ANZCA

AUSTRALIAN AND NEW ZEALAND
COLLEGE OF ANAESTHETISTS

AUSTRALASIAN ANAESTHESIA 2013

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AUSTRALASIAN ANAESTHESIA 2013

Invited papers and selected
continuing education lectures

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Published in 2013 by:
Australian and New Zealand
College of Anaesthetists
630 St Kilda Road
Melbourne VIC 3004

ISSN 978-0-9775174-9-7

Printed by: DigitalHouse
70 Wirraway Drive, Port Melbourne, VIC, 3207

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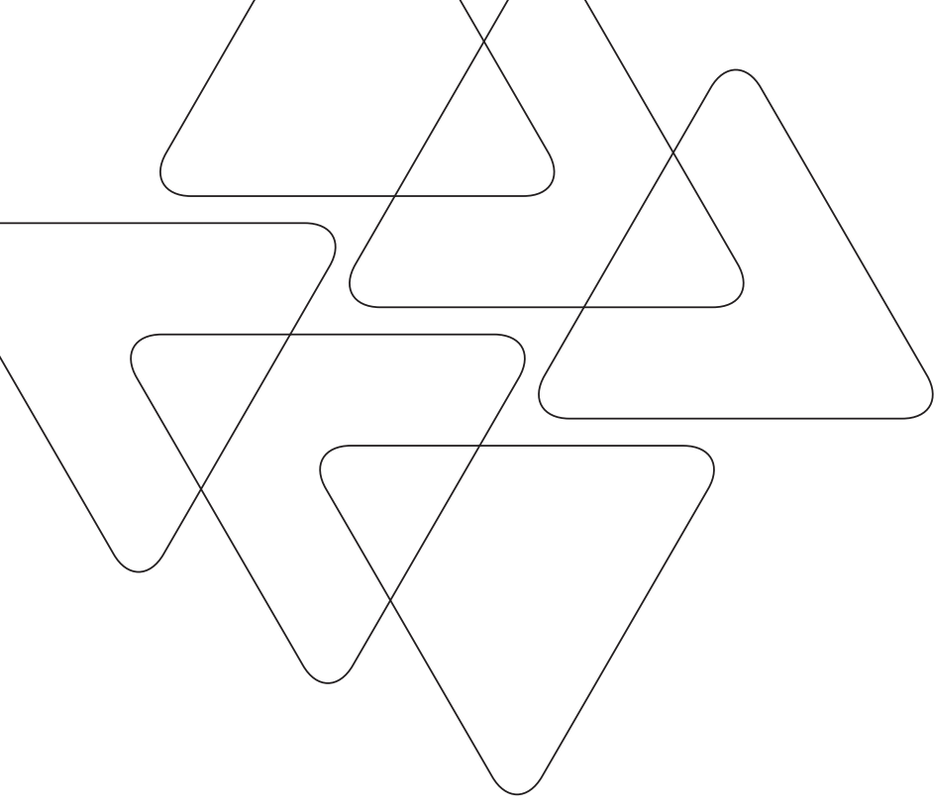

Preface

Welcome to the 2013 edition of Australasian Anaesthesia. This edition is available in digital and hard copy versions. There has been much discussion by Fellows about these changes and I thank those who have made contact to express their views. Publishing is undergoing massive change and traditional media are being replaced by electronic formats. Newspapers are disappearing, or sacking staff; e-zines and other on-line resources are thriving. One colleague let me know that he used the internet as his principal resource to prepare for the Part II examination. I hope that you will take advantage of the immediacy and flexibility of the digital edition and let ANZCA know how this publication can match your requirements in the future.

Please know that bonus material, such as video files or brochures, can be found on the ANZCA website (http://www.anzca.edu.au/resources/college-publications or use the QR code with your smartphone). The authors have generously allowed their articles to be distributed in this way to maximise the educational impact of their work.

Finally, this issue of the Blue Book once again provides a diverse range of topics for your interest. I thank the authors, the regional editors and Katherine Hinton, Laura Foley, and Chriss Marinoni for the work and support in producing this edition. Please take the opportunity to thank our authors personally when you can and also consider writing yourself for a future edition.

Richard Riley

Evolution of airway training at a large metropolitan teaching hospital

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Professor David Story facilitates research teaching and engagement in anaesthesia perioperative and pain medicine at the 14 hospitals affiliated with the University of Melbourne. He has a passion for evidence based practice.

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Visiting anaesthetist, Department of Anaesthesia, Austin Health, Melbourne, Australia

Dr Francis Parker has co-authored a number of papers in the fields of anaesthesia, gastroenterology and urology. He has a particular interest in the management of difficult airways.

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INTRODUCTION

In an editorial in 1998 entitled "Education and training in airway management", Mason lamented that: "In what other profession would untrained teachers, with little time and fewer facilities, be expected to provide comprehensive education for trainees with such widely different levels of experience."[1] Within the Department of Anaesthesia at Austin Health we have developed an airway-teaching program that, we think, has addressed some of these problems. This article describes some of the features of our airway program and how it was developed.

Table 1. Features of the Austin Training Program

- Designated anaesthesia department airway co-ordinator.
- Airway co-ordinator provided with adequate out of theatre time.
- Core instructor group developed with airway and simulation expertise.
- Ongoing review of educational resources and attendance at external courses.
- Review of unexpected difficult airway algorithms including approach to surgical airway for anaesthetists.
- Department airway manual provided.
- Dedicated airway training room and access to wet lab and simulation room.
- Both technical and non-technical skills taught.
- Anaesthesia nurses involved in simulation to emphasise team approach.
- Attendance at ENT clinics and respiratory medicine bronchoscopy lists.
- Collaboration with ICU and emergency medicine.
- Collaboration with broader hospital education services.
- Airway refresher and fibreoptic program run as separate entities.
- Audit and governance.
- Network with other centres.

There is increasing recognition of the importance of airway training.[1-3] The authors of the "4th National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society: Major complications of airway management in the United Kingdom" (NAP4) identified poor judgement, and education and training, as the second and third most frequent causal and contributory factors in the reported anaesthesia events.[4]

The 2013 Australian and New Zealand College of Anaesthetists (ANZCA) curriculum revision included a requirement for more structured airway training.[5] While the clinical environment remains the most important learning ground for airway expertise, there is strong support for dedicated airway training outside the operating room.[1,2] External workshops are partially able to address this training requirement but should be complemented by comprehensive teaching in the training hospital.[1,6] Only half of the 60% of training programs in the United States and Canada who responded to a 2008 survey had formal airway rotations.[7]

Expert opinion recommends that such hospital airway training could include: airway assessment and planning; approaches to the expected and unexpected difficult airway; specific airway equipment training including new devices; surgical airway training; development of fibreoptic skills and development of human factor expertise.[1-3, 6]

AIRWAY TRAINING RESOURCES

Airway training co-ordinator and instructors

The Austin is a large metropolitan hospital affiliated with the University of Melbourne, undertaking surgery in all specialties except obstetrics. In 2004 a staff anaesthetist (JG) was appointed as airway training co-ordinator (airway co-ordinator) and provided with out of theatre time to perform this role. The airway co-ordinator's task was to harness the considerable airway expertise in the department into a cohesive training program for the department's trainees. Creating such a role is considered important to the success of airway training.[1,2,8] Formal airway training commenced in 2006 and has evolved each year since then. During that time, 12 anaesthesia consultants have provided instruction in the operating room or in airway training outside the operating room. Our anaesthesia trainees are rostered to receive five hours per week for out of theatre education. Approximately 45 anaesthesia trainees rotate through our department annually for periods of three to 12 months. Typically trainees are attached to the training program which includes the Austin for three to four years and would spend some time in our hospital in each of those years. An additional 15 doctors, including intensive care trainees, emergency trainees and junior resident medical officers, work in our department for similar periods to the anaesthesia trainees.

The airway co-ordinator has been an instructor on the Effective Management of Anaesthesia Crises (EMAC) course since 2006.[9] This has provided exposure to the EMAC emergency airway approach,[10] and an opportunity to develop expertise in simulation. The airway co-ordinator has completed the Royal Melbourne Fibre-optic Workshop in 2004;[11] the Difficult Airway Course for Anesthesia (Airway Management Education Center) in 2008[12] and has twice attended the Airway Skills Course in 2007 and 2012 (AirwaySkillsTM).[13] Attendance at each of these courses, discussions with experienced colleagues and academic sources have all contributed towards the development of Austin airway training.[1, 2,14-16]

Unexpected difficult airway pathway

Mason emphasised the importance of an agreed simplified department-wide approach to the unexpected difficult airway, with the intention that this be used as a guide to teaching and the arrangement of difficult airway equipment.[1]

Soon after the airway co-ordinator's appointment, he and a colleague revised the department's suggested pathway for unexpected difficult intubation. This revision included detailed consideration of the Difficult Airway Society (DAS) guideline, the American Society of Anesthesiologists (ASA) guideline and the airway section in the EMAC Instructors Manual.[10,17,18] After a consultation process with key department staff, the unexpected difficult airway pathway was developed and is attached to all anaesthesia machines and to the difficult airway trolleys (DATs).

Airway equipment

The contents of the DATs were revised after development of the unexpected difficult airway pathway and have subsequently been revised to comply with the ANZCA guideline.[1,19,20] In a 2007 Auckland survey, 20% of respondents had never been orientated to the DAT in the place in which they were working.[21] In recent years on the orientation day at the start of the training year, trainees have been shown the location of: the DAT; Royal Perth surgical airway bags; the grab bag for off the floor (that is, outside of the operating theatre suite) airway emergencies and the airway training room.[1] Unfortunately this does not include all trainees and, from 2013, trainees who are not present at the orientation day will be personally oriented to these locations by the airway co-ordinator, or a colleague, when their rotation commences at the Austin.

In the operating theatre at Austin we have access to 11 video intubation bronchoscopes of varying external diameters between four and six mm,[22] which we share with our thoracic surgery and respiratory medicine colleagues. It has been suggested that using intubation bronchoscopes via a screen rather than an eyepiece provides benefit for trainees.[23]

Airway manual

We have developed an extensive department manual incorporating all of the material covered during the airway training. This manual is provided in hard copy to trainees at the commencement of the training year. This manual is constantly updated and from 2013 will be provided in electronic form. The manual has been used by other providers of airway training to assist with preparation of participant reading material.[24]

Training facilities

Dedicated airway training rooms have been identified as important training resources.[1,6] In 2006 the Austin redeveloped the operating theatres. At that time we were able to secure an area of the old day surgery unit, which is very close to the operating theatres, to establish an airway training room. The airway training room contains; a DAT resembling those in the operating theatre stocked with expired equipment; a number of fibreoptic scopes and several light sources; a fibreoptic dexterity trainer (DexterTM, Replicant, Wellington, New Zealand);[25] a trolley containing tubes and blockers for lung isolation; a simulated tracheal bronchial tree for lung isolation training and several manikins. The room has a whiteboard and a dozen chairs for interactive teaching and a large cupboard to store expired equipment as it becomes available for teaching.

In 2008 the Austin opened its own simulation centre. This is an additional resource for airway training which includes a simulation room, equipped with a sophisticated mannequin (Simman^{R}, Laerdal, Stavanger, Norway), and viewing and debriefing rooms. There is also a wet lab in which the surgical airway sessions can be taught.

The Australasian College of Surgeons Skills Laboratory, which is half an hour journey by car or train, is equipped with a bronchoscopy simulator (Accutouch endoscopy simulator, Immersion Medical, San Jose, USA). Such simulators have been demonstrated to improve fibreoptic skills at other centres.[26,27]

Simulation

Simulation allows participants to practise leadership in crises and other challenging clinical situations and to receive feedback regarding their management of these events.[28] Human factor training and the opportunity for multidisciplinary teams to train together within simulated difficult airway scenarios were recommendations of NAP4.[29]

Simulation has formed part of airway training at Austin since its inception; in recent years nursing staff have participated in addition to anaesthesia trainees. In 2009, five consultants attended a two-day workshop on simulation education at the Southern Health Simulation Centre in Melbourne. In 2011, two consultants, a provisional fellow and two nurse educators completed the week-long Co-ordinated Approach to Simulation Training course at Southern Health Simulation Centre. Two of the consultants attended both training opportunities. Most of these staff remain involved in the simulation component of Austin airway training.

Surgical airway

There is uncertainty about the best approach to the emergency surgical airway for anaesthetists and this is reflected in the DAS and ASA guidelines, which suggest options rather than a definitive instruction as to how to proceed.[17, 18] Surgical airways were generally poorly performed by anaesthetists in the NAP4, most frequently a cannula approach was chosen.[30] Delay in performing an emergency surgical airway has been implicated in adverse outcomes.[31] The authors of NAP4 recommend that all anaesthetists should be trained and maintain expertise in cannula and surgical cricothyroidotomy and recommend that further research be pursued into reasons for needle cricothyroidotomy failure.[32] Strong support for surgical airway training for anaesthetists has also been expressed in Australia and New Zealand, with particular emphasis on the importance of human factor training.[33] The Royal Perth Hospital can't intubate, can't oxygenate (CICO) algorithm incorporates a cannula approach, a Seldinger approach (5.0 cuffed melkerTM) and a surgical approach (scalpel bougie and scalpel finger cannula) in a logical progression.[34,35] A recent publication using these guidelines has emphasised the importance of prepared equipment and a rehearsed team strategy in the management of the CICO scenario.[36] The airway co-ordinator has visited the Royal Perth Hospital to observe a training session led by Dr Andrew Heard and remains in contact with him so that modifications to that hospital's approach are taught at the Austin. The equipment to perform a surgical airway following the Royal Perth Hospital approach is available in the emergency department, intensive care and at multiple locations in the operating theatre in our hospital. The Royal Perth CICO algorithm is attached to all the anaesthesia machines and the DATs on the reverse side of the unexpected difficult airway pathway placard.

