively higher potency of the available for community prescribers, combined with multiple-dose formulations of each product without the benefit daily dose or MEDD) by some prescribers may be lacking. The rapid increase in the range of different strong opioids as failure to recognise when prescribing is heading toward the “high dose, high-risk range” and expectations of regard to opioid ceiling dose and prescription duration recommendations for chronic non-cancer pain. This manifests of harm has been greater than expected. In the clinical scenario described previously, benefit from strong opioid was limited and the development of tolerance encouraged dose escalation, leading to serious adverse events. In looking at the bigger picture behind the clinical scenario outlined, it is recognised that the elderly have a higher prevalence of pain than other age groups in the community and this is more likely to be undertreated. This is reflected in a rapid escalation of opioid use in the elderly over the past 10 years compared with opioid use in other age groups. Predictably, this age group is more at risk of adverse events due to their less robust general health and frequent poly-pharmacy. In the clinical situation highlighted, the patient’s long-term codeine intake prior to the initiation of fentanyl may have been a significant contributor to inducing opioid tolerance and possibly opioid-induced pain sensitivity. This is exacerbated by the fact that some clinicians appear to be unaware of current thinking in regard to opioid ceiling dose and prescription duration recommendations for chronic non-cancer pain. This manifests as failure to recognise when prescribing is heading toward the “high dose, high-risk range” and expectations of medium-term use only, rather than lifelong dosing and efficacy. Of more concern, basic understanding of the relative opioid equivalence of different opioids (morphine-equivalent daily dose or MEDD) by some prescribers may be lacking. The rapid increase in the range of different strong opioids available for community prescribers, combined with multiple-dose formulations of each product without the benefit of MEDD labelling, has added to the potential for inadvertent misadventure. The relatively higher potency of the newer agents (oxycodone, fentanyl, hydromorphone) in comparison with morphine may be encouraging unrecognised over-dosing rather than under-dosing. AILMENTS AND AGEING The general community burden of disease from low back pain, neck pain and other musculoskeletal disorders is becoming clearer. The Global Burden of Disease study 2010 provides the rankings for years lived with disability from medical conditions. Not surprisingly to those who work in the area, low back pain was ranked first with neck pain and other musculoskeletal disorders both within the top six. The wide ranging BEACH program of primary healthcare research recently surveyed chronic pain in Australian general practice patients with 192 general practitioners surveying 5800 patients. In this survey, 20 per cent of patients reported chronic pain – osteoarthritis and back pain provided close to 80 per cent of diagnoses. Almost two thirds of the disease burden was in patients over the age of 65. Medication alone was used in 56 per cent of the population, which may reflect unrealistic expectations of benefit of “painkillers”, along with difficulties in accessing non-pharmacological therapies. Of the opioid-based medications used, codeine 30mg combinations were prescribed

Pain, older people and opioids

TIM SEMPLE, MB, BS, FANZCA, FFPMANZCA

Specialist anaesthetist, Royal Adelaide Hospital, Adelaide. Dr Tim Semple works at Royal Adelaide Hospital with time shared equally between anaesthesia and pain medicine. He is involved in pain medicine outreach services to regional South Australia and the Northern Territory. He maintains anaesthesia interests in cardiothoracic and orthogeriatric surgery.

CLINICAL SCENARIO

An inpatient consultation request to the pain management service: To provide a pain management review for a female, 92 years old, admitted with severe abdominal pain and agitation, unresponsive to oxycodone. Her background: A nursing home resident with moderate dementia and widespread musculoskeletal pain on transdermal fentanyl patches 100mg and 50mg every third day. Further prescription history revealed she had been prescribed Panadeine Forte six tablets per day for two years and changed to fentanyl patch 25mg some six months earlier. An initial benefit had been noted, but dose escalation occurred after two months and then at monthly intervals. Medical and surgical reviews had found no new or acute pathology in her abdomen. A presumed diagnosis of opioid-induced agitation/pain was confirmed when she settled with rapid reduction and cessation of fentanyl and conversion to transdermal buprenorphine patch 10mg weekly. Her nursing home prescriber was surprised when informed the daily oral morphine equivalence of her prescribed fentanyl patch was almost 500mg and was the cause of the severe pain.

This clinical situation perfectly illustrates the subject matter of a recent editorial in Pain Medicine, “Optimal pharmacological pain management in the older adult – an ongoing quagmire”. So, how did we get ourselves into this quagmire?

THE ROOT OF THE PROBLEM

Many clinicians working in pain medicine some 20 years ago in the period when opioids were becoming more commonly prescribed in chronic non-cancer pain (CNCP) had high expectations of their benefit. In retrospect, their expectations may have been unrealistic. The arrival of systematic reviews and meta-analyses on opioid efficacy led to a calculation of an NNT (number needed to treat) around 2.4 for short-term use. This implies that three out of five patients will not benefit from opioid analgesia in the context of chronic non-cancer pain. If a responder, the analgesic benefit was recognised to be unlikely to be greater than 50 per cent at best and only as a component of a multimodal approach. Also, the widely accepted term “strong painkiller” for opioids may have encouraged similarly unrealistic expectations from patients. In brief, the evidence of benefit was less than expected and the evidence of harm has been greater than expected. In the clinical scenario described previously, benefit from strong opioid was limited and the development of tolerance encouraged dose escalation, leading to serious adverse events. In looking at the bigger picture behind the clinical scenario outlined, it is recognised that the elderly have a higher prevalence of pain than other age groups in the community and this is more likely to be undertreated. This is reflected in a rapid escalation of opioid use in the elderly over the past 10 years compared with opioid use in other age groups. Predictably, this age group is more at risk of adverse events due to their less robust general health and frequent poly-pharmacy. In the clinical situation highlighted, the patient’s long-term codeine intake prior to the initiation of fentanyl may have been a significant contributor to inducing opioid tolerance and possibly opioid-induced pain sensitivity. This is exacerbated by the fact that some clinicians appear to be unaware of current thinking in regard to opioid ceiling dose and prescription duration recommendations for chronic non-cancer pain. This manifests as failure to recognise when prescribing is heading toward the “high dose, high-risk range” and expectations of medium-term use only, rather than lifelong dosing and efficacy. Of more concern, basic understanding of the relative opioid equivalence of different opioids (morphine-equivalent daily dose or MEDD) by some prescribers may be lacking. The rapid increase in the range of different strong opioids available for community prescribers, combined with multiple-dose formulations of each product without the benefit of MEDD labelling, has added to the potential for inadvertent misadventure. The relatively higher potency of the newer agents (oxycodone, fentanyl, hydromorphone) in comparison with morphine may be encouraging unrecognised over-dosing rather than under-dosing.
in 11 per cent, with tramadol in 8.9 per cent and oxycodone in 7.7 per cent. The most common non-pharmacological treatment was physiotherapy, used in 13 per cent. Advice/education and exercise was provided to less than 4 per cent. With referral to specialist care for only 3.7 per cent, it would appear that more than 96 per cent of individuals with chronic non-cancer pain are managed by their general practitioners. The apparent reliance upon analgesics as the sole modality of care in chronic non-cancer pain management is misguided at best.

Recent work from the USA highlighted that in the decade from 1999, opioid prescribing for older adults has doubled. Recognising the difficulties of distinguishing “good” or “not good” prescribing or not noting the unmet pain management needs in this age group, in Australia, Gadzhanova et al.9 explored which analgesics older people use prior to initiating oxycodone for non-cancer pain in 11,000 DVA clients in 2010. They were concerned that the initiation (and strategic prescribing) occurred in over one-third of community-living DVA clients without prior use of simple analgesics or weaker opioids. Roxburgh et al.10 reviewed prescriptions for morphine and oxycodone dispensed via the Pharmaceutical Benefits Scheme from 2002 to 2008 and again noted that in the 80-years-plus age group, morphine prescribing had diminished and oxycodone use had escalated almost fourfold. Further work by the same author in regard to fentanyl patch prescriptions between 2002 and 2010 noted an almost sevenfold escalation in fentanyl patch use in the 80-years-plus population – they too were unable to determine whether this reflected quality prescribing or not. Some indications of the appropriateness or otherwise of opioid prescribing have been explored by Rogers et al.11 by the Pharmaceutical Benefits Scheme prescription review (2006 to 2009) of the 100,000 Australians being followed in “45 and up” cohort. They note that 5 per cent of their study population was taking long-term opioids, 5 per cent was on intermittent opioids and 50 per cent of prescriptions were for those over 70 years of age. They were concerned by the possible adverse selection highlighted in the multidimensional profile of individuals receiving opioids; in particular, opioid dispensing was associated with smoking, obesity and lower levels of physical activity. These individuals also had lower income, reduced private health-insurance rates, were often living outside a major city, and displayed higher markers of psychological distress. Of interest, however, rates of opioid dispensing were highest in the youngest age group studied (45 to 49 years). It will be of great interest to follow the progress of this cohort if opioid prescribing is maintained as they age, observing the long-term sequelae of opioid prescribing in this population to ascertain if this causes an additional set of health burdens. Prospective work by the NDARC team12, who are piloting opioid prescribing for older people in NSW who were dispensed opioids, has revealed that older people with ongoing opioid dispensing and psychological distress as well as poor health and lower income, with social and psychological factors playing a more significant role in younger patients.

Both studies imply that opioid prescribing is more likely in those with complex and difficult lives (as well as medical conditions) and lower capacity to access non-pharmacological therapies – apparent adverse selection from a risk/benefit viewpoint.

Home medicine reviews (physician-conducted comprehensive medical review) provide an opportunity in Australia to evaluate medications and the increased risk of medication-related adverse events. Almost 20,000 medication reviews between 2010 and 2012 were analysed by Veal et al.12 with over 22 per cent of the study group taking opioids regularly (89 per cent of these being over 60 years of age). They highlighted the suboptimal use of multimodal analgesia in 28 per cent of patients who were dispensed opioids, and highlighted that over 45 per cent of patients were taking concurrent anxiolytic/hypnotics. Almost 12 per cent of patients were taking a MEDD of greater than 120mg (the recommended ceiling dose). The reporting of a mean daily dose of 36mg in the group of patients taking less than 120mg per day is somewhat reassuring, but the mean dose of 245mg daily in the higher dose group is concerning. The higher dose group more commonly used anxiolytics and hypnotics as well as other adjuvant adjuncts.