Collaborative relationships

Key relationships with other departments have been gradually developed. Each fortnight for several years, an anaesthesia trainee has attended the ear nose and throat (ENT) outpatient clinic to gain experience with nasendoscopy.[37] Anecdotally, these interactions have improved communication between the ENT unit and the anaesthesia department about patients presenting for surgery with expected difficult airways. Once a week an anaesthesia trainee attends a clinical bronchoscopy list under the supervision of respiratory physicians. At these sessions the anaesthesia trainees perform the initial part of the bronchoscopy until the scope is past the vocal cords.[38] Anaesthesia trainees attend only about one third of the ENT clinics and bronchoscopy lists, which minimises the burden of training anaesthetists on these separate specialty groups.

Fibreoptic training is also undertaken on maxillofacial and thyroid elective theatre lists. These lists were chosen as these two patient groups often require intubation and not infrequently require fibreoptic intubation. In usual circumstances one patient on the list is intubated fibreoptically for clinical reasons or for educational purposes. Hospital legal opinion was sought before commencing this part of the airway program. If it is planned that airway management is to be altered for teaching purposes, patient consent is sought during the anaesthetic pre assessment on the day of surgery.[6,16]

The same consultant anaesthetists are rostered to each of these lists and are committed to the educational opportunities they provide. This continuity also ensures that there is no effect on the efficiency of the list. The surgeons on these lists were personally approached when this part of the program was established and value the experience gained by their anaesthetic colleagues. A paralysed apnoeic approach is typically used when fibreoptic intubation is performed in anaesthetised patients for educational purposes.[16]

With the assistance of anaesthesia and intensive care colleagues the airway co-ordinator has provided airway training to ICU trainees for the past four years. This training delivers the material that is covered in the airway refresher for anaesthesia trainees in an abbreviated form and includes simulation and practical instruction in the use of airway equipment. The airway co-ordinator also has regular contact with the lead airway consultants in the emergency department, so that each is aware of the teaching being provided in both departments. Difficult airway equipment has become standardised across the departments.[39] A hospital airway group was established in 2012 to ensure that in the future there is a regular forum to discuss shared airway concerns.

The Austin's airway training has included teaching relating to tracheostomy emergencies for several years and the need for this was reinforced in NAP4.[39] The teaching material was developed after a review of the literature and consultation with the directors of ENT and thoracic surgery, two of the senior intensive care consultants and with the Austin's Tracheostomy Review and Management Service (TRAMS).[40-42] TRAMS is an integrated service of doctors, nurses, physiotherapists and speech pathologists, which manages inpatients and outpatients with tracheostomy and trains other staff who care for these patients.

STRUCTURE OF AIRWAY TRAINING

Airway training at the Austin has two components. The airway refresher is incorporated into the planned department teaching program and is intended to involve all trainees once a year. The second component is the fibreoptic program, which is an option available to 16 trainees annually. It involves two trainees for four weeks. It is intended that each trainee completes this program once early in their training and once towards the end of their training. Participation is limited to anaesthetic trainees and priority is given to the most senior. Trainees who complete the fibreoptic program would also be expected to complete the airway refresher that year.

Airway refresher

The airway refresher is made up of three three-and-a-half hour sessions using the regular weekly department training time. It is undertaken as close as possible to the beginning of the training year to assist with trainee orientation and perhaps improve patient safety.[1,43] Considerable effort is made to include trainees who are at the Austin near the beginning of the training year and those who will rotate to the Austin later in the year. It is intended that all attend the airway refresher annually, as this has been validated as a realistic retention interval for complex procedural skills reinforced in a simulation environment.[44]

(1) Surgical airway and equipment session

This session is made up of four different components, which the trainees rotate through in two groups. The first component is an interactive hands-on exposure to fibreoptic scopes, laryngoscopes, lung isolation devices and other airway equipment. Trainees are able to practise the use of airway equipment on simple mannequins.[1] The fibreoptic scopes available at our institution are presented and the relative merits of the endotracheal tubes available for fibreoptic intubation are discussed. Measures to improve the view for fibreoptic intubation and to improve the likelihood of successfully passing the endotracheal tube over the fibreoptic bronchoscope and through the glottis without impingement are also considered.[22] A number of airway devices and techniques are demonstrated and then practised including: the Berman airway[45] (Vital signs, Totowa, USA); the endoscopy mask[46] (VBM Medizintechnik, Sulz a.N., Germany); techniques of blind and fibreoptic intubation via the intubating laryngeal mask[18] (LMA, Jersey, UK); intubation with the Aintree catheter[18,47] (Cook Medical, Bloomington, USA); use of the straight blade laryngoscope,[48] McCoy laryngoscope[49] (Penlon, Abingdon, England); the Airtraq[50] (Prodrol, Vizcaya, Spain); the Pentax airway scope[51] (Pentax corporation, Tokyo, Japan) and airway exchange catheters (Cook Medical, Bloomington, USA) including discussion of safe techniques of using these devices for endotracheal tube exchange and difficult extubation.[14,52,53]

In the second component in the wet lab, the Royal Perth Hospital CICO algorithm is presented. The trainees observe and then practise performing a surgical airway using a pig larynx mounted on a board, and delivering oxygen via a cannula on a mannequin.

The third component covers principles of lung isolation. Anatomical models are used to focus on the anatomy of the trachea and main bronchi relevant to lung isolation with emphasis on the variable anatomy of the right upper lobe.[54,55] Clinical and fibreoptic methods of placement and confirmation of position of double lumen tubes, bronchial blockers and endobronchial tubes are presented.[56] The features of the different styles of double lumen tubes are considered, particularly the variability in the design of right sided tubes. Effective methods of ventilation using the rigid bronchoscope are demonstrated.[57]

The final component involves an interactive discussion about the apparently blocked endotracheal tube and tracheostomy emergencies. A systematic approach is presented for the management of a patient with an endotracheal tube, which requires very high ventilatory pressures or is apparently obstructed.[10,58] The discussion regarding tracheostomy emergencies covers equipment and tubes and immediate information required when managing a patient with a problematic tracheostomy. Suggested pathways for management of accidental decannulation and the apparently obstructed tracheostomy tube are presented.

(2) Simulation

Five or six participants at a time undertake this session. The session commences with a short film followed by an interactive conversation emphasising the importance of human factors in airway management.[58,59] Following this there is a discussion about how to optimise attempts at bag mask ventilation and intubation. Emphasis is placed on the importance of distinguishing between patients who are unable to be intubated but able to be bag mask ventilated, from those who are unable to be intubated or bag mask ventilated. The surgical airway is presented as the final step for patients with a failed airway who are not awakening. It is emphasised that the surgical airway must be preceded by optimised attempts to bag mask ventilate, intubate and insert a supraglottic device.[10,60] These principles are used to explain the unexpected difficult airway pathway. Participants are then introduced to simulation principles and to the simulation room.

Typically, five scenarios are completed. One of the participants acts as primary responder for an airway scenario, with a second participant available to attend as help. Anaesthesia nurses are also immersed in the scenario and are full participants. Facilitated debriefing is performed in a separate room after each scenario, with the pause and discuss technique occasionally also being used during scenarios.[61]

Within the five scenarios, different participants are expected to demonstrate: optimised attempts at bag masking; optimised attempts at intubation including when to desist; recognition that a laryngeal mask is a reliable rescue when bag masking and intubation fails; be prepared to perform a surgical airway when required; manage the apparently displaced or blocked tracheostomy tube; manage an apparently blocked endotracheal tube and lead or act as an effective team member.

(3) Expected difficult airway

This is an interactive discussion of clinical cases from our institution and from the literature. It is led by the airway co-ordinator and a senior anaesthetist and incorporates clinical histories, photographs and radiological investigations (see table 2).

Table 2. Expected difficult airway scenarios discussed

- Obese patient with expected difficult airway.
- Ankylosing spondylitis requiring intubation.
- Bleeding tongue tumour for biopsy.
- Retropharyngeal abscess with airway obstruction.
- Submandibular abscess for drainage.
- Laryngeal cancer presenting with airway obstruction.
- Laser microlaryngeal surgery.
- When, where and how to extubate a patient with a difficult airway.
- Fractured unstable cervical spine for fixation.
- Severe rheumatoid arthritis.
- Neck swelling post carotid endarterectomy.
- Airway burns.
- Quinsy.
- Angioedema with upper airway obstruction.
- Adult acute epiglottitis.
- Neck dissection with past neck radiotherapy.
- Maxillofacial fractures.
- Laryngeal injury.
- Goitre.

Emphasis is placed on the importance of a comprehensive airway assessment that addresses the likelihood of success with all modalities of airway management including bag mask ventilation, laryngeal mask placement, intubation and a surgical airway.[17,62] Participants are encouraged to consider systematically the possible methods of securing the airway in patients with anticipated airway difficulty[17] and to plan airway management for the duration of the patient's care.[14] The relative indications and contraindications to fibreoptic intubation are discussed.[63,64] Use of gas induction in a patient with an expected difficult airway is considered, including strategies to manage airway obstruction if it occurs during gas induction. There is comprehensive discussion of assessment and management of patients with upper airway obstruction, with particular emphasis on the importance of having a surgeon present to perform rigid bronchoscopy or a surgical airway if required.[65] Approaches to airway management during micro laryngeal surgery are presented with particular emphasis on patients requiring jet ventilation and/or laser surgery (Richard Barnes, consultant anaesthetist, Monash Medical Centre, personal communication).

Fibreoptic program

Limited opportunity to practise fibreoptic intubation has been previously identified as a problem for trainees. The median number of fibreoptic intubations performed by trainees in a New Zealand survey was four per year.[66] The intention of the fibreoptic program is to provide a period of concentrated exposure to increase expertise and confidence.

The fibreoptic program is composed of four educational sessions, using the training time that is normally allocated to trainees, and four normal theatre clinical sessions, which have opportunities for fibreoptic intubation.

Four three-and-a-half hour out-of-theatre educational sessions are devoted to the following:
(i) Self-guided endoscopy dexterity training using Dexter.
(ii) ENT outpatient clinic.
(iii) Two respiratory medicine bronchoscopy lists.

Theatre clinical sessions which have opportunities for fibreoptic intubation drawn from:
(i) Two maxillofacial lists.
(ii) Two thyroid surgery lists.
These sessions constitute 64 elective operating lists a year used for this teaching purpose.

Trainees are also encouraged to use the bronchoscopy simulator at the skills laboratory at the Australasian College of Surgeons, however specific training time is not allocated to this.

AUDIT SURVEY

As part of audit for the airway refresher[6] we developed a brief survey (table 3). Trainees who completed the airway refresher in the first part of 2011 were asked eight questions assessing their confidence at managing important airway situations before commencing the program, immediately after the relevant education session and then four months later (see table 3). Questions were designed for the participant to choose a discrete numbered box response from one to five, with one indicating a beginner and five an expert. All forms were completed voluntarily and anonymously. The hospital ethics committee approved the survey. Changes in confidence scores were analysed as ordinal categorical data using the Wilcoxon matched pairs signed-rank test, with a p-value of 0.05 considered to be statistically significant. The group scores are presented as medians.

Twenty three trainees were eligible to complete the survey. To make comparisons meaningful, only the responses of the participants who completed the commencement form, the relevant session audit form and the form four months post-training were included in the analysis. In all eight questions there was a significant increase in the trainees self perceived confidence levels after four months. In seven of the eight questions there was also a significant increase in the trainees self-perceived confidence levels immediately following the session. Our survey demonstrates a persisting one-step improvement of median response in the participants' self-perceived ability. We recognise that this is not the same as an objective assessment of competence. As part of ongoing quality and governance we will repeat the survey on future participants in our airway training.

Table 3. Analysis of change in response to eight key questions compared to commencement questionnaire expressed as medians and interquartile range in brackets.

Question	Baseline	After simulation	After surgical airway and equipment	After expected difficult airway	At 4 months
How would you rate your ability to manage a patient who was unexpectedly difficult to intubate? N=9	1 (1-2)	3 (3-3) P=0.011			3 (3-3) P=0.011
How would you rate your ability to manage a patient who was unexpectedly difficult to intubate and unexpectedly difficult to bag and mask ventilate? N=9	1 (1-2)	3 (3-3) P=0.008			3 (3-3) P=0.011
Do you feel confident that you would know when it is appropriate to perform a surgical airway on an anaesthetised patient? N=9	2 (2-3)	4 (3-4) P = 0.012	3 (2-3) P=0.026		4 (3-4) P = 0.008
If you had to perform a surgical airway, how competent would you feel to do it? N=14	2 (1-2)		3 (3-4) P=0.001		3 (2-4) P = 0.001
How well could you manage a patient who can't breathe or be ventilated via their tracheostomy tube? N=9	2 (1-3)	2 (2-4) P = 0.015	3 (3-3) P = 0.011		3 (2-4) P=0.008
Do you feel confident you would choose an appropriate management plan for a patient who presented with a difficult airway? N=11	2 (1-4)			3 (2-4) P = 0.052	4 (3-4) P=0.026
How well could you manage a patient who presented with acute upper airway obstruction? N=11	2 (1-3)			4 (3-4) P = 0.006	4 (3-4) P = 0.010
How well could you perform an awake fibreoptic intubation? N=14	1 (1-3)		2.5 (2-4) P = 0.004		2 (2-4) P = 0.011

Comparisons were performed using the Wilcoxon matched pairs signed-rank test.
N = number analysed (completed both relevant session and four month form).

CONCLUSION

Our airway training program contains features (table 1) derived from the available literature as well as from direct communication with those with a particular interest in airway education. While we cannot comment on benefits to patient safety, our audit suggests trainees may benefit from the airway refresher component of the program. The Austin airway training program undergoes constant change to meet the needs of our trainees and their training body[5]. We think our airway training has features that may interest other centres.

No author has a conflict of interest.

ACKNOWLEDGEMENTS

Dr Will Howard edited the manuscript and provided valuable feedback.

Thanks to all contributors to airway training at Austin Health since 2006. Special thanks to Drs G Brace, H Deifuss, C Fiddes, R Gebert, J Geertsema, G Godsall, E Kayak, J Kok, W Howard, L Ellard, L Aykut, J Colin-Thome, J Cornes, J Fernandes, T Kelly, C Kolivas, C Lai, P Laverty, I Letson, E Mariampillai, S Matzelle, M McDonald, A Nanuan, L O'Shea, and to M Dunstan, F Nasra. Special thanks also to: the Department of Anaesthesia, anaesthesia nursing staff, theatre technical staff, Austin Simulation Centre, Department of Respiratory Medicine staff, Radiology Department, Ear Nose and Throat Unit, Thoracic Surgical Unit, Intensive Care Unit, Medical Engineering and the Australasian College of Surgeons Skills Laboratory.