The use of higher doses of opioids in the elderly has been flagged recently as a significant contributor to fractures. While delirium is known to be a significant risk factor for falls, the low use of non-opioid analgesics in older adults is concerning. From a study of 10,852 patients, 45 per cent were taking concurrent anxiolytic/hypnotics. Almost 12 per cent of patients were taking a MEDD of greater than 120mg (the recommended ceiling dose). The reporting of a mean daily dose of 36mg in the group of patients taking less than 120mg per day is somewhat reassuring, but the mean dose of 245mg daily in the higher dose group is concerning. The higher dose group more commonly used anxiolytics and hypnotics as well as other adjuvant adjuncts.

The longitudinal cohort study of older people taking opioids in the Multidisciplinary Pain Management Service, Sydney, revealed that 86 per cent of patients were taking analgesics even when no acute pain was reported. The analysis of pain disability scores revealed that almost 50 per cent of patients were taking opioids for less than 30 days in the year preceding the study, while 23 per cent were taking opioids for greater than 90 days. The study also revealed that the usage of opioid analgesics, particularly oxycodone, was associated with delirium, depression, confusion, and a range of other adverse events including lower cognitive function, sleep disturbance and decreased physical activity. The study also noted that patients taking opioids for longer than 90 days were more likely to require higher doses of opioid analgesics, which was further evidence that the use of opioid analgesics was associated with poor outcomes.

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EDITOR'S NOTE
The following article is not typical of those normally published in Australasian Anaesthesia. However, I believe the personal insights into drug addiction provided by Dr Charles Slack are something all clinicians should read. I invited Dr Slack, a former Harvard professor of psychology now living in Perth, to speak at the annual dinner of the Department of Anaesthesia, Royal Perth Hospital, in 1999. I soon discovered his many and varied experiences in life; his encounters with Albert Einstein, his research with Timothy Leary into psychoactive substances, personal addiction and then recovery. Finally, that he has devoted his professional life to assisting others with histories of substance abuse.

His remarkable story is too fascinating to remain untold.

Dr Richard Riley, Editor, Australasian Anaesthesia

A cautionary tale with a promising finish

CHARLES WILLIAM SLACK, PHD.

PhD in experimental psychology in 1954; Assistant Professor Clinical Psychology, Harvard 1955-60. Migrated to Australia in 1976 and employed by the Victorian Department of Social Welfare. In 1990 was employed by Department of Corrective Services (now Department of Justice) of Western Australia as clinical psychologist/program officer.

MY PROBLEM
In 1961, strictly by reason of being a research scientist, I took 500 micrograms of lysergic acid diethylamide (LSD) in a “house-party” setting. LSD was legal at that time and was labelled psychotomimetic. Psychologists at the Harvard Psychological Clinic, including Timothy Leary and I, were eager to correct that misclassification. We experimental psychologists (in contrast to clinical psychiatrists of the day) were convinced that mental set and environmental setting were major determinants of drug effects. If LSD was to be administered in a social setting with a festival atmosphere, instead of a medical (notably a mental-hospital) environment, outcomes would be salubrious.

As a strictly professional participant-observer at a house-party in a mansion on the banks of the Hudson River I saw God in a light-bulb, merged with the carpet, landed on a tiny moon crater which felt like a toilet seat, and was overall overcome by the overwhelming conviction that my altered state of mind was exceptionally beneficial. Those lacking this transcendental experience might insinuate similarities to psychosis but not I. Being certain that I had never been more sane or more privileged, I firmly believed three conclusive truths had been revealed to me:

- LSD was absolutely not habit forming and should be administered frequently to heighten awareness of remarkable mental phenomena.
- The inner workings of my brain had been unveiled in such a way as to completely invalidate any form of naive realism as a world view.
- Psychedelic substances had enabled me to possess other indescribable absolute truths.

My purpose in telling you my story is 1) to confess that, despite my professional career and perhaps partly because of it, I became an intransigent, poly-drug addict and 2) to show how I recovered through complete abstinence. When I arrived in Australia in October 1976 I’d been drug and alcohol free for eight months. At this writing, 39 years have passed since I’ve ingested or injected any mind- or mood-altering substance.

Being a social scientist with the best of intentions did NOT prevent me from becoming addicted. Crazy behaviour, the madness of the 1960s, was a consequence, not a cause, of my problem. Being a colleague of such hippy luminaries as Timothy Leary and Baba Ram Dass (nee Dick Alpert) and taking LSD with them is an interesting part of my story. However, a more important part is that, whereas most of my celebrated companions from the Sixties are dead (or brain dead), I remained drug-free by pulling my head in and associating with humble, even anonymous, persons who also maintained continuing abstinence.

The fact that lysergic acid diethylamide did not seem habit-forming, and was unrelated to amphetamines and opioids, only meant that I believed I could take it as often as necessary to continue to experience all its effects. The fact my friends and I were high-status professionals doing important research with legal drugs was of no consequence to the regions of our nervous systems that encoded motor programs and repeat behaviour. Later, when, with the very best of intentions, we “researched” first-hand the effects of certain opioids, our accumbens nuclei also reacted without reference to our professional status.

Let me state clearly what I believe to be the reason I became addicted. It was my actions, not my motives. Upon ingesting or injecting the substance, the immediate neurological consequences greatly increased the probability that the behaviour would be repeated. The reason why I took the drug was less important than the fact that I took it. The behaviour was reinforced no matter what my motive was for the behaviour. Any time I took a drug for any reason, the probability I would take it again – for any or no reason – increased. It took me 15 years to go from being an Assistant Professor of Clinical Psychology at Harvard to being unemployed in Birmingham, Alabama.
How and why I took drugs is less important than why and how I quit. I attended a meeting of the American Correctional Association to look for work in a jail or institution (my career had slumped to the point where a “clink-shrink” job was my only hope). At that meeting, the novel concept of my attending a 12-step program was effectively planted in my mind by a renowned criminologist and former colleague. Identifying me as an alcoholic who needed help, Dr Alex Bassin refrained from giving advice, instead asked me to lecture to his morning criminology class! Years had passed since I’d received such a request. I agreed without reservation and was careful not to drink on the day and to arrive on time. Alex introduced me to the class but then made a strange proposition. He said, “Today we do something different. Dr Slack will speak for 10 minutes and then I will speak for 10 minutes and so on – alternating throughout the hour.” I had to agree – it was his class.

I think it is relevant that today I cannot remember what I said in any of my three 10-minute talks. However, I shall never forget what he said: Relating each of my talks to Alcoholics Anonymous. Criminology was crying out for someone like me to provide a professional assessment of why AA appears to be so successful. What kind of social relationship was at work in AA? What theory underlay that program of recovery? He thought my theoretical position remarkably similar to AA’s. A cultural/anthropological informant was clearly required to attend, work the program and report findings. Heading north from Florida, I resumed drinking again in Mobile, Alabama. It was Mardi Gras; citizens drank on street corners and so did I until I lost consciousness. I came to on March 3 in a strange bed in a strange house where a stranger was informing me of my untoward behaviour. Among other transgressions I had apparently encountered a Supreme Court Justice of the State of Alabama and had informed him of precisely what was wrong with the justice system of that state.

Driving back from Mobile to where I lived near Birmingham, and having come to the end of my rope, I stopped the car and began to cry. I had reached what AA calls “rock bottom”. Not long thereafter I attended the first of well over 5000 12-step meetings to date. My recovery requires complete abstinence on a daily basis; sustained by my associating regularly with others practicing a similar program. I have found that being easily influenced is no great handicap, providing I associate with those who are doing what I need to do. It’s not what I do but the way that I do it. And it’s not what I don’t do but with whom I don’t do it. Since March 3, 1976 I have remained completely abstinent from all mind- and mood-altering drugs including alcohol and nicotine. I like to say there is nothing in my blood but blood.

I migrated to Australia in October 1976 to get work. In 1980 I became a Christian. I attend church regularly and view the bible as a text-book on how to avoid being addicted (enslaved) to sinful things like drugs by becoming addicted (devoted) to Godly things like helping fellow addicts in recovery. Being fascinated by rehabilitation, personality change, reformation, character development, indeed anything related to the kind of identity transformation that accompanies what the bible calls “repentance”, I still attend recovery meetings. I find it thrilling to observe improvement in others and to have others observe it in me.

Nearly 30 years ago, my oldest daughter phoned from California to say she had been attending 12-step meetings for two years. I asked her why she hadn’t told me sooner and she said that she’d wanted to but, because I was such a “blab-mouth” I would have told everybody in the US. She said I could tell all my friends in Australia but that she didn’t want everyone in America to know her whole story. I asked her why she’d chosen a 12-step program. She said she knew it worked. I asked how she knew. She said she could tell by my voice over the phone!

I was in Victoria and then Western Australia and she was in California. Unemployed, she was living what I used to call the hippy-lifestyle of the Haight-Ashbury district of San Francisco. Although I never consciously tried to influence her, the change in her father was obvious enough to spark a change in his daughter. With sobriety, her life took a remarkable turn. She got a good job, saved her money, earned a MA in Psychology, and is now director of a community-based mental-health centre in Oakland. Other gratifying, remarkable things have happened to me since I became abstinent and began to make conscious contact with a loving deity.

Finally I must admit I cannot claim to have led a successful life. Nevertheless I do have the benefits – happy marriage, successful retirement, respect of colleagues, love of friends and family, and an opportunity to help others – as though I had been successful! To paraphrase televangelist, Joyce Meyer: “I must give the glory to God and the credit to my spouse and superiors, while I just take the privilege.”

REFERENCES
2. “Naive realism is the belief that we see reality as it really is (objectively and without bias); that the facts are plain for all to see; that rational people will agree with us; and that those who don’t are either uninformed, lazy, irrational, or biased.” Naive realism (psychology) [Internet]. 2015 [cited 2015 September 26]. Available from: https://en.wikipedia.org/wiki/Naive_realism_(psychology).
3. I have been administered anaesthetics and pain killers in hospital on at least three occasions. Always careful to avoid medical personnel of my history and to be accountable after release, I have not relapsed into self-used upon discharge.
4. Dr Alex Bassin, Professor of Criminology, Florida State University, formerly Chief Psychologist, New York State Supreme Court County of Kings.
5. Caffeine is an exception: I still drink coffee.
6. L’chaim Community Mental Health Center, Oakland, California (http://www.lacheim.org). For more information, contact Frances Slack Raeside, Clinic Director at frances@lacheim.org
Anaesthesia teaching for medical students

NATALIE ANNE SMITH, BSC(MED)HONS I, MBBS HONS II, FRCA (2003), FANZCA, POSTGRADCERTMED

Senior staff specialist, The Wollongong Hospital, NSW.

Dr Natalie Smith is a senior staff specialist at The Wollongong Hospital and an honorary clinical associate professor in the Graduate School of Medicine at the University of Wollongong. She has varied interests in both the practice of and research in clinical anaesthesia and medical education.

LOUISE ELLARD, MBBS, FANZCA

Staff anaesthetist, Austin Health, Victoria.

Dr Louise Ellard is a staff anaesthetist at Austin Health in Heidelberg Victoria. She is the co-ordinator of medical students in anaesthesia at Austin Health. She is also the joint co-ordinator for the airway training and mentor program. Her clinical interests include cardiac anaesthesia, liver transplantation and difficult airway management.

NAVEEDEEP S SIDHU, MBCHB, PGCERTHEALSC(RESUS), FANZCA, MCLINED

Consultant anaesthetist, North Shore Hospital, Auckland.

Dr Nav Sidhu is a consultant anaesthetist in the Department of Anaesthesia and Perioperative Medicine, North Shore Hospital, Auckland, NZ, and is a senior clinical lecturer in the Department of Anaesthesiology, University of Auckland, Auckland, NZ. His clinical interests are in regional anaesthesia and medical education and research.

MATTHEW JOHN OVERTON, BSCI HONS (NANOTECHNOLOGY), MBBS

Intensive care registrar, The Wollongong Hospital, NSW.

Dr Matt Overton is an intensive care registrar at The Wollongong Hospital. He is interested in pre-hospital care, critical care in the austere environment, airway management, anaesthesia in the critically ill and medical education.

INTRODUCTION

“The proposition that it is desirable to include in the curriculum prescribed by the General Medical Council the study of anaesthetics may appear too obvious for formal consideration.”

Dudley Buxton, On the advisability of the inclusion of the study of anaesthetics as a compulsory subject in the medical curriculum. BMJ, 1901.

In Australia alone, medical schools graduated more than 3,300 new doctors in 2013 – double the number of graduands from a decade ago1. Anaesthesia, critical care, perioperative and pain medicine are taught in most Australian and New Zealand medical school curricula to some degree. However, no uniform curriculum exists between universities, and no standardisation occurs for the relevant knowledge and competencies of graduating doctors.

In this article we provide answers to a number of questions that may be asked about anaesthesia curricula for medical student teaching.

THE QUESTIONS

What is the rationale for teaching anaesthesia and perioperative medicine in the undergraduate curriculum?

Anaesthetists possess a wide range of knowledge and skills and are well suited to teach a variety of topics that benefit all medical undergraduates. As well as clinical anaesthesia, they can provide training in areas such as cardio-pulmonary resuscitation, care of the critically ill, preoperative assessment, perioperative medicine, important procedural skills, acute and chronic pain management, and applied physiology and pharmacology. Anaesthetists are also well positioned to explore other themes including aspects of teamwork, multidisciplinary work, patient safety, ethics and professionalism2.

Previous studies have demonstrated deficiencies in knowledge and skills in many of these areas at an undergraduate and early postgraduate level3. Anaesthesia is the third largest hospital-based specialty in Australia and New Zealand but forms a very small proportion of the curriculum in most medical schools4,5.

What is the state of current teaching of anaesthesia and perioperative medicine in medical schools?

This is highly variable throughout Australia and New Zealand. In a recent survey to which anaesthesia representatives from 57 per cent of medical schools in the two countries responded, half of the medical schools had a formal anaesthesia curriculum in place6. Anaesthesia teaching occurs primarily in the senior clinical years of the course, with durations ranging from optional lectures to three to four weeks of formal teaching and clinical placement. Two schools offered additional elective teaching on top of their pre-existing curricula. Where no formal curriculum exists, some anaesthesia topics are taught in either critical care blocks, as student electives, or in conjunction with surgical terms and basic science lectures.
The current content focuses on knowledge and skills, mainly relating to airway management, pharmacology, life support, and intravenous fluids and cannulation. However, advances in technology and anaesthetic techniques are continually being developed. Many departments now use high-fidelity simulation as a teaching tool to enhance learning. This chapter will provide an overview of anaesthesia and perioperative medicine as a specialty, describe the roles of anaesthetists and other perioperative professionals, and discuss the education and training of medical students in this field. The chapter will also address the practical aspects of teaching medical students in anaesthesia and perioperative medicine, including the development of skills and competencies, the role of simulation in education, and the assessment of student performance.

What level of knowledge of anaesthesia and perioperative medicine do students possess?

There are no recent studies assessing knowledge of anaesthesia, nor simulation. However, recent studies indicate that medical students possess a basic understanding of anaesthesia and perioperative medicine. This understanding is likely to be influenced by their prior educational experiences and their exposure to anaesthesia and perioperative medicine. The level of knowledge possessed by medical students may vary depending on the institution and the programme of study.

Is there a place for high-fidelity simulation in undergraduate anaesthesia education?

High-fidelity simulation is a valuable tool for teaching medical students. It provides a safe and controlled environment for students to practice their skills, and it helps them to develop confidence and competence in airway management. However, high-fidelity simulation is not a substitute for clinical experience, and it is important that students also have opportunities to learn in the clinical setting. The use of simulation should be integrated into a comprehensive curriculum that includes a combination of teaching methods, such as lectures, tutorials, and practical sessions.

Therefore, the ideal teacher in anaesthesia is a motivated, interested, and experienced professional who is familiar with the needs of the students. He or she should have a good understanding of the subject matter and be able to communicate effectively with the students. This chapter will provide guidance on how to develop the skills and competencies required to be an effective teacher in anaesthesia.
Table 1. Content of an ideal anaesthesia student curriculum (reference 6)

<table>
<thead>
<tr>
<th>Area</th>
<th>Learning objectives</th>
</tr>
</thead>
</table>
| Perioperative medicine      | Preoperative assessment and preparation  
Assessment of comorbid conditions  
Exercise tolerance  
Management of medications preoperatively |
| Critical care               | Basic and advanced life support  
Recognition and management of the deteriorating patient  
Care of the unconscious patient  
Management of shock, hypovolaemia, hypoxia |
| Applied basic sciences      | Interpretation of standard blood test results  
Analgesic pharmacology  
ECG interpretation |
| Patient monitoring          | Oxygen administration and monitoring |
| Airway management           | Triple manoeuvre  
Bag-mask ventilation  
Nasopharyngeal airway insertion  
LMA insertion |
| Pain management             | Acute pain  
Multimodal analgesia  
Postoperative pain |
| Intravenous fluid management| Principles of fluid therapy  
Assessing fluid balance  
Prescribing fluids  
Blood transfusion – indications, precautions, side effects |
| Procedural skills to learn  | Intravenous cannulation  
Aseptic technique |
| (not covered above)         | Professional skills  
Recognition of need to ask for help  
Human factors and communication in an emergency setting  
Decision-making and teamwork principles |
| Ethical skills              | Consent principles  
Patient confidentiality  
End of life management  
Assessment and communication of risk |

Table 2. Lessons learnt/Tips for success

- One overall co-ordinator is essential for success of a medical student rotation to anaesthesia, especially in busy departments with large numbers of anaesthetists.
- Making students feel welcome is very important as the theatre environment is pretty daunting at first. We name the students on our weekly roster in individual theatres and provide an introductory morning and physical orientation to the theatre complex.
- Students need to have block time that is free from other distractions.
- Both students and anaesthetists need reminding that teaching should not focus on the specifics of anaesthesia. This needs reiterating at frequent intervals.
- Provide a list of learning objectives as a prompt to help guide teaching. For example, one of our in-theatre teaching sessions focuses on fluid management and transfusion medicine. A list of learning objectives for the student to initiate questions might include:
  - What are the major differences in composition of the different crystalloids?
  - What is the consequence of giving many litres of normal saline?
  - At what haemoglobin level is transfusion considered?
- Both students and anaesthetists need reminding that teaching should not focus on the specifics of anaesthesia. This needs reiterating at frequent intervals.

Source: Austin Health, Victoria

REFERENCES


Integrating CONSORT into journal clubs

CRAIG NOONAN, FANZCA
Deputy director, Department of Anaesthesia and Perioperative Medicine, Monash Health, Clayton, Victoria.

Dr Craig Noonan is an enthusiastic educator and is a deputy director at Monash Health, Clayton, where he has run a journal club for the past 12 years. He is a former examiner for the ANZCA Primary Examination, lectures on statistics and trial design for the ANZCA final course and is a member of the Victorian Regional Committee.

INTRODUCTION
Journal clubs are often activities that people think are good to establish but are limited by poor organisation, poor preparation and an unstructured process, which makes it unlikely for participants to leave the journal club with any sense of conclusion or ambition to change their practice. This article will present a fresh approach to conducting journal clubs with a discussion of a structured approach to reporting (and reviewing) trials and practical suggestions to improve participant satisfaction.

WHAT IS CONSORT?
CONSORT is an abbreviation for the Consolidated Standards of Reporting Trials, which is a checklist of items that should be included in the reporting of randomised-controlled trials to minimise bias or to allow better evaluation of trials.

In 1993, two groups in Canada and the US independently began developing lists of recommended items for inclusion within the reporting of randomised-controlled trials. In 1996, Drummond Rennie, a deputy editor at JAMA: The Journal of the American Medical Association, brought together representatives from each group to merge the best of these proposals into a single set of recommendations, initially published in 1996.

Further meetings have resulted in revisions in 2001 and 2010, with broadening of requirements to include “highly desirable” items, as well as “essential” items.

WHY IS CONSORT USEFUL?
The most recent CONSORT iteration includes 25 main items, with 12 divided into two sub-items. The items are grouped into headings of title and abstract, introduction, methods, results, discussion and other information. Each has been selected as a necessary inclusion to evaluate the trial or to reduce bias. Table 1 lists all of these. The rationale for inclusion has been detailed in an explanatory document first developed in 2001, and updated as part of each major review.

EXTENSIONS TO CONSORT
After the initial successful uptake as a reporting standard for randomised-controlled trials, the CONSORT group also has developed guidelines for cluster trials, non-inferiority and equivalence trials, pragmatic trials, herbal medicine interventions, non-pharmacological treatment interventions and acupuncture interventions. The group also has suggested improvements to the reporting of patient-reported outcomes, harms and abstracts.