For airway training sessions: Cook supplied some airway disposables, Covidien a Manujet ventilator, and CR Kennedy a Pentax AWS laryngoscope.

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Videolaryngoscopes and the 'Fremantle score'

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INTRODUCTION

Direct laryngoscopy has been the gold standard for tracheal intubation for the past 100 years. The recent advent of videolaryngoscopy in Australia and indeed worldwide has, however, led to anaesthetists becoming much more familiar and experienced in the use of myriad alternative intubation devices that are now widely available.

The aim of this article is to review the videolaryngoscopes commonly used in Australia and New Zealand and to discuss particular characteristics of these devices, coupled with their potential advantages and limitations. A three-stage process of successful intubation using these devices will be described and a new scoring system, the 'Fremantle score' to improve the description of intubation in videolaryngoscopy is proposed.

WHAT ARE VIDEOLARYNGOSCOPES?

Videolaryngoscopes are devices to assist intubation and contain a miniature video-camera (or other optical device), which achieves laryngeal exposure through indirect imaging. A distal camera looks around the curve of the tongue and bypasses the direct line of vision created with direct laryngoscopy, which allows the operator to have an indirect view of the glottis. They can be broadly categorised into those without integrated channels for placement of the endotracheal tube (ETT) and those with integrated channels.

Videolaryngscopes without integrated channels includes the C-Mac (Karl Storz, Tuttlingen, Germany), McGrath (Aircraft Medical, Edinburgh, Scotland), GlideScope (Verathon Medical, Bothell, WA) and AP Advance (Venner Medical, Switzerland).

Devices with integrated channels for placement of the ETT include the Pentax Airway Scope (Ambu, Copenhagen, Denmark) and the AirTraq (Prodol Meditec, Guecho Vizcaya, Spain). Technically, the Airtraq is not a videolaryngoscope, but an optical laryngoscope, which uses a series of mirrors and prisms and a hooded eyepiece with no video camera. However a connection to the eyepiece can allow visualisation externally on a monitor.

It is important to appreciate that the technique for using a videolaryngoscope is different to direct laryngoscopy. Direct laryngoscopy involves creating a direct line of vision to the target and intubating the glottic opening without obscuring the line of sight. Conversely, a videolarygnoscope has no direct line of vision and the ETT is manoeuvred 'around the corner' to reach the target under visualisation on a screen. A variety of adjuncts may be used to aid ease of intubation with each device offering particular advantages and disadvantages, depending on the airway situation with which the anaesthetist is faced.

WHY USE VIDEOLARYNGOSCOPY?

Videolaryngoscopy may confer potential advantages over traditional methods; ability to achieve a laryngeal view in the difficult airway situation when direct laryngoscopy has proved unsuccessful,[1] use of less force[2] and the ability for multiple anaesthetists to observe in real time on a screen providing supervision and an excellent teaching opportunity.

Furthermore, videolaryngoscopes do not seem to offer anything more than Macintosh in easy laryngoscopy (Cormack and Lehane grades I or II), but in difficult airways (C/L grades III or IV) it may convert 'blind' intubations into intubations under visual control and may achieve the same or higher intubation success rate.[1]

CHARACTERISTICS OF DIFFERENT VIDEOLARYNGOSCOPES[3]

Figure 1. Devices without an integrated channel for placement of the ETT

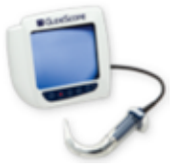
Device	Technique to achieve glottic exposure	Adjunct	Advantages and disadvantages
C-Mac 	The blade is modelled on the traditional Macintosh blade and it is recommended to initially attempt to achieve a direct laryngoscopy view. If this proves to be unsuccessful, the screen can be viewed and an appropriate adjunct used.	Preformed ETT with stylet or bougie with coudé tip.	+ Similar curvature as Macintosh, allowing the operator to use a technique similar to conventional laryngoscopy. Can be used as a direct or indirect device. + Good quality screen; useful for teaching and supervision. + Also available with a difficult 'D' blade. - Plasma sterilisation required. - Bougie often required.
AP Advance 	Blade of device placed on floor of mouth and lifts mandible and submandibular tissues in a similar fashion to conventional laryngoscopy.	Preformed ETT with stylet or bougie with coudé tip.	+ Small, transportable & quick to set up. + Small detachable blade making it easier if patient has a small mouth opening, short neck or is obese. + Available with a 'difficult' blade and tube guide. - Small screen. - Screen at end of handle may make insertion difficult. - Can be prone to fogging.
GlideScope 	Blade of device inserted in midline over dorsum of tongue; the operator does not use the device to lift the mandible or submandibular tissue.	Preformed ETT with stylet.	+ Large good quality screen. + Disposable blades. + User friendly. High success rate reported in both experienced and inexperienced users[4-5] in many studies. + High success rate in first attempt intubations in non-experts.[6] - No direct laryngoscopy view. - Requires a stylet which may be difficult to remove. - Bougie is less reliable compared to other devices.
McGrath 	Blade of device inserted in midline over dorsum of tongue; the operator does not use the device to lift the mandible or submandibular tissue.	Preformed ETT with stylet.	+ Detachable blade which may be advantageous in patients with short necks, obesity or barrel chest. - Screen at end of handle may make insertion difficult.

Figure 2. Devices with an integrated channel for placement of the ETT

Device	Technique to achieve glottic exposure	Adjunct	Advantages and disadvantages
Pentax 	Blade of device inserted in midline over dorsum of tongue; the operator does not use the device to lift the mandible or submandibular tissue. Requires the epiglottis to be lifted directly.	In-built conduit where the ETT sits.	+ High success rate reported in inexperienced users. + 2nd channel for suction and LA administration. + Portable, single unit. - No direct laryngoscopic view. - Deep profile may make insertion difficult in patients with poor mouth opening. - Tube guide only allows ETT to target centre of screen.
Airtraq 	Blade of device inserted in midline over dorsum of tongue; the operator does not use the device to lift the mandible or submandibular tissue. Can be used with the blade tip either in the vallecula or under the epiglottis.	In-built conduit where the ETT sits.	+ A port to allow suctioning, LA administration or O2 delivery. + Portable inexpensive single unit. - No direct laryngoscopic view. - Bulky device may make insertion in patients with poor difficult in patients with poor mouth opening. - Can be prone to fogging.

USING THE VIDEOLARYNGOSCOPE VIA THREE STAGES

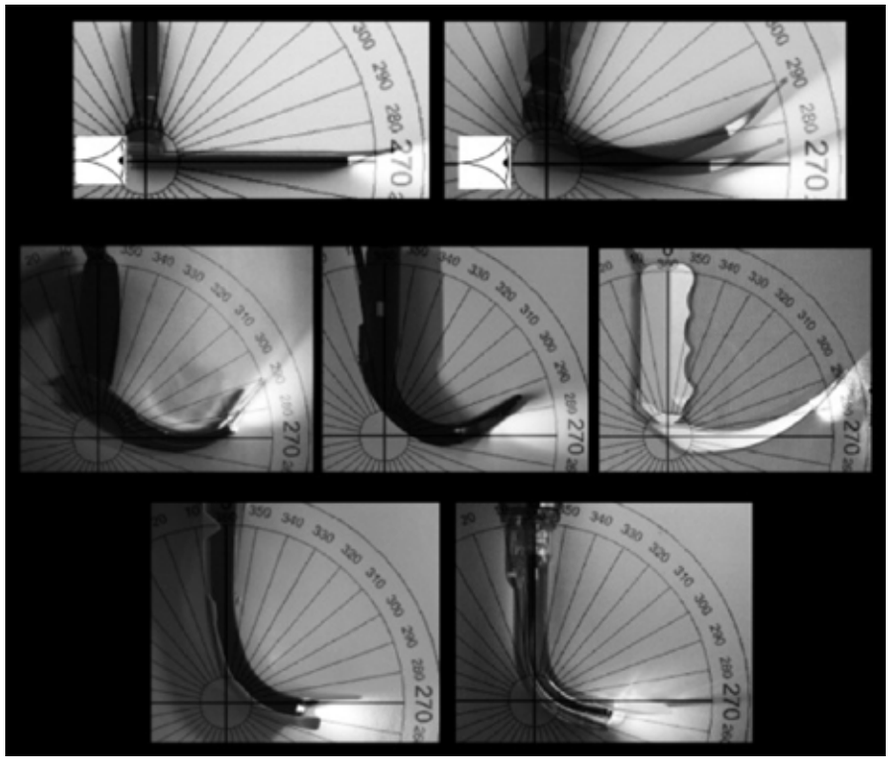
Levitan et al.[7] believe the process of using a videolarygnoscope is best understood when broken down into three stages:

(1) Laryngeal exposure.
(2) Delivery of the endotracheal tube to the glottic opening.
(3) Advancing the endotracheal tube into the trachea.

(1) Laryngeal exposure and defining axis of the view

One standardised way to compare the angle at which an ETT passes into the trachea is to look at the angle of each device, assuming that the handle is 0 degrees and is an axis reference point.

Figure 3. A standardised approach to assessing the axis of different intubation devices



Reproduced with kind permission from Levitan et al.[7]
(i) Miller (top left), Macintosh (top right)
(ii) Storz C-Mac (middle left), GlideScope (middle), McGrath (middle right)
(iii) Pentax (bottom left, Airtraq (right)

(i) Miller and standard Macintosh blade

The view axis in direct laryngoscopy is straight, achieving a direct line of sight 90 degrees to the handle along the 90 to 270-degree line.

(ii) Storz C-Mac, GlideScope and McGrath (devices without integrated channels)

The distal tip of the blade points towards the 290-degree mark, providing a look around the curve from 0 degrees, counter clockwise, to a visual axis of 270-300 degrees. It is evident that the view angle is no longer a direct line of sight but determined by the orientation of the imaging device.

These cameras offer a wide view both superiorly from above the epiglottis and posteriorly to the base of tongue and from left to right.

(iii) Pentax and Airtraq (devices with integrated channels)

These two devices with an integrated channel have distal blades which are distinctly less steep than the non-channelled devices, pointing towards the 260-270 degrees. The Airtraq, the least steep of all the devices, has been optically manipulated counter-clockwise to approximately 270 degrees.

(2) Delivery of the endotracheal tube to the glottic opening

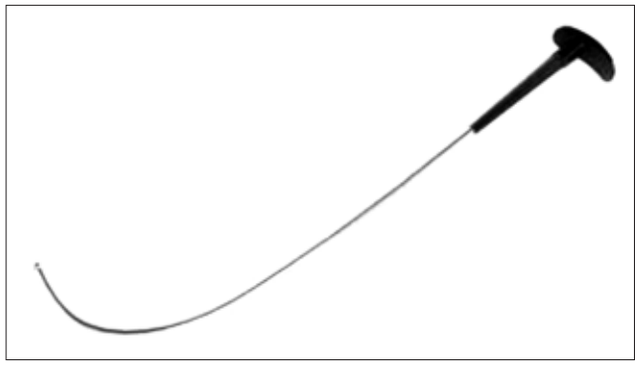
(i) Storz C-Mac, GlideScope and McGrath (devices without an integrated channel)

It is evident from figure 3, demonstrating videolaryngoscope devices superimposed on protractors, that the GlideScope and McGrath have the steepest axis views. The cameras are positioned around the curve of the tongue in order to visualise the glottic opening. Because the device is not creating a direct channel for placement of the ETT, the tube must be manoeuvred around the device and the tongue in order to reach the glottis.

In order to achieve this, manufacturers often recommend the use of a stylet to pre-form the ETT. In one study comparing the performances of different videolaryngoscopes, a stylet was required in 76% and 60% of cases with the McGrath and GlideScope respectively.[8]

GlideScope now offer a "GlideRite stylet" with a distal bend of 70 degrees, relative to the proximal straight section. The McGrath VL does not include a specialised stylet, but a malleable stylet can be used within an ETT and preformed to the desired shape to match the blade. Similarly this can also be done with the GlideScope if a less rigid stylet is required.

Figure 4. GlideRite stylet



The Storz C-Mac was designed to resemble a standard Macintosh laryngoscope blade. The distal camera provides a view around the curve, despite the proximal blade resembling a standard Macintosh form. Delivery of the ETT to the glottis tends to be much more straightforward compared with that of the GlideScope and McGrath because the technique resembles direct laryngoscopy. A standard bougie with a small coude tip is an appropriate adjunct in many difficult airways where elevation of the epiglottis is incomplete.

In contrast to the McGrath and GlideScope, in which a stylet is needed for a majority of cases, a stylet is required only in 10% of cases using the C-Mac.[8]

(ii) Pentax and Airtraq (devices with integrated channels)

Both of these devices incorporate an integrated channel to preload the ETT and direct to the tube to the target, thus avoiding the need of a stylet.

Pentax is reported to have a high success rate but may fail in patients with long necks.

There are reports that tube delivery to the glottis may not be straightforward in all cases[9,10,11] because the pathway of the tube and the view axis are slightly incongruent, and a non-styletted PVC ETT has an inherent shape that curves the tube upwards.

Insertion of a bougie down the conduit has been reported to be successful in situations where the Pentax blade fails to reach and elevate the epiglottis.

(3) Advancing the endotracheal tube into the trachea

A disparity between the blade angle at the base of the tongue and the posterior inclination of the trachea creates a potential problem for devices that use imaging to look around the curve, especially in devices such as the GlideScope and McGrath, which have a small flange and steep axis view. The steep angle of these videolarygnoscope blades relative to the axis of the trachea may improve the indirect view of the laryngeal inlet, but it is necessary to redirect the tracheal tube more anteriorly, which can make it more difficult to achieve successful intubation of the trachea. There are numerous reports in the literature of devices managing to achieve an improvement in view but still being unable to pass an endotracheal tube.[11-16] A recent editorial by Ahmed-Nusrath et al.[17] states that "a poor view has been validated as a marker for difficult intubation using conventional laryngoscopes, but does not necessarily reflect the degree of difficulty in intubation using videolaryngoscopes, where the main problem lies in directing the tracheal tube".

One large series (728 patients), using the GlideScope, found that 99% of patients had a grade 1 or 2 Cormack-Lehane laryngeal view. Despite this, intubation efforts were abandoned in 3.7% of cases.[12] The authors noted "Laryngeal exposure was rarely the cause of failed intubation, but the inability to deliver the tracheal tube to a visualised larynx is both frustrating and largely unavoidable". Similarly, in a study of the McGrath videolaryngoscope, glottis views were good, but time to intubation was much longer (47 seconds versus 29 seconds), and four times as many patients had prolonged intubation (>70 seconds) times compared with direct laryngoscopy.

Excessive angle of the stylet can also create tube advancement issues. The sharply angled videolaryngoscopes, GlideScope and McGrath, require angles greater than 35 degrees to navigate the tube towards the target. The C-Mac has a straighter blade and a sharp stylet angle is not necessary to deliver the tube to the glottis.

A second problem can occur in a steep angled ETT delivery, once a tracheal tube enters the trachea and contacts the tracheal rings. The anterior tracheal rings can add a further mechanical obstruction and prevent tracheal insertion.

Some users have advocated use of a bougie, tube rotation clockwise to disengage the bevelled tube from the tracheal rings, or "reverse loading" the tube on the stylet to address this issue.[18-21] Reverse loading the ETT on the stylet involves loading the ETT onto a rigid stylet in a direction opposite to its natural curve and when the stylet is withdrawn, the ETT will descend into the trachea. It is likely these techniques need practice and experience before the challenge of a true difficult airway.

The manufacturers of the GlideScope acknowledge this problem of abutting the tracheal rings and advocate using the GlideRite ETT manufactured by Parker Medical (Highlands Ranch, CO) which has a symmetric, ski-tip distal tip which glides over the tracheal rings, unlike a standard left-facing bevelled inflexible ETT.

LIMITATIONS

It is clear that an obvious problem with videolarygnoscopy is the literature reporting poor correlation of view and placement of the ETT.

Other reported problems relate to stylet perforations of the pharynx and hypopharynx using the GlideScope and McGrath when operators have blindly inserted the styletted ETT whilst concentrating on the video monitor.[22-23]

As described in this article, the technique using a videolarygnoscope is significantly different to that of direct laryngoscopy and something that requires training and experience. It may be naive to think of it as an emergency last attempt device used by the inexperienced user in a truly difficult airway to replace the trained anaesthetist. One study, comparing the use of GlideScope to the C-Mac videolarygnoscope for intubation in the emergency department[24] found that both had similar rates of intubation success (GlideScope 221/230 and C-Mac 225/233) but admits to using direct laryngoscopy to rescue all cases of failed intubation.

There is inconclusive evidence indicating that videolaryngoscopy should replace direct laryngoscopy in patients with normal or difficult airways.[1]

THE FREMANTLE SCORE

In an attempt to address the inadequacy of a Cormack and Lehane score to describe videoscopic intubation, in our recent article[25] we propose a simple three-part scoring system; view, ease and device, otherwise known as 'the Fremantle score'.

Preliminary evaluation of this system has demonstrated that the system is easy to use, easy to understand and relevant to what we ultimately want to know as an anaesthetist, which we believe is the ease of intubation when challenged with the potentially difficult airway.

The 'Fremantle score' has been developed by airway enthusiasts in our department, and is an attempt to form a simple, informative and reproducible score that can be used for any of the videolaryngoscopic devices available.

We strongly feel that there needs to be a stand-alone score for videolaryngoscopy that is distinct from the Cormack and Lehane system.

The problem with videolaryngoscopy is that there is poor correlation between view obtained and ease of intubation. Several studies have shown these devices are excellent at getting a good view of the cords, yet it is remains difficult to pass the ETT through the cords.[11-16] Some devices do not require, or allow, a full view of the cords to be obtained. The AP Advance scope DAB requires that the bottom bar of the partial tube guide is lines up with the arytenoids in order to facilitate intubation. This may mean that a 'full' view of the cords is never attained but successful intubation is easily achieved.

Although the existing Cormack and Lehane system for direct view may provide more information pertaining the view of the laryngeal inlet, we feel this is unnecessary detail and that a simplified system is easier to use and more reproducible. We have used a lettering system in order to make it distinct from the Cormack and Lehane system and instantly recognisable as a score for videolaryngoscopy.

It is important that the difficulty of inserting the ETT is recorded in the notes. This is the driving force behind the second part to the scoring system, the 'ease of use' score.

When assessing a potentially difficult airway, and on looking through past anaesthetic notes, the most important facts a clinician wants to know (in addition to ease of ventilation) are:

1. What devices were used to attempt intubation previously?
2. What view was obtained?
3. How easy was it to use?

If videolaryngoscopy is planned and a device has been previously documented to easily facilitate intubation at the first attempt then view obtained on the video screen is only a small part of the information that an anaesthetist wants to know. The same cannot be said for the relevance of a direct Cormack and Lehane view obtained at previous non-video assisted intubation.

There is no substitute for descriptive notes written at the time of laryngoscopy. This, however, is performed inconsistently by anaesthetists of all levels and because of this a simple system is needed. The Fremantle score allows this to be done quickly and communicated effectively without replying on detailed notes of exactly what was done at the time.

In order for a scoring system for intubation to be useful it should assist in the prediction of difficult (or easy) subsequent attempts. It should also be simple, instantly recognisable as being associated with a particular system or practice, and easy to use.

The Fremantle score has three elements:

Figure 5. The Fremantle score

View:	**Full**	**Partial**	**None**
			
Ease:	**1. Easy**	**2. Modified**	**3. Unachievable**
Device:		**Blade:**	

1) A score for the best 'view' obtained with the video-laryngoscope

The best laryngeal view obtained with or without anterior laryngeal pressure is recorded.

F Full when the whole of the laryngeal inlet is visible.

P Partial when only part of the glottic structures are visible.

N No view is achieved when no laryngeal structures are visible, or you can see epiglottis alone.

2) A score for the 'ease of use'

1 **Easy** – the ETT is passed first time, using the technique specified by the manufacturer of the device.

2 **Modified** – the ETT is passed with either more than one attempt, by using a technique not described by the manufacturer of the device, or by the use of an adjunct (Bougie etc).

3 **Unachievable** – the ETT is unable to be passed, or the technique is abandoned.

3) The name of the specific device and blade used is recorded

Hence, when using the Pentax AWS scope, if you obtain a full view of the cords and the ETT is advanced successfully, first time, with no other manipulation, the score would be 'F 1 Pentax AWS'.

If using a GlideScope Ranger to obtain a full view of the cords, and passing the ETT required more than one attempt, the score would be 'F 2 GlideScope Ranger'.

We feel that the simplicity of use, and the extra information conferred by the Fremantle Scoring system for videolaryngoscopy will prove to be useful to subsequent anaesthetists, as demonstrated by the high level of agreement recorded by clinicians.

CONCLUSIONS

Videolaryngoscopes are devices to assist intubation and contain a miniature video-camera, which achieves laryngeal exposure through indirect imaging. They can be broadly categorised into those without integrated channels for placement of the endotracheal tube (ETT) and those with. The process of using a videolaryngoscope can be best understood when broken down into three stages; laryngeal exposure, delivery of the endotracheal tube to the glottic opening and advancing the endotracheal tube into the trachea.

The evidence suggests that in the difficult intubation scenario, laryngeal exposure can be superior to conventional laryngoscopy. However the ease of intubation, as expected in a difficult airway, can be problematic and for this there are a variety of adjuncts.

Overall, videolaryngoscopes are useful devices to assist achieve successful intubation. Their optimal use requires the user to be trained, experienced and familiar with the equipment. Use of the Fremantle score may help in distinguishing the use of a videolaryngoscope from a direct laryngoscope, is simple enough to be reproducible by any anaesthetist and can quickly convey relevant information regarding the functionality of a device in an individual patient.

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Urine output: To chase or not to chase?

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INTRODUCTION

Good urine output during surgery has long been a sign for anaesthetists that all is well with the kidneys. Conversely, poor urine flow is troubling, invokes a vague unease about hypovolaemia and a sense that "something" should be done, usually involving more intravenous fluid. There is concern about causing renal failure.

There are two issues here.

Firstly, where does the idea of oliguria and renal failure come from? Where is the evidence a low urine output during anaesthesia will result in renal failure? And how does chasing urine output with large amounts of intravenous fluid fit with recent thinking about restrictive versus liberal fluid management?

And secondly, given that in the vast majority of cases, oliguria during anaesthesia is clearly and obviously *not associated* with hypovolaemia, the question remains what is the cause? Is it antidiuretic hormone (ADH) as is commonly assumed or is it something else?

HYPOVOLAEMIA AND RENAL OUTCOME

In the 1970s, an orthodoxy developed concerning oliguria and hypovolaemia. It posited a spectrum beginning with dehydration where renal function, measured by glomerular filtration rate (GFR), was normal and oliguria the result of strong tubular reabsorption. Greater degrees of hypovolaemia were associated with reduced renal blood flow (RBF) and GFR. This was termed vasomotor nephropathy, and although there was impairment of function, there was no structural damage. And finally, the end-stage was ischaemic damage to the kidney called acute tubular necrosis (ATN). Medical students were warned that all oliguria was hypovolaemia until proved otherwise, and that a fluid challenge could be expected to fix the problem. Woe to anyone who failed to give fluid and thereby caused renal failure.

This model has some validity for the early stages of hypovolaemia. However, the end stage with renal failure is where things have been confusing.

There is a condition, well-described in autopsy studies, called bilateral cortical necrosis (BCN). Fortunately rare, it usually involves haemorrhagic shock with delayed resuscitation, so there may be an element of reperfusion injury. The findings are of confluent necrosis of all renal cell types in the cortex. It is interesting that the medulla, the most metabolically active renal tissue, is spared.

A case report[1] describes the histology:

> Total necrosis involving glomeruli, interstitium, and tubules. The interlobular and arcuate arteries of these areas were necrosed and contained thrombi, most of which were undergoing, or had undergone, fibrous organisation. The small portions of cortex not involved in the necrotic process were remarkably well preserved and, from a histological standpoint, appeared capable of producing normal urine; the total area of surviving cortex, however, was very small. Calcification was an outstanding feature of the necrosed areas, and affected the whole of the small necroses but only the outer margins of the large ones. The walls of the arteries and glomerular capillaries were particularly involved in the calcifying process. The medullary portions of the kidney were relatively normal except for the presence of haem casts in many of the collecting tubules. There was no evidence of pre-existing renal disease.

BCN is uncommon, but its existence shows that structural renal failure can occur in the setting of severe haemorrhage. What is more common is ATN, now called acute kidney injury (AKI). AKI is a clinical diagnosis, not a histopathologic one. The term is used for acute renal failure in critical care settings, usually involving multiple contributing factors; including sepsis, hypotension, tissue trauma, inotropic drugs, radiocontrast agents, aminoglycoside antibiotics, and sometimes hypovolaemia. It seemed reasonable in the past to think that reductions in RBF in these settings might cause ischaemic damage to the kidney. The problem was that renal biopsies, when performed, were usually normal or showed only minimal patchy histologic change, usually confined to proximal tubule and thick ascending limb of loop of Henle. The distal tubule was almost never involved. When present, changes included denuded tubular epithelium, apical blebs, loss of brush border membrane, loss of tight junction integrity, back leak of filtrate and granular casts. Basement membrane is intact, and tubular regeneration is possible. Glomerular damage is always absent.

While hypovolaemia may contribute to AKI, and should be corrected, it is not the dominant mechanism. In some cases, a major issue is poor renal perfusion caused by a low cardiac output state (for example, acute coronary syndromes or exacerbations of chronic ischaemia). In other cases, renal impairment can be found in high cardiac output states where there is profound vasodilation, such as systemic inflammatory response syndrome (SIRS), commonly seen in sepsis, major tissue trauma and sometimes the post cardiopulmonary bypass state. Profound vasodilation causes a low mean arterial pressure (MAP), and dilates the efferent arteriole. Both these mechanisms reduce glomerular filtration pressure and GFR, elevating the plasma creatinine.

RENAL PHYSIOLOGY OF HYPOVOLAEMIA

Oliguria is an appropriate response to hypovolaemia as the body strives to hold on to precious salt and water. The urine is concentrated. Urinary osmolality is high, at between two to four times plasma osmolality, depending on severity. Salt retention is marked. Urine sodium is always low (usually less than 20 mmol/L) and the urine colour is invariably dark.

It is important to understand the mechanism the kidneys use to make concentrated urine. Two things must happen, both of which are mediated by antidiuretic hormone (ADH). First, water permeability of the collecting ducts has to be increased. This is achieved by a V2-receptor-mediated action on aquaporin cycling. The second thing, which has not been stressed but is critical, is the creation of a hypertonic medulla to draw water though the aquaporin channels. *Urine cannot have a higher osmolality than the medullary interstitium*.

A hyperosmolar medulla is achieved by ADH acting on V1 vascular receptors to *change the distribution of blood flow within the kidney*. Preferential vasoconstriction in the glomeruli of cortical nephrons diverts RBF to juxtamedullary (JM) nephrons.[2] It is only the latter nephrons that have the long loops of Henle needed for the counter-current mechanism which creates a hypertonic medulla. The more blood shunted to JM nephrons, the more efficiently the counter-current mechanism works and the more hypertonic the medullary interstitium becomes.

Failure of this mechanism severely limits the ability of the kidney to create a hyperosmotic medullary interstitium. This may be the reason why non-selective vasodilation by volatile anaesthetics tends to impair urinary concentrating ability (see below). On the other hand, the mechanism may become so extreme in severe haemorrhagic shock, that RBF to the outer cortex becomes so diminished as to cause BCN as described above.

ADH also preferentially constricts the efferent arteriole. It is thought that intrarenal prostaglandins protect the afferent arterioles from the constrictor actions of ADH and other constrictors such as angiotensin. Although efferent constriction reduces RBF, it increases glomerular capillary pressure and filtration fraction. This helps maintain GFR and hence renal function. Efferent vasoconstriction in JM nephrons also reduces vasa recta blood flow, lessening washout of the rising medullary interstitial osmolality.