Table 1. Consort 2010: Checklist of information to include when reporting a randomised trial

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>Item no</th>
<th>Checklist item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results and conclusions</td>
</tr>
<tr>
<td>Introduction</td>
<td>2a</td>
<td>Scientific background and rationale</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
</tr>
<tr>
<td>Methods</td>
<td>3a</td>
<td>Description of trial design, including allocation ratio</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Important changes to methods after trial commencement, with reasons</td>
</tr>
<tr>
<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
</tr>
</tbody>
</table>
LITERATURE ABOUT JOURNAL CLUBS

A journal club is a group of individuals who meet regularly to critically discuss the clinical applicability of articles in current medical journals. William Osler is widely acknowledged as having started the first journal club with the intention of sharing scant resources and translating best information of the day into clinical practice. In a review of the role of the journal club in medical education, Linzer notes that, over time, the teaching of critical appraisal skills has been added to the objectives. Critical appraisal is the process of carefully and systematically examining a research report to judge its trustworthiness, make sense of the results and assess the relevance of the findings in a particular context. Although value is placed on journal clubs by organisations, educators and learners and, given their ubiquity in learning environments, little research has been done on how these can best be conducted or what can be achieved within them.

Ebbert and colleagues (2001), from the Mayo Clinic conducted a systematic review of journal clubs and found seven papers worthy of inclusion. They defined benefit as effective for improving patient care, teaching critical appraisal skills, improving reading habits, increasing knowledge of clinical epidemiology and biostatistics, and increasing the use of medical literature in clinical practice. He found conflicting evidence of benefit. In his discussion, he lamented the lack of rigour in the evaluation of potential benefit. He also discussed the potential usefulness of a critical appraisal checklist in running the journal club.

In a later systematic review of medical journal clubs, Deenadayalan and colleagues (2008) found 12 papers of relevant quality for inclusion, with five of the seven papers from Ebbert. Effectiveness was defined by improving knowledge and critical appraisal skills. Much of the outcome data is favourable but relies on self-reporting of perceived improvements in related skills. From this review, Deenadayalan made a number of recommendations to improve the quality of journal clubs. These are summarised in Table 2.

Table 2. Summary of recommendations from Deenadayalan

- Members should be the same discipline or have similar interests.
- Establish an overarching goal, which should be reviewed regularly.
- Establish the purpose of each meeting, link this to paper or skill acquisition.
- Attendance should be an expectation and be recorded.
- Conduct meetings at regular, predictable intervals, probably monthly.
- Conduct at appropriate time of day.
- Consider including food.
- Leaders increase effectiveness.
- Leaders should choose articles, with input from members.
- Train the leader in relevant research design and/or statistical knowledge.
- The leader can change from meeting to meeting, tension between authority and expertise/knowledge.
- Provide access to statistician for support for leader.
- Choose relevant case-based or clinical articles.
- Provide all participants with pre-reading at a suitable time period.
- Use internet as medium for distribution, maintaining resources.
- Use established critical appraisal approaches, and structured worksheets.
- Formally conclude each journal club by putting the article in context of clinical practice.
STRUCTURING AN APPROACH

With both reviews highlighting the need for a checklist to guide inquiry and evaluation, the question is which checklist to use? Although various checklists exist, none have the broad base of support that CONSORT does. However, using a list of 37 items is cumbersome and makes grasping the overall worth of the article much more difficult. Using summary questions to guide the evaluation makes the process seem manageable and achievable. There are four principal aspects to a study:

1. Why was it done?
Justification needs to be provided in the introduction section that the study is original, is based on scientific evidence and is a significant issue worthy of the effort of investigation.

2. How was it done?
Evaluation of the methodology includes understanding the design, and that steps have been taken to reduce bias and the planned statistical analysis.

3. What did it show?
The number of participants that were eligible, approached, recruited, randomised, treated and evaluated should be seen.
An understanding of the primary and secondary outcomes is necessary, and the principles of the analysis.

4. What relevance is it?
What this study shows in the context of the broader literature.
By adding a question on relevant aspect of statistics or trial design, the aim to foster improved understanding of this area is addressed.

WHY THESE QUESTIONS?
These questions align with the major domains of the CONSORT criteria and provide a framework to guide initial inquiry and discussion. They are brief enough to remember and still address the major aspects of the article. The detailed CONSORT criteria within each area can be used to amplify answers to these questions. The explanation and elaboration document that accompanies CONSORT provide a wealth of information about trial design and reporting. All of these are recommended to the reader to consider incorporating into journal clubs.

REFERENCES
Getting serious about research: measuring outcomes that matter

MULLEIN THORLEIFSON, BSC, MD, FRCP

Dr Thorleifson is a Fellow in cardiothoracic anaesthesia at the Department of Anaesthesia and Perioperative Medicine, The Alfred hospital, Melbourne, after having completed training in Canada.

MARK SHULMAN, MB, BS, BMEDSCI, MPH, FANZCA

Dr Shulman is a staff anaesthetist at the Department of Anaesthesia and Perioperative Medicine, The Alfred hospital and Monash University, Melbourne. His research interests include preoperative risk stratification and postoperative patient-centred outcomes.

INTRODUCTION

Anaesthesia and perioperative medicine research trial design has evolved; large, well-designed randomised controlled trials (RCTs) are now commonplace. For these trials to make a meaningful contribution to our practice, they must ask important clinical questions, and measure outcomes that are meaningful to clinicians and patients alike. As outcomes such as mortality and stroke are rare, investigators often use surrogate or composite outcome measures to reduce the sample size needed to adequately power a trial. The results of such trials can be difficult to interpret and apply to the clinical setting. The trials of the future should use patient-centred outcome measures, such as disability-free survival, to provide meaningful outcome data in appropriately sized clinical trials.

THE EVOLUTION OF ANAESTHETIC RESEARCH

Early anaesthesia research concerned the efficacy of novel anaesthetic agents such as nitrous oxide, ether and chloroform. These observational experiments were conducted on patients, colleagues or the investigator themselves. In 1844, dentist Horace Wells submitted himself to having his own wisdom tooth extracted by Dr John M. Riggs while nitrous oxide was administered by Gardner Quincy Colton. Impressed, Wells used nitrous oxide to provide painless dentistry for his patients until his failed demonstration of the anaesthetic properties of nitrous oxide in Boston the following year1. Notwithstanding this initial setback, there was near-universal adoption of nitrous oxide into anaesthetic practice, but it would be 163 years before large, well-designed randomised controlled trials would investigate the drug’s safety2,3.

In 1920, Guedel documented the eye signs of ether anaesthesia in The American Journal of Surgery4. This was the first of many small observational studies into the physiological and pharmacological effects of anaesthesia that dominated the literature for many years. Most of these studies were performed on a small non-random sample of volunteers and have never been repeated on a larger scale. Despite this, these seminal papers continue to be referenced in common texts and have formed accepted anaesthetic dogma. For example, our understanding of the alterations of respiratory mechanics due to surgical positioning is based on one study involving 10 patients5.

A notable example of accepted dogma failing to translate to clinical outcome can be found in the area of blood transfusion. Until relatively recently, anaesthetists (and other clinicians) believed that blood transfusion was inherently good for patients. We transfused blood in a liberal manner to improve oxygen delivery to tissues. It wasn’t until 1999, when the TRICC (Transfusion Requirements in Critical Care) trial demonstrated no difference in survival with restrictive (haemoglobin goal of 7-9 g/dL) versus liberal (haemoglobin goal of 10-12 g/dL) transfusion in critically ill patients that our practices changed.6 Another recent example is the ABLE trial, which examined the common belief that older blood is associated with poorer outcomes. In fact, no outcome differences were discovered7.

Anesthetists, like other clinicians, were prone to adopting new technologies, drugs, or practices after early studies showed promise and the basic science seemed to make sense. Often these studies were industry sponsored and therefore biased towards favourable results8. Other small clinical studies showed surprisingly large treatment effects and guided clinical practice until subsequent large trials showed conflicting results. An example of this was the recommendation by perioperative guideline committees of beta-blockers for high-risk cardiac patients undergoing non-cardiac surgery9.

The quality of anaesthesia trials has improved over the past three decades10,11, with the recognition of the importance of large multi-centre randomised controlled trials (RCTs) in anaesthesia and perioperative medicine12,13. These trials are considered to provide the highest level of evidence for a single trial. The first anaesthetic trial of this type in Australia was the MASTEr trial, which evaluated epidural analgesia versus intravenous opioids for major abdominal surgery. Contrary to popular belief, this trial demonstrated no reduction in mortality or major complications in patients that received an epidural and significantly changed anaesthetic practice around the world14.

With the growth of anaesthetic research, large groups such as the Australian and New Zealand College of Anaesthetists Clinical Trials Network have been established to answer important clinical questions through collaboration between researchers and large multi-centre studies. As research funding and resources are finite, it has become increasingly important to justify the quality and value of our trials. It is therefore essential that future research conducted by these groups is designed to answer important clinical questions and measures outcomes that provide clear and meaningful answers.
With the expanding role of the anaesthetist as a perioperative physician, there has been a change in focus to the preoperative and intraoperative management strategies that affect short-and long-term postoperative outcomes. In this framework, trials have been designed to answer an important clinical question where genuine equipoise exists. These questions must be important to both clinicians and patients and focus on long-term outcomes. Ideally, they should also be appealing to healthcare systems and be easily understood by funding bodies. In order to address this issue, the Research Council of the National Institute of Academic Anaesthesia in the United Kingdom published a document that endeavoured to determine research priorities in anaesthesia. The suggestions were organised by a panel of representative and varied clinicians, as well as research experts, into a list of 14 key questions in anaesthesia (Table 1).

### Table 1. Research priorities for anaesthesia and perioperative medicine*

<table>
<thead>
<tr>
<th>What interventions can prevent perioperative cardiac complications?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does a brief period of preoperative exercise training improve outcomes after major surgery?</td>
</tr>
<tr>
<td>What perioperative management strategies improve outcome in head injury?</td>
</tr>
<tr>
<td>What interventions prevent the development of chronic pain after surgery?</td>
</tr>
<tr>
<td>Does an enhanced perioperative care package improve outcome?</td>
</tr>
<tr>
<td>Under what circumstances should aspirin be discontinued in the perioperative period?</td>
</tr>
<tr>
<td>Would actively targeting preoperative blood pressure in the intraoperative period reduce the incidence of postoperative complications?</td>
</tr>
<tr>
<td>Does conventional (as opposed to tight) glycaemic control improve perioperative outcome?</td>
</tr>
<tr>
<td>What is the place of “anti-neuropathic” pain medications in the treatment of postoperative pain?</td>
</tr>
<tr>
<td>What are the best arrangements for the preoperative assessment of elective surgical patients?</td>
</tr>
<tr>
<td>Would higher nurse-to-patient ratios during the first 48 h after operation reduce the complication rate after major abdominal surgery?</td>
</tr>
<tr>
<td>What is the impact of same-day surgery on primary care?</td>
</tr>
<tr>
<td>How should patients for day surgery and 23 h surgery be selected?</td>
</tr>
<tr>
<td>Does the use of local or regional anaesthesia prevent cancer recurrence?</td>
</tr>
</tbody>
</table>

*Reproduced from Howell et al.17*

These questions are framed around clinical questions rather than basic science. That is not to discount the importance of understanding the genetic, cellular, physiological and pathological processes that contribute to disease. But rather, as Devereaux et al. argue, basic science research is “not designed to guide patient care, preventive strategies, or health policy decisions”. They cite the example of minilith, an inductor previously used by cardiologists to treat heart failure. Evidence from a small (n = 12) physiological study showed that minilith increased exercise capacity by 22 per cent in patients with cardiac failure. However, a subsequent RCT (n = 1,088) demonstrated that minilith increased mortality by 28 per cent relative to placebo. This example also demonstrates the importance of using the right outcome measure. In the first small trial the assumption was made that patients with increased exercise capacity must have improved cardiac function and were therefore more likely to survive. The second, larger study was powered to detect a difference in survival, the real outcome of interest in this case.

### OUTCOMES WORTH MEASURING

With more than 230 million major surgical procedures being performed annually, adverse patient outcomes following major surgery are considered a global public health issue. When designing a perioperative clinical trial, choosing the ideal outcome measure can be challenging. Funding and other practical limitations may preclude measurement of the outcome that seems most important. Despite this, researchers must ensure that the primary outcome measure of a study responds to the real question that is asked. Fisher described the phenomenon of surrogate outcome measures in research involving post-operative nausea and vomiting and diminished quality of life after surgery as a result of using the right outcome measure. In the first small trial the assumption was made that patients with increased exercise capacity must have improved cardiac function and were therefore more likely to survive. The second, larger study was powered to detect a difference in survival, the real outcome of interest in this case.

### PATIENT-CENTRED OUTCOME MEASURES

Patient-centred outcome measures are commonly used to monitor disease progression and response to treatment from the patient’s perspective. These outcomes focus on the quality of life the patient experiences, rather than the patient’s biological or functional status. That is not to discount the importance of objective, physiological measures (e.g. mortality, non-fatal MI and non-fatal cardiac arrest). However, there were significantly higher rates of stroke and death in patients taking metoprolol. How do we weigh these conflicting results? Is it likely that few patients would accept a lower risk of MI at the cost of a higher risk of stroke, but to answer this question one must view the outcomes from the patient’s perspective. It is essential to know the degree of long-term disability that patients experience as a result of the MI or stroke. To measure this, a patient-centred outcome measure must be used.

Prior to use in a clinical trial, patient-centred outcome measures need to undergo rigorous evaluation in the intended population and for the intended clinical situation. In a systematic review, the only instrument designed to measure quality of recovery that fulfilled all criteria was the 40-item Quality of Recovery score (QoR-40). The QoR-40 is a measure of global recovery that assesses five domains of wellbeing: emotional state, physical comfort, psychological support, physical independence and pain. It has been modified for use in different cultures and languages since its original publication. A shorter version of the QoR-40 was validated – the QoR-15, utilising only 15 of the 40 questions previously asked. This version was completed in an average of 2.4 minutes, compared with about five minutes for the QoR-40, making it more efficient and clinically acceptable, while retaining its excellent reliability and responsiveness.
Table 2: Eight questions that need to be addressed in relation to a patient-centred outcome measure being considered for a clinical trial

<table>
<thead>
<tr>
<th>Question</th>
<th>Consideration</th>
</tr>
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<td>1) Is the content of the instrument appropriate to the questions that the clinical trial is intended to address? ( Appropriateness)</td>
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<td>2) Does the instrument produce results that are reproducible and internally consistent? (Reliability)</td>
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<td>3) Does the instrument accurately measure what it claims to measure? ( Validity)</td>
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<td>4) Does the instrument measure changes over time that matter to patients? (Responsiveness)</td>
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<td>5) How precise are the scores of the instrument? (Precision)</td>
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<td>6) How interpretable are the scores of the instrument? (Interpretability)</td>
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<td>7) Is the instrument non-invasive and acceptable to patients? (Acceptability)</td>
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<td>8) Is the instrument easy to administer and process? (Feasibility)</td>
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*Adapted from Fitzpatrick et al*14

The QoR-40 and QoR-15 are designed to evaluate short-term recovery from surgery. While a good recovery after cardiac surgery, as measured by the QoR-40, is associated with increased quality of life over three years postoperatively, the QoR-40 was never designed to measure medium to long-term outcomes after surgery. In the past, quality-of-life measures such as the SF-36 have been used to assess global patient health following surgery and to measure longitudinal changes in overall patient wellbeing in the months following surgery. Quality-of-life instruments can range from a spectrum with no discrete cut-off point for “good” quality of life versus “poor” quality of life and no ability to define an adverse outcome or disability. As a result, they cannot be dichotomised for use as an end point in a clinical trial.

Disability is a concept that has meaning to patients and clinicians alike and is defined by the World Health Organization (WHO) International Classification of Functioning, Disability and Health as “difficulties in any area of functioning as they relate to environmental and personal factors”14. A tool that examines postoperative disability should not simply measure the presence or severity of symptoms, but should also seek to evaluate the impact of these symptoms on the patient’s daily functioning and ability to participate in the usual activities of life.50. Until recently, no instrument had been used to measure disability in perioperative medicine. Shared language around patient-centred outcomes allows us to clearly share information and learn from others’ experiences. In this way, the measurement of postoperative disability is an ideal method for clinical audit and quality assurance, an area of research that is often dominated by process measures.

Perioperative medicine is a growing field in which anaesthetists are seeking to find a leading role in studies. Alternatively, for observational studies with a heterogeneous group of patients, it may be more practical to measure disability-free survival as the percentage of participants who were both alive and had a WHODAS score of <25 per cent from the preoperative state, thus providing two dichotomous outcomes. Further, they defined disability-free survival as the percentage of participants who were both alive and had a WHODAS score of <25 per cent at a given time point after surgery.

Disability is also an ideal outcome in perioperative research because it is common. In the above study, 27 per cent of participants had WHODAS-defined disability preoperatively, with disability persisting in 22 per cent of participants at three months and 18 per cent at six months. New disability, which persisted to 12 months after surgery, was present in 13 per cent of participants. The relative frequency with which clinically significant disability occurred suggests that future studies could be designed to achieve adequate statistical power with modest sample sizes.

Measurement of disability-free survival is an attractive concept. Unlike health-related quality-of-life measures, which exclude non-survivors from analysis, this binary outcome measure includes all trial participants. In this way, it can be used as a single primary end point, or participants can be followed in the medium to long-term for survival analysis. Disability-free survival may be a particularly useful end point in trials in which participant groups have a similar baseline rate of disability and one wants to determine the effect of therapy. Alternatively, for observational studies with a heterogeneous group of patients, it may be more practical to measure the rate of new or significantly increased disability.

Going forward, it is important that the understanding and definition of disability should be consistent across future studies in perioperative medicine. Shared language around patient-centred outcomes allows us to clearly share information and learn from others’ experiences. In this way, the measurement of postoperative disability is an ideal method for clinical audit and quality assurance, an area of research that is often dominated by process measures. Perioperative medicine is a growing field in which anaesthetists are seeking to find a leading role in studies.

REFERENCES

Combining clinical judgment and formalised risk assessment techniques in anaesthesiology: Lessons from bushfire emergency management

NICHOLAS B DE WEYDENTHAL, BA, MENV
Doctoral candidate, University of Melbourne, Melbourne.

Dr Nick de Weydenthal is a doctoral candidate based in the School of Historical and Philosophical Studies with an affiliation in the Department of Management and Marketing at the University of Melbourne. His current research concerns practices of risk and organisation in environmental and emergency management.

BRUCE HEARN MACKINNON, BEC, LLB, MCOM, PHD
Senior lecturer in management, Deakin University, Melbourne.

Dr Bruce Hearn Mackinnon is a senior lecturer in management with the Department of Management at the Deakin Business School, Deakin University. His research integrates industrial relations, business strategy and critical management.

GRAHAM SEWELL, BSC, PHD
Professor of management, University of Melbourne, Melbourne.

Dr Graham Sewell is professor of management in the Department of Management and Marketing, University of Melbourne. He is best known for his research into the psychological and social effects of surveillance.

INTRODUCTION
The underlying thinking in bushfire management has much to offer anaesthetists. Although it is imperative to develop improved methods of predicting the risk of perioperative patient morbidity and mortality, we must avoid them being used in a way that can undermine both individual clinical judgment on a case-by-case basis and the effectiveness of the methods themselves. This requires all concerned to be aware of the reliability and validity of the algorithms used to provide such predictions as well as the quality of the data upon which they are based. Like fire behaviour analysts, anaesthetists should still be free to trust their knowledge, expertise and experience. When experienced fire fighters sense a conflict between what the evidence on the ground is telling them and what a predictive fire map is saying, they use their understanding of limitations of the fire analysts’ predictions to inform their own professional judgment.