It is important to note that the vasoconstricting V1 effects of ADH are very strong during hypovolaemia, but that they are much less potent during vasodilated, normovolaemic states.[3]

RENAL FUNCTION DURING NORMOVOLAEMIC ANAESTHESIA

Concern about perioperative renal failure from anaesthesia is usually misplaced. Postoperative renal failure is extremely rare. When it occurs, it is usually after cardiac or major vascular surgery complicated by surgical factors resulting in embolic trashing of the renal arteries or by a major cardiac event leading to cardiogenic shock and high dose inotrope treatment. Occasionally, a rise in postoperative creatinine is associated with the perioperative use of non-steroidal anti-inflammatory drugs (NSAIDs). Outside these contexts, renal failure is vanishingly rare. And with the demise of the potentially nephrotoxic agents, methoxyflurane and enflurane, anaesthesia per se, is incredibly benign, even protective to the kidneys.

Renal function during anaesthesia depends on the volume status of the patient. With well-established dehydration or significant blood loss, renal physiology during anaesthesia seems the same as in the unanaesthetised state. The ADH effects are overwhelming. The urine is dark, its volume low and the need for fluid treatment clear-cut.

However, this is rarely the case with elective surgery. When the first hour's urine output is measured and found to be low, most patients will have received enough intravenous fluid to be in at least neutral, if not positive fluid balance. A formal fluid balance assessment can help exclude significant hypovolaemia, but the old assumptions underlying deficit calculations need to be questioned. Calculating preoperative fasting fluid deficits as 1.5 mL/kg/hour times hours fasting will often lead to estimated fasting deficits of over a litre even for a first morning case. Everyday experience tells us a glass of water (250 mL) first thing in the morning is sufficient to rehydrate most people. Similarly, previous estimates of up to seven to eight mL/kg/hour for oedema from surgical handing of tissues are now widely recognised as gross overestimates.

It has long been known that the renal handling of intravenous fluid loading is very different during anaesthesia than in the awake state.[4] A fluid load rapidly excreted awake, may curiously remain unexcreted in the same patient anaesthetised. Why anaesthetised patients in positive fluid balance retain fluid has not been well explained.

It is thought that inhalational anaesthetic agents per se have no significant effect on RBF or GFR. However, subjects in studies that show no change, invariably have MAPs well above the lower limit of autoregulation (80 mmHg). But, in real world anaesthesia, with generous co-administration of potent opioids or with effective regional anaesthesia, this is often not the case. Mild hypotension during anaesthesia is common, generally well tolerated and often not aggressively treated.

The effect of volatile anaesthetic-associated vasodilatory hypotension on renal function generally, and urine output in particular, is not well documented. Empirically, the kidneys function in many ways like a haemoconcentrator unit on a cardiopulmonary bypass circuit. The GFR and the urine output seem passively dependent on the MAP. It may be different with intravenous anaesthesia when the vasodilatory state is less pronounced. During propofol/remifentanil anaesthesia, GFR is maintained when MAP is reduced to 60 mmHg.[5]

The nature of the urine produced

In the euvolaemic or mildly hypervolaemic patient under anaesthesia, one may notice two very characteristic features of urine and urine production.

First, the urine is pale in colour. So pale, one is tempted to call it dilute. Oliguria with pale, dilute-looking urine is not easy to explain. In my practice, I have been analysing such urine and have found it to have a consistently high sodium content (in the range of 50-100 mmol/L) and an osmolality between 300-500 mOsm/kg. After adjustment for the salt content, it can be considered isothenuric, neither particularly concentrated nor dilute. The absence of concentrated urine is inconsistent with hypovolaemia (recall urinary sodium levels are less than 20 mmol/L during dehydration). Lack of dilute urine is surprising given the pale colour.

The second interesting observation is the pressure-dependence of urine flow under anaesthesia. Oliguria is common when mean arterial blood pressure drops below the autoregulatory threshold (80 mmHg). On the other hand, impressive polyuria (> 500 mL/h) can be seen if blood pressure is increased with a metaraminol infusion. That a vasoconstrictor could increase urine output is counterintuitive, but it is a reproducible finding. Paradoxically, the polyuria of metaraminol can sometimes be so great as to cause a negative fluid balance.

ADH stress response

Large rises in ADH do occur in response to major surgical stimulation.[6] However, both high-dose potent opioids and regional anaesthesia significantly blunt such responses. Also, minimally-invasive surgical techniques such as laparoscopy may be associated with lower ADH levels than older open techniques. As a result, surges in ADH levels are probably less common in current practice settings than before.

However, to the extent that ADH levels do go up during anaesthesia and surgery, ADH itself is not a good explanation for intraoperative oliguria in the absence of hypovolaemia. This is because the urine of ADH-induced oliguria should be concentrated and dark. And this is certainly not the case during routine anaesthesia in the absence of significant dehydration or major blood loss.

Volatile anaesthetic agents inhibit the V1-vasoconstrictive effects of ADH[7] required to make a hypertonic medulla. Interference with this mechanism impairs the ability of the kidney to make concentrated urine. Anaesthetic agents may also vasodilate the efferent arteriole reducing GFR and urine output further. There is also some evidence that V2 effects of ADH may be blunted by volatile anaesthetics.[8] Taken together, volatile anaesthetics seem to have some potential to cause ADH resistance. The levels are high, but the effects blunted. Oliguria seems more the result of a low GFR than strong water reabsorption.

Sympathetic stimulation

The kidneys are well supplied by the sympathetic nervous system.[9] Noxious stimulation causes activation of the renin-angiotensin-aldosterone system. The overall effect of sympathetic activation on the kidneys is a balance between systemic effects (cardiac output and blood pressure), renal hormonal effects (renin, angiotensin, aldosterone) and intra-renal vascular effects. In the absence of hypovolaemia, sympathetic stimulation usually promotes fluid retention via hormonal effects.

Intravenous fluid administration

During anaesthesia, patients are often placed into positive fluid balance by the generous administration of intravenous fluids high in sodium. Volume overload inhibits aldosterone production and stimulates atrial natiuretic factor (ANF) production. The result is a high sodium excretion (saline in, saline out).

NSAIDs and COX-2 Inhibitors

Inhibition of prostaglandins by NSAIDs and COX-2 inhibitors are known in medical settings to cause salt and water retention,[10] which promotes oedema and makes the management of essential hypertension more difficult. When these agents are used by anaesthetists for pain management, they may promote fluid retention.[11] If the subsequent oliguria is treated with additional fluids, this can make a positive fluid balance even more positive.

Fasting

Twenty-four hour food fasting in healthy rats with free access to water causes significant impairment of urinary concentrating ability.[12] This is associated with a reversible down-regulation of aquaporin-2 expression in the collecting ducts (that is, an anti-V2 ADH effect). Addition of glucose to the drinking water does not prevent this. Shorter fasts have not been studied, and the relevance of this to humans fasting for surgery is unknown.

CONCLUSIONS

Oliguria is common during anaesthesia in patients with neutral or positive fluid balance. Hypotension is an important contributing factor. ADH does not play a major role. Increasing the blood pressure with vasoconstrictors is effective at promoting urine flow. Pale urine in this context is not dilute, but does serve to rule out significant dehydration.

Providing that fluid balance is positive, that mean arterial blood pressure is above the lower limit of autoregulation (80 mmHg), that the urine is pale, and that NSAIDs and COX2 inhibitors are not used, there is no evidence that leaving oliguria untreated leads to renal impairment. Chasing urine output in this context with liberal fluid administration can cause dilutional anaemia and dilutional coagulopathy, and needs to be considered carefully rather than embarked upon blindly.

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Monoclonal antibody therapy – Implications for anaesthesia, intensive care and pain medicine

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INTRODUCTION

Therapy for malignant diseases traditionally encompassed non-selective chemotherapeutic agents. As many of the biochemical and molecular changes of disease processes are being better defined, potential targets for new therapeutic strategies are identified. Immunomodulators and biological agents are examples of targeted therapies now in clinical use. These agents have expanded the therapeutic opportunities for many serious malignant and also non-malignant diseases.

Among these, the efficacy of monoclonal antibody (Mab) therapy is now established and its use is likely to be encountered in our practice in anaesthesia, intensive care and pain medicine. Although there is no known specific interaction between Mabs and anaesthetic agents, their use is clinically relevant for anaesthetists involved in the perioperative management of patients who are on Mab therapy, as there are clinical issues that may be encountered due to the adverse effects of these agents. In addition, there has also been interest in the potential uses of Mabs in intensive care and pain medicine.

In intensive care, patients on Mabs are likely to be encountered due to the severity of the underlying diseases for which they are being treated. The main concern with these patients would be immunosuppression during critical illness but there are also some other serious adverse effects.

Despite much initial interest in the role of Mabs in the management of severe sepsis, at present, there is a lack of evidence for a beneficial role for biologic agents targeted to host response in severe sepsis. However the disease-modifying properties of these agents are useful in the long-term management of some diseases such as severe asthma.

In pain medicine, biological agents that modify chronic painful conditions such as rheumatoid arthritis are of interest. By reducing disease severity, these agents may be potentially beneficial in pain management.

MONOCLONAL ANTIBODIES

Mabs can modulate the natural course of disease by targeting particular antigens expressed on the surface of cells during the pathogenic process.[1] Their main mechanism of action is by activation of the antibody dependent cytotoxic pathway and complement mediated cytotoxicity. They also act by apoptotic signalling and growth inhibitory pathways.[2]

Mabs are produced using a single clone of antibody-producing cells. The first Mabs were created by fusion of a mouse myeloma cell with an antibody-producing mouse B-cell. With technical advances, there has been a transition from the production of murine (mouse) to chimeric or humanised, to fully human Mabs via recombinant techniques.[3] This has improved the safety and efficacy profile of these agents.

CLINICAL USES

Although initially used for cancer immunotherapy, the use of Mab therapy has now expanded to include many non-malignant conditions such as inflammatory bowel diseases, skin and joint diseases, multiple sclerosis, prevention and treatment of rejection in organ transplantation, allergic disorders and as anti-thrombotic agents.

As an example, in rheumatoid arthritis, the benefits of infliximab and adalimumab use include reduced pain, improvements in all disease measures, inhibition of structural damage, and reduction in surgery and hospitalisation.[1,4]

Mabs are an example of protein therapeutics with targeted actions. Their advantages over conventional drugs for similar indications include high specificity which facilitates precise action and their long half-lives, which allow infrequent dosing. Developments in molecular engineering technologies have meant that the structure of Mabs can be fine-tuned for specific therapy and to minimise immunogenicity, thereby improving their risk-benefit ratio. This is reflected in Mabs having approval rates for clinical use of around 20% compared with 5% for other new chemical entities.[3] Mab therapy has been extensively evaluated and shown to have high response rates and durable remissions for some previously refractory, advanced diseases such as rituximab in haematological malignancies (for example, B-cell lymphomas) and trastuzumab in metastatic breast cancer.

Rituximab maintenance treatment has been shown to improve the overall survival of patients with refractory or relapsed follicular lymphoma[5] and there is mature data confirming the efficacy of trastuzumab in breast cancer with significant improvement in the disease-free survival and overall survival.[6] Hence, Mabs are now widely used for these and other malignancies, as indicated.

In non-malignant diseases such as rheumatoid arthritis, it is important to take into account the fact that they are usually used when treatment targets are not reached with the first-in-line disease-modifying agents. These patients may have poor prognostic factors which reflect underlying moderate to severe disease before they are commenced on Mabs as adjuvant or alternative therapy.

Currently approved Mabs in New Zealand and their indications of use are summarised in table 1.[7] The most common drugs in current use in New Zealand are infliximab and rituximab for rheumatoid arthritis, bevacizumab in ophthalmology and basiliximab and abciximab in cardiology.

Table 1. Currently approved monoclonal antibodies in New Zealand*

Name	Trade Name	Type	Mechanism of action	Indications
Abciximab	Reopro	Anti-platelet glycoprotein IIb/IIIa receptor antibody	Inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive molecules to GP IIb/IIIa receptor sites on activated platelets.	Adjunct to heparin and aspirin for: - percutaneous coronary intervention - unstable angina
Adalimumab	Humira	Antibody against tumour necrosis factor (TNF-α) receptor	Neutralises the biological function of TNF by blocking its interaction with receptors. TNF is a naturally occurring cytokine involved in normal inflammatory and immune responses.	- Rheumatoid arthritis - Polyarticular juvenile idiopathic arthritis - Psoriatic arthritis - Psoriasis - Ankylosing spondylitis - Crohn's disease
Alemtuzumab	MabCampath	Antibody against lymphocyte cell surface glycoprotein CD52 antigen	Causes lysis of lymphocytes by binding to CD52 antigen via complement fixation and antibody – dependent cell mediated cytotoxicity	Third line treatment of patients with chronic lymphocytic leukaemia (CLL)
Basiliximab	Simulect	Antibody against interleukin-2 receptor CD25 antigen on activated T-lmphocytes	Prevents binding of interleukin-2, the signal for T-cell proliferation	Prophylaxis of acute organ rejection in de novo renal transplantation in combination with other immunosuppressants
Bevacizumab	Avastin	Antibody against human vascular endothelial growth factor (VEGF)	Neutralising the biologic activity of VEGF reduces tumour angiogenesis, thereby inhibiting tumour growth	As part of combination chemotherapy for: - Metastatic colorectal and breast cancer - Advanced &/or metastatic renal cell cancer - Advanced, metastatic or recurrent NSCLC - Relapsed high grade malignant glioma
Canakinumab	Ilaris	Anti-human interleukin-1β (IL-1β) antibody	Preventing IL-1β-induced gene activation and the production of inflammatory mediators such as interleukin-6 or cyclooxygenase-2	Cryopyrin-Associated Periodic Syndromes