IS THERE A TENSION BETWEEN PROFESSIONAL JUDGMENT AND FORMALISED RISK ASSESSMENT?
Anaesthesia is a necessary feature of most surgical procedures and poses various risks to the patient. Most perioperative complications directly attributable to the administration of anaesthesia are relatively minor (for example, oral injury) but it can contribute to critical incidents that quickly become life-threatening. Of these, more critical incidents, cardio-respiratory complications such as myocardial infarction, are the most common cause of perioperative mortality for patients undergoing non-cardiac elective surgery. This is not to discount that a complex mix of factors also can contribute to perioperative patient morbidity. This complexity makes it difficult for anaesthetists to make precise and accurate patient risk assessments prior to surgery and it is usually left for them to exercise their clinical judgment on this matter. This requires the anaesthesiologist to draw on their prior knowledge and general cognitive abilities, as well as their understanding of the immediate clinical situation, to develop a risk assessment for individual patients. This is frequently an intuitive and ad hoc decision-making scenario and, as such, researchers have begun to focus on human decision-making theory and the behavioural sciences to understand the way in which errors and cognitive biases affect individual anaesthesiologists’ clinical judgments. In parallel with this focus on “end-of-the-bed” judgment, important advances are being made in developing a systematic understanding of anaesthesia risk factors that can be translated into formal risk-assessment techniques and decision-making rules that go well beyond the ASA’s basic patient physical status classification system. Anaesthetists can then selectively apply such techniques and rules — for example, P-POSSUM — as part of the surgical team’s overall preoperative risk assessment activities. This increasingly common hybrid risk-assessment scenario in anaesthesiology — a combination of individual professional judgment (with all its potential biases and cognitive errors) and formalised techniques — has long been a common feature of emergency management and we draw on our research in this area to map out lessons for anaesthetists concerned with improving long-term patient outcomes following surgery.

The opposition between subjective professional judgment and objective formalised techniques is at the heart of conventional approaches to risk, whether in medical practice or emergency management. Since the notion of risk is posed in terms of consequence and likelihood, the logic with which one is to think and deal with risk is usually treated as being probabilistic in nature. On probabilistic grounds, the tension between subjective judgment and objective analysis plays out in the selection of either Bayesian or frequentist approaches. The former is based on a person’s perception of a situation and is measured in terms of degrees of belief. The latter is based on objective causal relations that lead to events that occur at relative frequencies. However, what we have found in our research of bushfire emergency managers is that they face a practical situation where the opposition between subjective and objective assessments of risk are much more ambiguous. Thus, what we want to draw attention to is not...
The practice of fire behaviour analysis is not new: It grew out of decades of forestry science and has been steadily incorporated into the emergency services as a way of managing risk. In the catastrophic Victorian bushfires of February 2009 and the subsequent Royal Commission inquiry has led Victoria to develop more formalised risk assessment techniques in anaesthesiology and environmental management. In clinical practice, the activity of symptomatology is traditionally followed by aetiology (establishing the cause of disease), followed by therapy (treating the illness). While most attention is directed to aetiology and the activities that follow, we forget that all these steps are subordinated to symptomatology. It is after the symptoms that they split from clinical practitioners. Whereas a meteorologist, for example, would be interested in the cause of wind change, the fire behaviour analyst tasked with predicting the spread of a fire front is not directly concerned with this. The analyst wants to move straight to the diagnosis (that is, to predict where fires are likely to unfold), and then to the intervention (that is, to suppress fires and mitigate these situations). As we shall see below, the way in which fire behaviour analysts do symptomatology leads them to skip the aetiological stage and go straight from symptoms to diagnosis. This move engenders new problems down the line for fire fighters and other emergency responders. These activities have been the focus of our study of fire behaviour analysis as they have developed formalised risk assessment techniques and we use this to draw lessons for risk management in anaesthesiology and, potentially, other areas of clinical practice.

WILL DEPICT FORMALISED RISK ASSESSMENT TECHNIQUES IN ANAESTHESIOLOGY?

From a risk management perspective, we would consider the rationale for developing formalised risk assessment techniques in anaesthesiology as follows. In clinical symptomatology, the clinician considers an array of indicators (that is, symptoms) over establishing underlying cause. It is only by making a holistic assessment of these signs, a diagnosis, that the clinician is able to proceed with prognosis and therapy on the basis of a symptomatological model. In other words, what the clinician is interested in is not just the identification of symptoms, but their potential relationship to each other and to other clinical conditions. This is in contrast to the approach used in the calculation of probabilities with regards to the spread of bushfires (although this is of great technical importance to specialist risk analysts), but rather how the mere presence of such predictions engenders new problems down the line for fire fighters and other emergency responders. These activities have to exercise their professional judgment in real time and in the face of real dangers? In short, we are interested in the practical implications of placing unjustified confidence in a number that is, at best, a rough estimate and, at worst, potentially a misleading one.

In order to draw a relevant link and explore the resonances between risk assessment in such apparently divergent disciplines as anaesthesiology and environmental management, we adopt a symptomatological approach. Although such an approach is familiar in clinical practice, its application in environmental management risk assessment is novel. By virtue of being preoccupied with the study of signs in general, and not necessarily medical ones, symptomatology presents an interesting point of convergence and divergence between medicine and environment management. In clinical practice, the activity of symptomatology is traditionally followed by aetiology (establishing the cause of illness) and therapy (treating the illness). The former is of great technical importance to specialist risk analysts, but rather how the mere presence of such predictions engenders new problems down the line for fire fighters and other emergency responders. These activities have to exercise their professional judgment in real time and in the face of real dangers? In short, we are interested in the practical implications of placing unjustified confidence in a number that is, at best, a rough estimate and, at worst, potentially a misleading one.

Contrasting Medical Risk and Environmental Risk

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From an analysis of these data, PHOENIX-RapidFire simulates the most likely ignition point and subsequent course of a fire, thus providing critical information for emergency management agencies to plan their most effective responses. Although this approach is highly formalised and gives the impression of being precise and accurate, use makenock it this relate to the rationality of the process. For example, the data on which the model is based is still based on individual expert judgment. Second, and as a corollary of the first point, there is still plenty of scope for those experts to disagree on the levels of fire risk factors. Third, there is also plenty of scope for each expert's reasoning about how PHOENIX-RapidFire program differentiates between predictive and descriptive techniques, the final point is most evident in the potential conflict between those agencies charged with protecting assets, such as when it must be decided whether to divert resources to protecting private housing at the expense of protecting public infrastructure.

Taking these three points together, we draw our first important lesson for anaesthetists and other clinicians. Even before PHOENIX-RapidFire was put into operation, it was evident to us that it was beginning to take on a status of infallibility that belied the contestable character of the data upon which its predictions were based. In some ways, there was a risk that emergency managers might begin to expect the algorithm to be the end of the line, but also as part of a quality control process by the statistical office. Similarly, anaesthetists must be conscious of the limitations of formalised risk assessment techniques as they go about exercising clinical judgment. From this observation, we go on to consider how the implementation of PHOENIX-RapidFire impacts on the decision-making activities of emergency management experts, who came to rely on its predictive capacities.

PHOENIX-RAPIDFIRE IN USE

As part of their routine practice in emergency management during the Victorian fire season (October-April), fire behaviour analysts now draw on PHOENIX-RapidFire and other models to produce three products: 1) An hour-by-hour map detailing the progression of a fire; 2) A more general map based on a 24-hour progression of the fire; and, 3) a fire-prediction report. All three can be viewed on computers and portable handheld devices. The detailed map is distributed among planners in the emergency services to help with allocating resources. The generalised map, which shows the fire front with a dashed line, is passed to the media for public messaging. The dashed line is used to display a fire that could progress within 24 hours (its level of precision intentionally lower than that produced by the program). The prediction report documents the caveats and assumptions made by the analysts in outlining what data was used, how it was used and whether there are any doubts regarding its accuracy. Importantly, the assumptions are documented, not only for scientific purposes of understanding the correlation between modelling and fire, but also as part of a quality control process by the statistical office. Planning of the emergency and resource allocation are intricately tied to the fire maps so changes in prediction need a trail for accountability purposes.

As part of this process, data are entered into the PHOENIX-RapidFire algorithmic modelling program in real-time. The constant assimilation of real-time information and collation with algorithmic modelling still requires, in the words of one analyst that we interviewed, “some sort of truthing or validation sort of process” to filter out the noise. The quantities of data collected during an event are so copious that they require parsing to pick out the syms most relevant to an adequate mapping of the fire, using the program more as a heuristic device that informs their expert judgment rather than a definitive predictor of its future progress. Incoming data are usually delayed and of poor quality, so predictive mapping often becomes experimental. This runs contrary to the expectations of other emergency experts who are less aware of the program’s data limitations and who, therefore, take its outputs to be observations rather than predictions. For example, in the event that a fire-fighting aircraft loses sight due to thick smoke, emergency managers expect the analysts to be able to immediately situate the fire and the potential impact it could have on the population. The PHOENIX-RapidFire tool could help and they will stop their current operation even if “it’s [not] the smartest thing to do”, according to the analyst. This analyst claims that water and trucks are not going to make much of a difference in those few hours, but reliable and accurate information that can be accessed and used will. Though they caution that “you have to be aware that not everyone is going to use that information wisely”, informing the public is impossible in their opinion, because the lack of intelligence prevents you from effectively fighting the fire, let alone giving reliable forecasts.

In the heat of the moment, risk assessments are not formalised explicitly in a matrix or metric, as is commonly recommended by risk management standards. While our informant suggests that risk calculation is still happening in people’s heads, fire behaviour analysts have formalised this assessment to some extent when they provide predictions that could help in reallocating and repositioning resources. They state “it’s very hard to get strategic thinking during an incident, especially in a rapidly evolving incident, but some operations will be undertaken with a probability of success at zero almost. So, they propose to stand back, wait and then apply resources to achieve a better outcome when, for example, the “main heat of the fire has dissipated and we’ll be able to work those crews for longer into a period of time when they can be more productive”.

CONCLUSIONS AND IMPLICATIONS FOR ANAESTHETIC PRACTICE

We have seen how the fire behaviour analysts work as diagnostics or “clinicians” of fire. By juxtaposing a set of signs and symptoms with past experience and accumulated knowledge, they produce a diagnosis which is then used to provide such predictions as well as the quality of the data upon which they are based. Like fire behaviour analysts, other emergency management professionals, anaesthetists should still be free to trust their professional judgment. The complication of taking the mapped prediction for the real fire is further compounded with the advanced visualisation and animation tools used in emergency management, the danger of an icon is that it is followed to the letter, even when it goes against the judgment of the expert using it. Fire behaviour analysts who produce the fire maps are aware that all the data going into the PHOENIX-RapidFire is not of equal quality and they recognise the fallibility of their predictions. They are, nevertheless, useful if applied the right way and with the appropriate degree of questioning. Once they get visually represented in the field, however, there is a real danger they become icons, where experts and decision-makers take the representation of a predicted fire front on a map to be the fire front itself. The consequences could be such that resources are allocated to fighting a fire located on the map in one place and met in actuality in another. Similarly, messages could be broadcast misinforming the population as to the amount of time they have to evacuate. These consequences could lead to disaster.

Our principal lesson for anaesthetists follows the same logic. Although it is imperative for us to develop improved methods of predicting the risk of perioperative patient morbidity and mortality, we must avoid them becoming iconic and useless in the same way that can undermine both the individual clinicians and the true quality of the methods themselves. This requires all concerned to be aware of the reliability and validity of the algorithms used to provide such predictions as well as the quality of the data upon which they are based. Like fire behaviour analysts, other emergency management professionals, anaesthetists must treat their knowledge, expertise and experience with the same degree of fallibility as is currently demonstrated by those experts. This calls for a critical assessment of both the methods themselves and the observers who use them.

Expectations are unrealistic because people do not fully understand the process. The same informant adds: “...on some occasions some of our predictions are pretty good so you can use them in lieu of the truth, if you like, until you verify that the perception is true. We are past a time when you get used beyond what ... the truth really is ... and we’ve got even a bigger problem with our computer modelling that we now use, because it looks so realistic and detailed that it could only come from a real fire” (emphasis added).

Concluding remark: That we now use, because it looks so realistic and detailed that it could only come from a real fire".

With a computer-generated map, “it creates an impression of being more credible than it deserves”. To deal with this, analysts have realised the implications and “go through a smoothing routine to take out some of the detail ... to roughen it up a bit”. In other words, they intentionally act to reduce the maps’ apparent authenticity so they are not interpreted literally. All the same, this is a much more serious problem than the obvious impression indicated this process involved uncertainties. This is why, today, a dashed line is still used for public communication to indicate that the fire is likely to be within a boundary but that the boundary is not the boundary of the real fire. In contrast, the PHOENIX-RapidFire program can be considered to be a map that is not a map, that is, that the visual map is distributed electronically, it loses that explanation and opens the possibility for misinterpretation.

As incidents start, resources are mobilised, allocated and committed. If a critical decision is to be made whether to provide resources from one incident to another, a strong argument grounded in more accurate data is needed. Importantly, our informant asserts that resources are not allocated “based on where they’re going to reduce the risk the most”. They believe the current culture in emergency management is reactive rather than proactive and strategic. Senior emergency services managers are aware of the predictive services’ work, but are not interested because other words managers do not affect emergency managers too much since they lack resources. So they would not possibly be enough help and they will stop their current operation even if “it’s [not] the smartest thing to do”, according to the analyst. This analyst claims that water and trucks are not going to make much of a difference in those few hours, but reliable and accurate information that can be accessed and used will.

Ideally, the goal of fire behaviour mapping can be simply stated as follows: it is to index risk. That is, the map of the fire is used to store the history of the fire, such that the users can access the data and use it. Though they caution that “you have to be aware that not everyone is going to use that information wisely”, informing the public is impossible in their opinion, because the lack of intelligence prevents you from effectively fighting the fire, let alone giving reliable forecasts.

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REFERENCES
The big question in veterinary anaesthesia

JENNIFER E CARTER, DVM, MANZCVS, DACVAA
Lecturer, University of Melbourne Faculty of Veterinary and Agricultural Sciences. Dr Jennifer Carter’s current interests include pain practice and education for students, nurses, and practitioners. She is also interested in debunking some of the long-standing myths of veterinary anaesthesia.

LEON N WARNE, BSC(BIOL), BBIOMEDSCI(HONS1), BSC(VETBIOL), BVMS, MVS
Clinical anaesthetist, post-graduate researcher, University of Melbourne Faculty of Veterinary and Agricultural Sciences. Dr Leon Warne’s current clinical interests include perioperative pain management in cats and wildlife anaesthesia.

INTRODUCTION

Intentionally causing pain to another human, in particular children, is regarded as one of the most socially abhorrent of actions. Similarly, painful procedures performed on animals are among the most emotive of public concerns. The commonality here lies in the notion of protecting the vulnerable. Indeed, it has been said that many of the greatness of a society is judged on the basis of how it treats its weakest members.

Approaches towards treatment of pain in children are still evolving, with some arguing about the importance of pain in infants less than a year of age. Similarly, up until the late 1980s the majority of animal researchers were not providing analgesia to laboratory animals following invasive surgical procedures. Unfortunately, these disparities in the diagnosis and treatment of pain continued into the 1990s, with two major studies from tertiary teaching hospitals demonstrating significant institutional inadequacies in the teaching and clinical management of pain in veterinary patients. Despite the aforementioned inadequacies, attitudes regarding pain and suffering in animals have shifted considerably in recent years. Most people involved with animals of any kind would have no hesitation in stating categorically that animals experience pain. The ethical aspects as well as the morbidity associated with acute and chronic pain lead more veterinarians to focus on the treatment of pain and implement defined, goal-orientated approaches to pain therapy. In accordance with the Veterinarians’ Oath, each member admitted to our profession pledges to “… use my scientific knowledge and skills for the benefit of society through … the relief of animal suffering…” However, even when we acknowledge the potential for animals to experience pain, appropriate treatment does not always follow. The most recent information of this type comes from surveys of the veterinary profession in France. These questionnaires established that the majority of respondents (95 per cent) were “moderately or extremely concerned about recognition and alleviation of animal pain”. However, for cats and dogs, analgesic use by respondents ranged from a high of 84 per cent following orthopaedic surgery to a low of only 17 per cent following castration. The primary reasons provided for a lack of analgesic treatment were “difficulties in recognising pain” and “lack of knowledge about appropriate therapy”, highlighting the need for further research and training in this area.

THE PRE-EMPTIVE (ASSUMPTIVE) APPROACH

Pain in man is recognised as having both a sensory and an emotional component. Treatment of pain must be tailored to the individual animal and should be based, in part, on the species, breed, age, procedure performed and degree of tissue trauma, individual behavioural characteristics, degree of pain, health status and availability of drugs and techniques. It is generally assumed that if a procedure is painful in human beings, then it must also be painful in animals. However, while it may be useful to draw such parallels between humans and animals, the severity of the pain experience produced by various procedures is not always similar. Because it is difficult to compare the experience of pain in animals to that in humans, it is preferable to empirically administer analgesics pre-emptively if there is any question as to whether a procedure will induce pain in an animal patient.

In addition to measures directed towards alleviating or preventing pain, it is important to consider the overall care of the animal and the prevention of distress. The term “distress” is used in this context to describe conditions that are not in themselves painful, but are unpleasant and which the animal would normally choose to avoid; for example, emotional pain, such as the fear associated with recovering from anaesthesia in an unfamiliar environment. For the veterinary patient, which is essentially a non-consenting patient, lacking cognisance of the intervention or procedure they have received, the emergence from anaesthesia and the recovery period can elicit a great degree of distress and anxiety. The veterinary anaesthetist needs to diligently ensure that the recovery environment is such so as to minimise this. In addition to the use of an opioid, the incorporation of a sedative component (typically phenothiazine or alpha-2 agonist) to the premedication is routinely used to reduce perioperative distress and anxiety.

PROBLEMS SURROUNDING THE ASSESSMENT OF PAIN IN VETERINARY PATIENTS

Much as with human medicine, veterinary medicine lacks any major international governing body and, as such, no international standards for pain assessment. While this could be easily taken on by individual national veterinary authorities or associations, such as the Australian Veterinary Association or the American Veterinary Medical Association, these organisations tend to produce very generic policy to govern their members, most stating only that practitioners should look for pain and provide analgesia without any guidelines for the provision of such activities. In addition to this, although it is widely accepted that veterinary patients experience pain, there are no set guidelines or principles followed in the formal education of veterinarians, much less veterinary nurses, on the recognition and treatment of pain.
Pain scales are utilised commonly in human medicine and attempt to provide a measure of the subjective experience of an individual. They vary in complexity as well as accuracy. Translating a human pain scale for use in veterinary patients presents one obvious barrier; human pain scales are designed in a way such that the person experiencing the pain is asked to rate their pain rather than an observer asked to interpret it. As we are not able to “ask” our patients to rank their pain, these scales immediately become more subjective when applied to veterinary patients.

In early veterinary pain-assessment work, researchers therefore looked to human pain scales that were designed for use with human patients. In particular, the Toddler-Preschooler Postoperative Pain Scale, the Observation Scale of Behavioral Distress, and the Children’s Hospital of Eastern Ontario Pain Scale were modelled in early veterinary pain scales8–10.

CHOOSING A PAIN SCALE

Several factors must be considered when choosing a pain scale. The first is whether the scale is appropriate for the species being evaluated. Pain behaviours vary by species and even within breeds of animals in a species. For instance, prey species tend to hide even debilitating pain instinctually and no one would argue that, within dog breeds, a miniature poodle, for instance, would be much more likely to demonstrate painful behaviours than a stonier golden retriever. Another consideration is whether the scale is designed for the type of pain the animal is experiencing. Some scales are designed to evaluate acute or even post-operative pain settings and may not be appropriate for patients suffering with more chronic pain conditions such as osteoarthritis. Another consideration is whether the scale is accurate across observers. In veterinary medicine, care is given to animals by personnel that range from highly trained specialist veterinarians to veterinary assistants who may have no formal training or background in animal health or pain assessment. This provides an added challenge of designing assessment tools that have clear instructions and result in similar scores regardless of the assessors’ levels of training. We frequently use these scales as clinical monitoring devices and we cannot always guarantee in the clinical setting that the same observer will perform all the pain evaluations, so it is important that the inter-observer variability be as small as possible. Finally, one must consider the lesser of two evils: to ascribe pain to an animal that isn’t actually painful, or to miss pain in an animal who is actually painful. It generally agreed that it is better to ascribe pain and treat it when there is no pain than to risk missing a painful patient. As such, scales with low sensitivity are likely to be those with low specificity.

ASSESSING VALIDITY OF PAIN ASSESSMENT TOOLS

The assessment of validity is an essential part of the development of a pain assessment tool and the foundation of adequate pain management. Validity is defined as the effectiveness with which a test or scale measures the property or characteristic for which it is designed. In other words, it is the property of the scale that it performs all functions of the measurement equally well.

Pain measurement in humans who are incapable of self-reporting (for example, neonates, infants, people with learning disabilities or verbally handicapped patients) is exceedingly challenging. It is in this area that medical and veterinary clinicians share the challenge of establishing valid, reliable and reproducible pain assessment tools. The development of these scales and the validation criteria have been well documented by psychometricians12.

Reliability and validity for pain assessment are vital for use in recognising pain, quantifying pain intensity and evaluating treatment effectiveness13. At present, although multiple pain assessment tools have been developed for use in various veterinary species, few have undergone the rigours of formal statistical validation.