Name	Trade Name	Type	Mechanism of action	Indications
Certolizumab pegol	Cimzia	Antibody against TNF-α receptor	Inhibition of lipopolysaccharide-induced TNFα and interleukin-1β production in human monocytes	Moderate to severe active rheumatoid arthritis
Cetuximab	Erbitux	Antibody against epidermal growth factor receptor (EGFR)	Inhibits the proliferation and induces apoptosis of human tumour cells that express EGF, inhibits expression of angiogenic factors by tumour cells and causes a reduction in tumour neo-vascularisation and metastasis	- (EGFR)-expressing, K-RAS wild-type metastatic colorectal cancer - Squamous cell cancer of the head and neck
Denosumab	Prolia	Anti-RANK ligand (RANKL) antibody	Inhibits osteoclast formation, function and survival	Osteoporosis in postmenopausal women
Eculizumab	Soliris	Antibody against α-chain of the C5 complement protein	Restores terminal complement regulation in the blood of PNH patients and inhibits terminal complement mediated intravascular haemolysis in PNH patients	Paroxysmal nocturnal haemoglobinuria (PNH) to reduce haemolysis
Efalizumab	Raptiva	Antibody agains LFA-1 (leukocyte function associated antigen-1)	Inhibition of T lymphocyte proliferation, inhibition of T lymphocyte trafficking to psoriatic lesions; inhibition of T lymphocyte interaction with keratinocytes	Moderate to severe chronic plaque psoriasis
Golimumab	Simponi	Antibody against tumour necrosis factor (TNF-α) receptor	Neutralise TNF-induced cell-surface expression of adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and cellular adhesion molecule (ICAM)-1, inhibition of TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells	- Rheumatoid arthritis - Psoriatic arthritis - Ankylosing spondylitis
Infliximab	Remicade	Antibody against tumour necrosis factor (TNF-α) receptor	Neutralises the biological activity of TNFα	- Rheumatoid arthritis - Psoriatic arthritis - Psoriasis - Ankylosing spondylitis - Crohn's disease - Ulcerative colitis

Name	Trade Name	Type	Mechanism of action	Indications
Natalizumab	Tysabri	Antibody against α4-subunit of 4β1 and 4β7 integrins	Inhibits the α4-mediated adhesion of leucocytes to their receptors	Relapsing remitting multiple sclerosis
Omalizumab	Xolair	Antibody against human immunoglobulin E	Prevents binding of IgE to the high-affinity FcεRI receptor, thereby reducing the amount of free IgE that is available to trigger the allergic cascade	Severe persistent allergic asthma
Palivizumab	Synagis	Antibody directed to an epitope in antigenic site of fusion protein of respiratory syncytial virus (RSV)	Neutralising and fusion-inhibitory activity against RSV which inhibit RSV replication	Prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease
Ranibizumab	Lucentis	Antibody against human vascular endothelial growth factor A (VEGF-A)	Inhibits endothelial cell proliferation, neovascularisation and vascular leakage	- Neovascular age-related macular degeneration - Visual impairment due to diabetic macular oedema - Macular oedema secondary to retinal vein occlusion
Rituximab	Mabthera	Antibody against CD20 antigen on B-lymphocytes	Initiates immunologic reactions that mediate B-cell lysis	- CD20 positive B-cell non-Hodgkin's lymphoma - Chronic lymphocytic leukaemia - Severe active rheumatoid arthritis
Tocilizumab	Actemra	Antibody against IL-6 receptors	Inhibition of IL-6 (involved in local paracrine function as well as regulation of systemic physiological and pathological processes)	Moderate to severe active rheumatoid arthritis
Trastuzumab	Herceptin	Antibody against human epidermal growth factor receptor 2 protein (HER2)	Inhibit the proliferation of human tumour cells that overexpress HER2	- HER2-overexpressive metastatic breast cancer - HER2-positive early breast cancer - Advanced gastric cancer
Ustekinumab	Stelara	Antibody against human cytokines interleukin (IL)-12 and IL-23	Prevents IL-12 and IL-23 contributions to immune cell activation, such as intracellular signalling and cytokine secretion	Moderate to severe plaque psoriasis

*Table constructed from data available in Medsafe[7]

ADVERSE EFFECTS OF MONOCLONAL ANTIBODY THERAPY

Due to the inherent nature and the mechanism of action of Mabs, their use carries the risk of adverse effects such as immune reactions and infections that are well-described and expected with their use. As their use increases, new and unexpected side effects are being reported. Despite this, the benefits of Mab therapy outweigh the risks associated with these adverse effects for many severe, previously refractory diseases. These agents continue to be evaluated with the aim to identify and minimise the risk of these adverse effects.

The following is a discussion of selected adverse effects of Mabs and their relevant implications. At present, as there are no consensus guidelines available for perioperative management specific to individual Mabs and their potential adverse effects, the implications discussed are based on the literature available. The adverse effects of various agents approved in New Zealand are summarised in table 2.[7]

Table 2. Adverse effects of monoclonal antibodies approved in New Zealand*

Name	Trade Name	Selected adverse effects
Abciximab	Reopro	- Most common complication was bleeding during the first 36 hours - Associated with an increased risk of retroperitoneal bleeding with femoral vascular puncture - Hypersensitivity or allergic reactions have been observed rarely
Adalimumab	Humira	- Serious infections, sepsis, rare cases of tuberculosis (TB) and candidiasis - Associated with reactivation of hepatitis B virus (HBV) - Rare associations with new onset or exacerbation of CNS demyelinating disease, including multiple sclerosis and peripheral demyelinating disease, including Guillain Barré syndrome - Worsening congestive heart failure (CHF) - Impaired wound healing - Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged) - Muscle spasms (including blood creatine phosphokinase increased)
Alemtuzumab	MabCampath	- Profound lymphocyte depletion inevitably occurs and may be prolonged - Potential for GVHD in severely lymphopenic patients (irradiated blood products should be used) - Cardiac disorders
Basiliximab	Simulect	- Severe acute hypersensitivity reactions - Increased risk of developing lymphoproliferative disorders and opportunistic infections - Postoperative wound complications - Hyperkalaemia - Hypersensitivity/anaphylactoid reactions
Bevacizumab	Avastin	- May be at increased risk for development of gastrointestinal perforation and gallbladder perforation - Impairment of wound healing - Arterial and venous thromboembolic events - Haemorrhage including pulmonary and tumour-associated haemorrhage - Rare reports of Reversible Posterior Leukoencephalopathy Syndrome - Congestive heart failure
Canakinumab	Ilaris	- Infections, predominantly of the upper respiratory tract, in some instances serious - Normalisation of suppressed CYP450 expression- relevant in CYP450 substrates with a narrow therapeutic index
Certolizumab pegol	Cimzia	- Worsening CHF and increased mortality due to CHF - Rare cases of exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease including multiple sclerosis - Reactivation of HBV & TB - Interference with certain coagulation assays - Electrolyte imbalance - Long half-life: implications for post-surgical infections
Cetuximab	Erbitux	- Severe cardiovascular events in combination with fluoropyrimidines - Electrolyte imbalance including hypomagnesaemia, hypokalaemia & hypocalcaemia - Dehydration - Increased severe neutropenia and leukopenia in combination with platinum-based chemotherapy

Name	Trade Name	Selected adverse effects
Denosumab	Prolia	- Infections - Hypocalcaemia - Pancreatitis - Osteonecrosis of the jaw
Eculizumab	Soliris	- Increases susceptibility to meningococcal infections
Efalizumab	Raptiva	- Increased risk of Progressive Multifocal Leukoencephalopathy (PML) - Inflammatory polyradiculoneuropathy - Serious infections - Thrombocytopenia
Golimumab	Simponi	- Reactivation of HBV & TB - Increased severity of infections - Worsening and new onset CHF - Rare associations with new onset or exacerbation of CNS demyelinating disease, including multiple sclerosis and peripheral demyelinating disease, including Guillain Barré syndrome - Haematological cytopaenias - Long half-life: implications for post-surgical infections
Infliximab	Remicade	- Opportunistic infections - Serum-sickness-like reactions - Increased severity of infections - Worsening and new onset CHF
Natalizumab	Tysabri	- Increased risk of PML - Opportunistic infections - Hepatotoxicity
Omalizumab	Xolair	- Anaphylaxis - Idiopathic severe thrombocytopenia
Palivizumab	Synagis	- Apnoea - Convulsions - Thrombocytopaenia - Hypokalaemia - Cardiovascular disorders
Ranibizumab	Lucentis	- Stroke - Anaemia - Serious ocular events
Rituximab	Mabthera	- Pulmonary events including hypoxia, lung infiltration, and acute respiratory failure - Rapid lysis activity can lead to tumour lysis syndrome - Serious infections - Associated with reactivation of HBV - Increased risk of PML
Tocilizumab	Actemra	- Gastrointestinal perforation - Serious and opportunistic infections - Reactivation of HBV & TB - Normalisation of suppressed CYP450 expression- relevant in CYP450 substrates with a narrow therapeutic index
Trastuzumab	Herceptin	- Pulmonary toxicity, interstitial lung disease - Moderate to severe cardiac dysfunction - Pancreatitis, hepatic failure, - Anaemia, hypoprothrombinaemia
Ustekinumab	Stelara	- Serious and opportunistic infections

*Table constructed from data available in Medsafe[7]

1. Immune reactions

Mabs are generally well tolerated in humans, however infusion reactions, acute or with delayed onset of symptoms, can develop. They are caused by various mechanisms including acute anaphylactic (IgE-mediated) and anaphylactoid reactions, serum sickness, tumour lysis syndrome (TLS) and cytokine release syndrome (CRS).[3] These can range from mild skin reactions and pyrexia to severe acute anaphylaxis and systemic inflammatory response syndrome.

TLS is a serious, potentially fatal complication that can occur with Mab therapy for cancer as has been observed with rituximab used for chronic lymphocytic leukaemia and lymphomas.[3,8] The metabolic and biochemical abnormalities of TLS can result in kidney damage and acute renal failure.[3,9,10]

One important element of Mab therapy is the potential for development of CRS, which is the result of excessive secretion of pro-inflammatory mediators.[11] CRS can also occur with infections and non-infectious conditions such as graft versus host disease. In March 2006, life-threatening CRS was observed in patients treated with TGN1412 (a Mab) in a first in-human study which has led to increased awareness on the assessment of safety versus the overall benefits of disease reduction associated with biological agents.[3,11]

Implications:

- Management of acute severe immune reactions include stopping infusion of the drug and supportive treatment for haemodynamic and respiratory effects as with any other causes of acute anaphylaxis or systemic inflammatory response syndrome.
- The main principles of TLS and CRS management are identification of high-risk patients with initiation of preventive therapy and early recognition of metabolic and renal complications and the prompt administration of supportive care, including haemodialysis. Severe electrolyte disturbances, such as hyperkalaemia and hypocalcaemia, predispose patients to cardiac arrhythmia and seizure.

2. Infections

Like immune reactions, infections are a result of target-mediated effects of Mab therapy causing acquired immunodeficiency. Tumour necrosis factor (TNF) specific Mab therapy has been associated with an increased risk of serious infections and malignancies in a small number of patients.[3,12] Although uncommon, serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral or other opportunistic pathogens have been reported and when they occur there can be disseminated rather than localised disease, in patients taking concomitant immunosuppressants (such as methotrexate or corticosteroids with infliximab).[13,14]

One of the major problems in determining causality between biological therapy and infection is the fact that, in some cases, the underlying disease process itself can cause immunosuppression. This is the case for patients with cancer, autoimmune diseases and inflammatory conditions such as rheumatoid arthritis. In the case of rare infections, a true association is difficult to prove definitively due to the small number of events.[15]

Reactivation of latent tuberculosis (TB), presumably due to a key role for TNF-α in immunity to Mycobacterium tuberculosis, is a limiting side effect.[3,16,17] There have been reports of increased risk of TB in patients with inflammatory bowel disease treated with TNF-specific Mabs,[3,18] although infliximab was generally well tolerated among patients with Crohn's disease.[19]

Infliximab and rituximab have also been associated with hepatitis B reactivation.[13]

Implications:

- Immunosuppression occurs with the use of Mabs as with other chemotherapeutic agents. These patients may also be on multiple immunosuppressive agents at the same time. Meticulous attention to aseptic techniques during invasive interventions is important to avoid iatrogenic infection.
- In a non-operative setting, management of serious infections and malignancies associated with Mab use involves supportive treatment and consideration of cessation of Mab therapy in consultation with the treatment-initiating physician.
- Evaluation for TB risk factors, Quantiferon gold testing and a baseline chest X-ray, as indicated, is performed prior to initiation of therapy, and if the patient tests positive, chemoprophylaxis for latent TB is initiated prior to the start of treatment with TNF-α inhibitors. This is of interest as these may include isoniazid and rifampicin, with their own adverse effects and drug interactions.
- In general, it is not recommended that TNF-α inhibitors (or any other potentially immunosuppressive agents, for that matter) be started in patients with active infections, and caution should be used for patients with a history of chronic or recurrent infections.
- Hepatitis B virus reactivation has occurred with TNF-α inhibitors, and while product labels are equivocal regarding the safety of concomitant anti-viral therapy, limited data suggest that prophylaxis with lamivudine seems to be effective and well tolerated.[15]
- Compliance with local infection control policies and decontamination practices with respect to re-usable anaesthetic equipment are important in minimising the risk of cross-infection and nosocomial infections in these patients.

3. Impaired wound healing

Many patients may require surgery while on Mabs for other medical conditions as well as for the underlying condition for which they are on Mab therapy, for example, inflammatory bowel disease. There has been concern about postoperative wound complications especially with TNF and vascular endothelial growth factor (VEGF) targeted therapies. Unfortunately, there is no consensus on the perioperative management of Mabs. Due to the variabilities associated with different Mabs and disease factors, it is recommended that the use of Mabs in the perioperative period is reviewed on an individual basis.