Simple descriptive scales (SDS), numerical rating scales (NRS) and visual analogue scales (VAS) are all used in veterinary medicine; however, they are all considered to be very subjective, with lower sensitivity and some issues with inter-observer variability. Recently, multifactorial or composite pain scales (MPS) have been developed in veterinary medicine. These scales relate several aspects of pain behaviours and species-specific normal behaviours and generate a numerical composite score. Most MPS assessments include observational but rather interactive steps and appear to improve the sensitivity and specificity of pain assessment in veterinary patients. When more than one scale is used, multifactorial pain scales, there are well-established advantages. 

For example, the four-component Pain Profile Tool was developed by the University of Melbourne Pain Scale and the Glasgow Composite Pain Scale Short Form (CMPS-SF). The University of Melbourne Pain Scale has good inter-observer variability and appeared to have good sensitivity and specificity in the initial validation study, however, a review paper questioned this sensitivity by applying the scale to non-painful pain that was quiet and with vocalisation that was no pain14,15. The CMPS-SF has been demonstrated to be valid and reliable with minimal inter-observer variability when used in the clinical acute pain setting; however, a recent university study demonstrated poor inter-observer reliability, suggesting specialist anaesthetists and first-year veterinary students may have different pain thresholds16,17. Until recently, there were no validated MPS devices for the cat; however, practitioners could utilise one of several tools lacking validation. In 2011, a Brazilian group developed and initially validated a multidimensional composite pain scale for acute post-operative pain in the cat9. In 2013, the same group refined and validated the scale and determined that the individuals who would score the highest above which analgesic therapeutic doses would be provided, and it was validated for use in English18. While the scale is still very new, clinical pain research in cats has been published using this version, which suggests its potential use in the clinical setting. More recently, a group from the UK developed a new MPS-SF for acute pain in cats (CMPS-Cat). The scale is similar to the canine version, potentially making it easier to adopt clinically for practitioners already using the canine form. In the initial validation study, scores had good agreement with scoring from a NRS tool indicating the tool was valid; however, only one observer used the tool during the study period so no clear statement about inter-observer variability can be made at this time19.

ASSESSING CHRONIC OR ACUTE PAIN

Assessment of chronic pain in dogs and cats is often very different from that of acute pain, owing to the pathological mechanisms that underlie these conditions. The validated and commonly used scale for assessing chronic pain in dogs is the Helsinki Chronic Pain Index (HCPI)7. It is a questionnaire-style assessment that is administered by the ‘observer’ (with numerical rating) and by the owner (without numerical rating). It is similar to Human Quality of Life questionnaires. The HCPI is best used as a tool for repeated measures to gauge the patient’s response to a therapeutic regime. Despite its lack of validated pain scales for assessing chronic pain in cats, researchers at North Carolina State University are evaluating a tool called the Feline Musculoskeletal Pain Index, which is an observer questionnaire that has shown some promise in identifying chronic pain in cats.

One of the biggest limitations of both of these tools is their heavy slant towards musculoskeletal and osteoarthritic causes of chronic pain. This makes them less useful for more visceral or neuropathic pain conditions.

The understanding of the pathophysiology of pain in horses has led to the development of very specialised pain-scoring techniques that are applied to specific pathological conditions rather than general scoring scales. Although both NRS and VAS scales are used in pain settings, there are also several specialised scales available. For acute abdominal pain there are the two Equine Acute Abdominal Pain Scales (EAPS-1 and EAPS-2), which are behavioural-based scales to evaluate the level of pain associated with colic in the horse20. In the post-operative period after abdominal surgery, pain in the horse can be assessed using the Post-Abdominal Surgery Pain Assessment Scale (PAPAS), which is a multifactorial composite scale that includes physiological parameters such as heart rate21. For assessment of pain associated with laminitis, there are two SDS scales, the Ober score and the clinical grading scale (CGS) and some practitioners also use a VAS22. Lastly, a multifactorial pain scale for assessment of orthopaedic pain has also been developed23. This scale integrates both behavioural and physiological data.

The “FACES” OF PAIN

Finally, current veterinary pain research has turned towards the development of scales that evaluate facial changes in response to pain. These scales originated for use in laboratory animals, where patient interaction for assessment was either impractical or could influence the assessment. These grime scales for rats and mice are currently considered the gold standard for pain assessment in these species and are used frequently in research14,15. From these scales, a rabbit grimace scale was developed for use in rabbits in research and clinical practice24. Over the past few years, interest in developing such scales for our domestic animals has developed. In 2014, two such pain tool were published for use the assessment of pain in laminitis. The first was the Obel Laminitis Grading Scale, developed by researchers in the UK and has shown promise in predicting the outcome of the condition, but rather suggested that facial expressions should be included in other composite models of pain in order to strengthen their validity. Lastly, in 2014, a group in the UK developed a series of artistic renderings of the facial expression changes (such as ear carriage and nostril shape) associated with pain in horses. These created a feasible tool for use in research25,26. The Equine “FACES” Tool is not currently a clinical tool, however, the group is currently exploring combining the CMPS-F with the Feline Pain Face Scale for clinical assessment of acute pain in cats.

PROBLEMS SURROUNDING THE TREATMENT OF PAIN IN VETERINARY PATIENTS

Even if the presence of pain is identified in a veterinary patient, treatment of that pain remains inconsistent. A university in the United States evaluated analgesics prescribed by dogs and cats in an intensive care setting and found that only 89 per cent of dogs and 67 per cent of cats received analgesics recommended for traumatic injuries were prescribed analgesic medication27. Another university study found that about 50 per cent of dogs whose medical records indicated moderate to severe pain had not been administered an analgesic and, in the same study, only one out of 15 cats evaluated in the post-surgical period received analgesia28. Several studies have attempted to elucidate potential reasons for this disparity and have suggested concerns regarding the pharmacology and side effects of potent opioids, failure to identify pain appropriately (scoring), the number of times since graduation from veterinary school, the presence or absence of a veterinary nurse, a belief that some post-operative pain was beneficial, beliefs surrounding which procedures were painful, and, interestingly, the sex of the veterinarian, with female veterinarians more likely to score and treat pain29,30.

TRAINING IN PAIN RECOGNITION AND MANAGEMENT

In the authors’ opinions, these reasons highlight the underlying barrier to appropriate pain assessment and treatment in veterinary medicine, which is the lack of training in this important aspect. Veterinary education is not internationally recognised and the lack of education has led to a series of ‘best practices’ guidelines issued by professional bodies and without meaningful attempts at standardisation has led to a lack of standardised training or practice. One step in the right direction in this regard has been the recent focus on “day-one skills” in veterinary training. The ability to recognise and treat pain is considered a ‘day-one skill’ by both the American and European veterinary associations, although there is a recognition of which many Australian schools and some others in the UK are beginning to teach. These courses are becoming more widely offered and regularly in veterinary education. Two recent studies have demonstrated the value of the addition of formal pain assessment in veterinary education, which is an important step forward in veterinary education.
assessment teaching on the attitudes, knowledge base, and confidence level of veterinary students when assessing pain in dogs and cats. However, veterinary education does not end at graduation and continuing professional development is the key to lifelong learning and high-quality veterinary practice. In two recent surveys evaluating the recognition of pain and use of analgesics in dogs, cats, and horses by veterinary practitioners in New Zealand investigators found that more than 40 per cent of respondents felt their knowledge of the subject was inadequate. While there is an increasing recognition of opportunities surrounding the assessment and treatment of pain in veterinary patients, there are no regulations or guidelines for veterinarians or nurses for the type or quality of these opportunities and, as such, no requirement to attend any that focus on pain. This is likely a contributing factor to the studies that found poor recognition and treatment of pain with increasing years since graduation from veterinary school. Finally, veterinary medicine lacks any universal guidelines for pharmacologic intervention such as the WHO Analgesic Ladder. Although the WHO Ladder was originally intended for treatment of cancer pain, it is applied in the management of many different types of pain. There are some proponents of the application of the WHO Ladder to veterinary patients; however, as it is a human tool, it does not take into account the unique pharmacologic considerations of veterinary patients. For instance, the first level of the WHO ladder recommends administration of drugs such as paracetamol or non-steroidal anti-inflammatory medications (NSAIDs). Painful conditions toxic to cats and NSAIDs carry many concerns and contraindications in dogs and cats including gastrointestinal ulceration and perforation, liver and kidney failure. This means that many of these medicines will not be used in patients who need them the most, owing to their underlying or concurrent disease processes. Opioid therapy is a mainstay of acute pain treatment in dogs and cats, however, due to a very high first-pass effect, oral dosing of opioids is not very effective, making them less useful outside the hospital. Buprenorphine can be administered transmucosally in dogs, cats, and horses for alleviation of mild to moderate pain, but is fairly expensive and, as such, is not a very cost-effective drug for long-term therapy, especially in larger animals. Tramadol initially appeared to hold promise for dogs, however, pharmacological studies have shown that dogs do not make meaningful quantities of the mu receptor active metabolite, O-demethyltramadol, making it far less useful for acute pain in dogs. Further highlighting species differences, cats form very high levels of this metabolite, but tramadol’s use in them is still limited, in that oral buprenorphine is generally preferred over tramadol or oxymorphone owing to its bitter taste. Another interesting species difference that would apply to treatment decisions for pain in veterinary species lies in the finding that alpha-2 agonists provide more effective analgesia for visceral and superficial pain than both opioids and NSAIDs in horses. In addition, there is concern regarding gastrointestinal toxicity seen after opioid administration, leading to a risk for development of colic. Recent drugs such as gabapentin, amantadine and maropitant have become the focus of veterinary research in the constant quest to improve our ability to treat pain in our patients.

CONCLUSION
The recognition and treatment of pain in veterinary species is a complicated matter that is evolving; however, there are still major challenges to overcome. Veterinary medicine incorporates many non-human species, all of whom are non-verbal, which makes creating any standardised methodology for assessment or treatment impossible, owing to significant differences between species in the pathophysiology, behaviour and pharmacology of pain. There are multiple routes for oral and transmucosal pain medicine for the assessment of chronic and acute painful conditions. One of the major underlying difficulties in the advancement of pain assessment and treatment is the lack of regulations regarding education and continuing professional development surrounding this important subject. Although significant progress has been made in chronic pain management, veterinary medicine still lags behind human medicine in its emphasis on the importance of recognising and treating pain.

REFERENCES