Most reviews of the rheumatology literature recommend discontinuing any TNF inhibitor for a week prior to surgery, with resumption of treatment two to four weeks after surgery.[20] Even then, there is conflicting interpretation and some authors do not recommend the discontinuation of TNF inhibitors in the perioperative setting.[21]

Bevacizumab is a recombinant Mab that selectively binds to and neutralises the biological activity of human VEGF. It has a long half-life of approximately 20 days but can vary between 11 and 50 days.[22] Bevacizumab has been associated with impaired wound healing possibly due to its extended half-life.[22,23] It has been recommended that bevacizumab should not be initiated for at least 28 days after major surgery or until the surgical incision is completely healed.[24,25]

However, in patients with co-morbidities (for example, diabetes, peripheral vascular disease) or with wound-healing issues, there have been recommendations to extend the interval between surgery for colorectal cancer and bevacizumab therapy to six to eight weeks.[26]

Implications:

- Surgical stress, advanced age, co-morbid conditions and poor perioperative nutritional status as well as concomitant immunosuppressants contribute to an increased risk of infection in the surgical patient.
- Currently there is no consensus on the management of individual Mabs in the perioperative setting. The half-life and agent-specific effects as well as the type of surgery and concomitant use of other chemotherapeutic agents are all important factors to be considered in making decisions on continuation or initiation of Mab therapy in the perioperative period.
- Many rheumatology reviews take a cautious approach and recommend discontinuing any TNF inhibitor for a week prior to surgery, with resumption of treatment two to four weeks after surgery. However, in some cases where the discontinuation of therapy would have a significant impact on morbidity (for example, rapidly destructive Still's disease) it is important to consult with the treatment-initiating physician.
- In the case of bevacizumab, it has been recommended that it should not be initiated for at least 28 days after major surgery or until the surgical incision is completely healed.

4. Lung injury

The incidence and clinical characteristics of adverse pulmonary reactions resulting from Mab therapy have not been well described unlike the pulmonary complications associated with chemotherapeutic agents such as cyclophosphamide and bleomycin.

Rituximab has been in clinical use since 1997. It has been implicated in cases of interstitial pneumonitis but the incidence of lung injury is very rare. During clinical trials of rituximab, respiratory manifestations such as cough, bronchospasm, sinusitis and rhinitis were reported but not serious late onset pulmonary side effects.[27,28] In a review of 55 cases, reports of rituximab-induced lung injury included an acute reaction in the form of ARDS, delayed presentation in the form of acute to sub-acute hypoxaemic organising pneumonia and late onset macronodular organising pneumonia.[27,29-34]

The pathogenesis of rituximab-induced lung injury is proposed to be secondary to cytotoxic T lymphocytes activation, complement activation and cytokine release after rituximab infusion. Cytotoxic T lymphocytes cause vascular and alveolar damage. Complement activation in turn activates macrophages and mast cells which in turn produce cytokines, C3a and C5a.[30,35-37]

Implications:

- Lung injury, although less frequently seen, can be a complication of Mab therapy as with conventional cancer chemotherapeutic agents.
- In the preoperative assessment, history and examination suggestive of lung injury in the patient on Mab therapy warrants further evaluation to assess the extent of the problem including chest X-ray, arterial blood gas and pulmonary function tests as appropriate.

5. Cardiotoxicity

Hypo or hypertension, arrhythmias, congestive heart failure and left ventricular dysfunction have been observed in patients treated with Mabs, as with conventional chemotherapeutic agents. However, unlike the known dose-dependent cardiotoxicity with anthracyclines such as doxorubicin, there is currently a lack of clear risk profiling of cardiotoxicity with specific Mabs.[38] Trastuzumab (Herceptin) has been used successfully in HER2-positive metastatic breast cancer. Cardiotoxicity was an unexpected adverse effect of its use, observed in up to 4% of patients.[3,39-41] The cardiac dysfunction is usually an asymptomatic, reversible decrease in left ventricular ejection fraction. It was more likely to develop with trastuzumab used in combination with anthracyclines.[42] Cardiac dysfunction can progress to cardiac failure but this usually responds well to medical management.[43]

Implications:

- In the preoperative cardiac evaluation, along with assessment of other risk factors for cardiovascular disease, patients on Mabs and other chemotherapeutic agents should ideally have a transthoracic echocardiogram to identify any reduction in left ventricular ejection fraction and cardiomyopathy.
- Arrhythmias may be present and ECG is necessary. Electrolyte imbalances require correction.
- Invasive monitoring and inotropic support may be necessary in these patients.

6. Platelet and thrombotic disorders

Haematological complications can occur with many types of myelosuppressive medications including Mabs. Acute, severe, self-limiting thrombocytopaenia can occur with infliximab and rituximab.[3,44]

Abciximab is an antiplatelet glycoprotein IIb/IIIa receptor inhibitor that has been successfully used to reduce myocardial infarctions in patients with acute coronary syndromes having angioplasty.[1] It has also been used intra-procedurally for prevention of thrombus formation following endovascular coil placement in cerebral artery aneurysms.[45-47] Acute or sometimes delayed thrombocytopaenia can develop with its use.[3,48-51]

Pro-aggregatory effects that can cause thrombotic complications have also been observed.[3,52,53] Bevacizumab has been associated with arterial and venous thromboembolic events.[54,55]

Implications:

- Anti-platelet glycoprotein IIb/IIIa receptor inhibitors, such as abciximab inhibit platelet aggregation by interfering with platelet-fibrinogen binding and subsequent platelet-platelet interactions. Time to normal platelet aggregation after discontinuation of abciximab therapy is 48 hours. There is a risk of perioperative bleeding in patients undergoing surgery within this period and it warrants concern regarding the risk of anaesthesia-related haemorrhagic complications.[56]
- For regional anaesthesia, platelet function needs to recover before neuraxial block after administration of platelet GP IIb/IIIa receptor antagonists. For abciximab, this is 48 hours after cessation.
- There are no studies that examine the frequency and severity of haemorrhagic complications after central neuraxial or plexus block in patients on Mabs. Few reports of serious complications after neurovascular sheath cannulation for surgical, radiological, or cardiac indications have been reported. Given the paucity of information, it is not possible to make definitive recommendations.[57]
- The concurrent use of other anticoagulant drugs, platelet count and platelet function tests need to be taken into account when performing regional blocks in these patients. Techniques involving superficial and easily compressible vasculature would generally be considered safe.

7. Renal effects

Bevacizumab, sorafenib, and other anti-VEGF drugs are frequently complicated by mild proteinuria and hypertension. Other renal effects, such as high-grade proteinuria and acute kidney injury, have also been described. The most common histopathologic kidney lesion is thrombotic microangiopathy, with other glomerular lesions and interstitial nephritis occurring less frequently.[58]

Implications:

- Preoperative investigations should include renal function tests in patients on Mabs.
- Preoperative risk factors for developing acute renal dysfunction for patients on Mabs include the disease process for which they are on Mab therapy, advanced age, chronic renal disease, hypovolaemia, sepsis as well as drug nephrotoxicity.
- The identification of high-risk patients and the implementation of prophylactic measures are the goals of perioperative renal protection. These include intravascular volume expansion, maintenance of renal blood flow and renal perfusion pressure, avoidance of nephrotoxic agents, glycaemic control, and appropriate management of postoperative complications.[59]

8. Neurological effects

No studies have been done to look at potential Mab interactions with anaesthesia. There have only been a few case reports implicating Mabs with neurological effects postoperatively. However, there is a likelihood that neurological effects that can be a potential adverse effect of Mab therapy may manifest as more pronounced changes in the post-anaesthetic period.

Several cases of demyelinating events of the nervous system have been reported, prompting a heightened surveillance of patients on Mab therapy. Recent data are reassuring, suggesting that the incidence of such events is relatively low. Natalizumab, a Mab that is efficient in relapsing-remitting multiple sclerosis, has been associated with progressive multifocal leukoencephalopathy (PML). It has been suggested that rituximab is a risk factor for PML, however, evidence of such a link is unclear.[60]

In a case report of infliximab-related muscle weakness manifesting immediately after anaesthesia, an initial diagnosis of acute demyelination was made, presumed to be secondary to recent infliximab infusion.[61] However, there was rapid radiological improvement and a diagnosis of reversible encephalopathy syndrome was made. This syndrome is also associated with other immunosuppressive drugs including tacrolimus and cyclosporine.

There has also been one case report of prolonged succinylcholine action during electroconvulsive therapy after cytarabine, vincristine and rituximab chemotherapy.[62]

Implications:

- Patients on Mab therapy, especially in combination with other chemotherapeutic agents may have sub-clinical neuropathy or muscle weakness that may become more pronounced in the postoperative period. Initial management is supportive and along with other causes commonly attributed to acute neurological signs, adverse effect of the Mab should be considered.
- If regional anaesthesia is considered for these patients, a thorough preoperative neurological examination and contemplation of risks versus benefits is warranted.

CLINICAL CONSIDERATIONS FOR ANAESTHETISTS

Patients with severe diseases are at increased risk of requiring surgical interventions and are at higher risk of complications. With the addition of Mab therapy, some of these complications may become more likely or pronounced. This may be due to the severity of the disease process itself, concomitant chemoradiotherapy, perioperative requirements of fasting, physiological changes due to the surgical insult, interactions with other medications and susceptibility of specific adverse effects developing in certain conditions. Although there is no known specific interaction between Mabs and anaesthetic agents, awareness of their potential adverse effects is useful should unexpected adverse events be encountered in the perioperative period.

MABS IN INTENSIVE CARE

Mabs may be encountered in the intensive care unit in transplant patients where they are used as immunosuppressants before and after transplantation. Basiliximab and daclizumab have been shown to reduce the frequency of acute rejection episodes among kidney recipients. In randomised trials, patients treated with basiliximab or daclizumab showed no greater incidence of adverse reactions than those treated with placebo. Neither agent elicited cytokine release syndrome.[63] There was much interest in the early stages of research into the potential uses of Mabs in sepsis. However, there is a lack of evidence for a beneficial role for biological agents targeted to host response in severe sepsis. Multiple previous studies have failed to find a significant mortality benefit.[64] The disease-modifying properties of these agents are useful in the long-term management of some diseases such as severe asthma. Treatment approaches that have been demonstrated to reduce severe exacerbation risk in difficult-to-treat allergic asthma include the use of a montelukast, a leukotriene receptor antagonist or omalizumab, a Mab directed against IgE.

Omalizumab is available for the treatment of allergic asthma and asthma treatment guidelines recommend its use in adults with difficult-to-treat asthma, who are sensitised to environmental allergens. Omalizumab has been effective in reducing asthma exacerbation risk in this patient population. It is, in general, well tolerated, but reports have identified rare episodes of anaphylaxis after administration, in less than 0.1% of treated patients. Its high cost has also limited its use in patients with difficult-to-treat asthma.[65]

The main concern with patients on Mabs with critical illness is acquired immunodeficiency. Management guidelines for sepsis associated with immunosuppressive medications, have been developed under the Surviving Sepsis campaign, to improve outcomes in severe sepsis.[66] The guidelines concluded that immunosuppressed patients are susceptible to a wider spectrum of infectious agents than immunologically normal patients, and thus, require a broader antibiotic regimen when they present with sepsis or septic shock.

Implications:

- Special expertise is needed when managing immunosuppressed patient populations, to predict and establish the correct diagnosis, and to choose both appropriate empiric and specific agents.[66]
- Extensive microbiological testing, early commencement of antimicrobial therapy, enteral immuno-nutrition and selective decontamination of the gut may also be necessary to prevent or reduce some of the more serious infective complications in patients taking immunosuppressants, including Mabs.[66]
- Mab therapy would be contraindicated for patients with clinically important and active infection.[67]

MABS IN PAIN MEDICINE

In the research into the use of Mabs for the treatment of pain, current targets are soluble mediators, for example, cytokines, growth factors and inflammatory mediators. TNF-α, interleukin-6 (IL-6) and nerve growth factor (NGF) are examples of potential therapeutic inflammatory and/or analgesic targets. Tanezumab, a Mab which sequesters NGF appears promising as a therapeutic Mab for pain associated with some conditions. In phase II trials, it was well tolerated and showed efficacy in reducing pain scores and global assessment scores in patients with osteoarthritis and chronic lower back pain. It is currently in phase III trials.[68] Pain may be a common and debilitating symptom of many chronic inflammatory conditions such as rheumatoid arthritis, ankylosing spondylitis and Crohn's disease. Although conventional analgesics such as opioid and non-opioid analgesics can help with pain control, they do not control disease activity. In rheumatoid arthritis for example, agents such as methotrexate and leflunomide can help reduce disease activity. Biological agents such as infliximab, adalimumab (anti-TNF Mabs), rituximab (Mab against B cells) and tocilizumab (anti-IL-6 Mab) have been shown to be highly effective as an adjunct to methotrexate or as alternative disease-modifying agents in rheumatoid arthritis. By reducing disease severity, these agents can be beneficial in reducing pain severity as well.[69]

Denosumab, a Mab against receptor activator of nuclear factor-κB ligand (RANKL) is available for targeted therapy for symptom palliation in osteoporosis and in bony metastases from prostate, breast and other cancers. In New Zealand, it is approved for use in osteoporosis in post-menopausal women to prevent bone loss and subsequent fractures. By inhibiting osteoclast activity, it limits bone turnover and resorption. This disease modification effect helps reduce pain and prevent subsequent skeletal complications which can result in decreased mobility and quality of life.[70]

Implications:

- By targeting mechanisms involved in the pain pathway, biological agents such as Mabs are potential therapeutic options for pain. Some Mabs are already in clinical use in other conditions such as chronic inflammatory diseases which are associated with pain.
- Mabs and other biologics may be beneficial as disease-modifying agents. Their use should be considered in patients with chronic inflammatory conditions who have incomplete response to conventional disease-modifying drugs. Although their use is limited due to cost and concerns about the adverse effects such as infections and immune reactions discussed above, in patients with severe, refractory disease, their benefits may outweigh these concerns.

CONCLUSION

In recent years research into new therapeutic modalities has resulted in currently available biological agents such as Mabs for serious, previously refractory diseases. Mabs have important disease-modifying properties that may have a beneficial impact in the management of some severe illnesses and they may also be advantageous in pain management by reduction of disease severity. However, it is important to bear in mind that the use of Mabs as adjuvant or alternative therapy is an indicator of underlying disease severity. Mabs have many potential benefits but an awareness of their increasing use and associated adverse effects is important to aid management if we encounter unexpected complications in our practice. As research progresses and more evidence becomes available, further recommendations on the use of new immunotherapies in the perioperative setting is anticipated.

GLOSSARY

Mab/Mabs	monoclonal antibody/monoclonal antibodies
IgE	immunoglobulin E
TLS	tumour lysis syndrome
CRS	cytokine release syndrome
TNF	tumour necrosis factor
TB	tuberculosis
VEGF	vascular endothelial growth factor
ARDS	acute respiratory distress syndrome
HER2	human epidermal growth factor receptor 2, encoded by *ERBB2*, a proto-oncogene located at the long arm of human chromosome 17
PML	progressive multifocal leucoencephalopathy
IL-6	interleukin-6
NGF	nerve growth factor

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Onco-anaesthesia – an emerging sub-specialty defining a 'cancer anaesthetic'?

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INTRODUCTION

Over the past 10 years increased focus has been placed on the role of anaesthetists as perioperative physicians – enhancing care through improvements in risk stratification, preoperative optimisation and short-term enhanced recovery goals. Consideration is now being made for the role of anaesthetists in the improvement of longer term outcomes for the patient undergoing cancer resection surgery: cancer recurrence and survival.

The effects of cancer and cancer therapies compound the challenges faced by anaesthetists caring for the often-described 'older and sicker' patient. In addition to diseases of increased age and the physiological demands imposed by their disease (malnutrition, anaemia), patients with cancer are often exposed to the debilitating effects of a 'double hit'[1] of combined neoadjuvant chemotherapy and radiotherapy and are often immune compromised. These factors predispose patients to increased risk of postoperative infection, venous thromboembolism and prolonged hospital stay.

That the physiological strain of the perioperative period further depresses immune compromise is well recognised.[2-5] The significance of perioperative immunity is heightened by the recognition that interventions at the time of surgery may impact on the risk of cancer recurrence. The challenge has been relating hypothesised cancer 'reducing' interventions to known cancer biology and implementing these into clinical practice, while awaiting the results of multicentre trials examining this question.

A thorough understanding of the systemic factors that induce immune suppression, as well as the factors inducing a local 'genetic switch' in the cancer, is central to the provision of perioperative care that minimises the temporary shift to a pro-angiogenic, pro-lymphangiogenic environment that may seed recurrence. Through this understanding, an approach to minimise the deleterious effects of anaesthesia, surgery and perioperative pharmacology on a patient's immune health may be constructed.

Anaesthetists are familiar with a 'cardiac anaesthetic' (favouring pro-angiogenic techniques) – current research is strengthening the evidence that supports a 'cancer anaesthetic' (favouring anti-angiogenic, anti-lymphangiogenic techniques) that, in turn, may birth a sub-specialty of onco-anaesthesia.

Central concepts in the provision of a 'cancer anaesthetic' is the minimisation of a disadvantageous perioperative immunological shift and depression in physiological homeostasis that, together, promote lymphatic flow and lymphangiogenesis of minimal residual disease (MRD) and migration of circulating tumour cells (CTC) known to be released during surgical resection.

IMMUNOLOGICAL/CANCER BIOLOGY

Immune suppression can be considered by examining the pathophysiological changes occurring in three distinct immune cell lines:

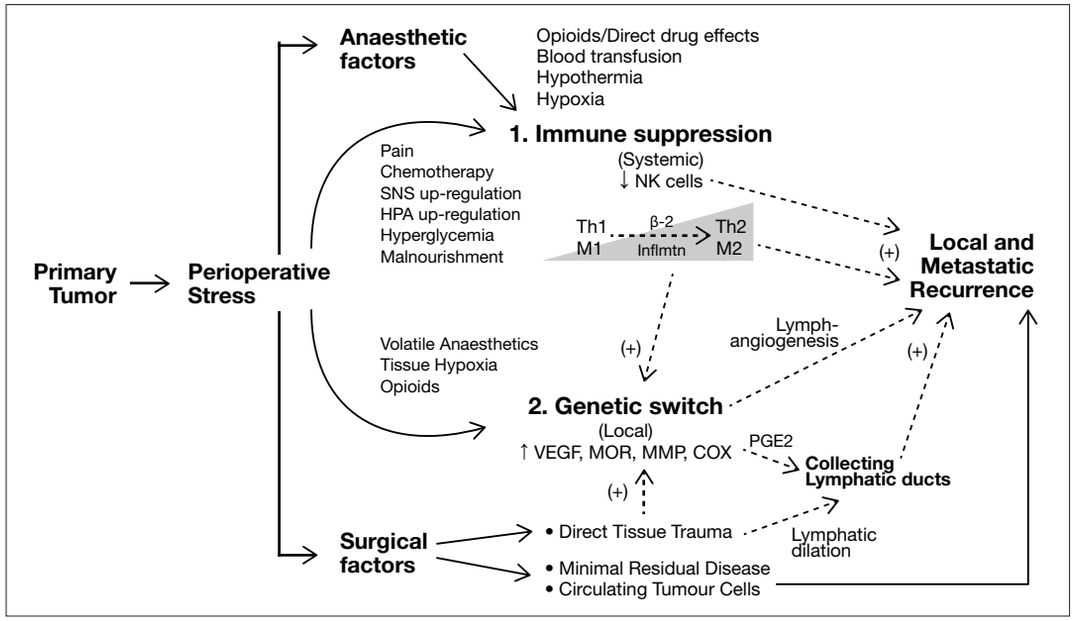
1. Natural killer (NK) cells
   - Have a key anti-tumour role (cancer cell destruction, restriction in tumour growth, metastasis elimination).
   - Are suppressed in pro-inflammatory states and by some (for example, volatile) anaesthetic agents.[6]
2. CD4 – Th0 'helper' lymphocytes
   - Exist in a progenitor form and differentiation (to Th1 or Th2) is dependent on the tissue microenvironment and their exposure to specific interleukin hormones – for example, IL-2/IL-4/IL-10.[7]
     - Th1: Anti-tumour effector cells (IL-2)
       - Activate CD8-Cytotoxic T lymphocytes (CTLs) and NK cells.
       - Activate antigen-presenting cells (macrophages) enhancing tumour surveillance.
     - Th2: Tumour establishment and growth (IL-4/IL-10)
       - Favor non-cellular immunity and actively inhibit NK/Th1/CTL.
       - Promote tumour growth and metastasis.

3. Macrophages
   - Are innate immunity cells sub-classified into classically activated (M1) and alternatively activated (M2) lineages.[8]
     – M1 macrophages:
       - Stimulate Th1 cells.
       - Secrete pro-inflammatory superoxide anions and free radicals to overwhelm cancer cells.
     – M2 macrophages ('tumour associated macrophage')
       - Are induced by a pro-inflammatory state and provide a localised immune suppressive environment for tumour growth, lymphangiogenesis and metastasis.

Perioperative significance:
Imperative to a 'cancer anaesthetic' is the use of anaesthetic drugs or adjuncts that enhance NK cell activity and Th1 and M1 status in the perioperative period where MRD and CTC release occurs. Three key physiological processes, specific to the perioperative period that result in the pro-cancer immune cell changes described above include:
1. Hypothalamic-pituitary axis up-regulation and cortisol release.[9]
2. Sympathetic nervous system activation.[10]
3. Loco-systemic prostaglandin,[11] cytokine,[12] and interleukin release.

The downstream effects of these changes impacting on the immune system at systemic and tumour genetic level are represented in figure 1.

Figure 1. Perioperative factors and their potential impact on cancer recurrence



Abbreviations: SNS – sympathetic nervous system; HPA – hypothalamic-pituitary axis; MOR – mu-opioid receptor; PGE2 – prostaglandin E2.

This figure illustrates the deleterious effects of the perioperative physiological stress response, pharmacological exposure and tissue trauma on immunological integrity. Immune suppression and stress induce a shift of Th0 differentiation from a Th1 (anti-tumour) to Th2 (tumour growth) dominance[13] together with direct inhibition of NK and CTL cell proliferation.[14] The up-regulated sympathetic nervous system shifts macrophages from an M1 to an M2 form via increased circulating noradrenaline. This polarisation, mediated by beta-2 adrenergic receptors on the macrophage membrane surface, is inhibited by beta-blockade (propranolol) that can produce substantial anti-tumour growth effects in animal models.[10] Tumour associated macrophages (M2) are synergistic in up-regulating tumour and stromal cyclo-oxygenase (COX), matrix metalloproteinase (MMP) and vascular endothelial growth factors (VEGF) expression.[8] This process can be thought of as a 'genetic switch' – an activation of pro-angiogenic and pro-lymphangiogenic mediators.[15,16] These paracrine hormones are further up-regulated in response to surgical trauma[17] and, in addition to their own direct lymphangiogenic effects, potentiate the genetic switch that promotes cancer invasion. Synergistic with the increased lymph flow resulting from tissue trauma COX, through PGE2 production, has been shown to be integral in lymphodilation.[18] Overall, these perioperative changes promote an immunological state that encourages tumour deposition and growth, and has been implicated in cancer recurrence and metastasis.[19]

These perioperative cellular and immunological changes underpin the importance of the many anaesthetic and surgical influences during the perioperative period of cancer surgery. Blood transfusion, hyperglycaemia, hypothermia, anxiety, uncontrolled pain, tissue hypoxia and direct effects of anaesthetic agents lead to immune compromise, up-regulation of the sympathetic nervous system and the associated shifts in lymphocyte and macrophage subtypes. Furthermore, from a surgical perspective, it has been well demonstrated that minimally invasive surgical techniques reduce perioperative immune suppression (and Th2 dominance).[13,20]

Skin incision inevitably results in tissue inflammation and lymphatic dilation – an innate response that promotes wound healing.[21] However, the immune suppression mechanisms described can be seen to be disadvantageous from a perspective of local or regional disease recurrence. The significance is greater when we consider that minimal residual disease (MRD) and the release of circulating tumour cells (CTCs) are an inevitable consequence of cancer surgery.[22-29] Figure 1 illustrates that the fate of this residual disease is partly dependent on the perioperative surgical and anaesthetic factors that determine the integrity of a patient's immune system.

THE PREOPERATIVE PERIOD AND 'IMMUNE-OPTIMISATION'

Patients with cancer awaiting surgery are at increased risk of becoming 'de-conditioned'. This is characterised by both physiological decline and physical 'effort intolerance': the inability to deliver oxygen and substrate to active muscles. This impaired functioning is attributed to several factors including age-related co-morbidities, combined neoadjuvant chemotherapy[30] and radiotherapy, the direct effects of the cancer and the inactivity (lifestyle choice) that commonly follows diagnosis. While awareness of the deleterious effects of these factors is important for the cancer anaesthetist, there is emerging evidence of implementable basic, preventative interventions that enhance patients' physiological and immune performance through the perioperative period.

Exercise

Functional capacity (fitness level), which can be objectively assessed by cardiopulmonary exercise testing, has been shown to be the strongest predictor of longevity.[31] More than 80 clinical trials demonstrate that exercise is a safe and well tolerated intervention in a range of cancer settings with beneficial effects on quality of life and functional capacity throughout treatment.[32] A growing body of literature suggests that exercise also improves cancer outcomes. Patients who engage in physical activity before and after colon cancer diagnosis have a risk reduction (hazard ratio [HR] = 0.58), while lack of exercise is associated with risk escalation (HR = 1.36) for all-cause mortality.[33] An editorialist suggested that to "prescribe a dog" might be better than any chemotherapy ever given to anyone.

Similarly, decline in functional capacity (deconditioning) is a strong predictor of postoperative complications.[34-37] The mechanism for this effect has been postulated to be through improved endothelial function and immune system up-regulation via expression of p-27.[38] While the benefits of 'enhanced recovery' protocols have been well demonstrated in patients receiving colorectal cancer surgery, the effects are limited to postoperative recovery.[39] Pre-surgical 'conditioning' has more recently been linked to reduced cancer mortality in both breast and colon cancer.[40-43] Although cancer surgery is not emergent, the assessment of patients' preoperative fitness and optimisation of impairment must consider delays that may lead to a tumour undergoing metastatic spread.

Immuno-nutrition

Conceptually, a deconditioned preoperative patient will have less capacity to respond to the physiological challenge of surgery. Interventions enhancing a surgical patient's nutritional state correlate with improved outcome.[44] Furthermore, preoperative iron supplementation has been shown to reduce blood transfusion, raise preoperative haemoglobin levels and reduce immune suppression.[45]

Clinical evidence demonstrates that preoperative exercise prescription as well as immune-nutritional and psychological support improve postoperative functional recovery in patients having colorectal,[46] abdominal[47] and lung cancer surgery.[48,49] Currently, there is no evidence to support the concept that preoperative nutritional interventions impact on the risk of cancer recurrence.[39] However, as perioperative physicians, anaesthetists have a role to engage patients, both through prescription and explanation, in processes that enhance exercise capacity, cease smoking, optimise nutrition and correct anaemia and, in doing so, through the process of preoperative immune optimisation, is likely to enhance patients' capacity to respond to the stress of cancer surgery.

The future: A cancer anaesthetic?

The concept of a 'cancer anaesthetic' has arisen from the increased understanding of the immune changes that occur during the perioperative period (discussed above) and their potential impact on long-term cancer sequelae. Patients with cancer are at particular risk in the perioperative period through deleterious immune modulation at a systemic level and through 'genetic switching' at a loco-regional level (Figure 1). Stated plainly, immune health is vital in controlling the progression of cancer.[8,19] The challenge for researchers is therefore to link the offset of perioperative immune decompensation (through the variety of proposed perioperative interventions) with demonstrated improved disease-free outcome. This is difficult.

Proponents of evidence-based healthcare delivery, and multicentre randomised trials underpinning practice will be disappointed with the paucity of stark, infallible, evidence when searching for seminal human research in this field. The reasons are multiple. First, the medical profession has never truly considered the hypothesis of perioperative interventions affecting cancer outcome. Peripheral to the focus of surgeons and medical oncologists, anaesthetists (inexperienced in oncology research) have only recently proposed more advanced research in this perioperative aspect of patient care. The earliest human retrospective study we are aware of was published in 2006.[50]

In an area of research where the primary outcome might be expected to occur several years after the recruitment of the first patient, conclusive trials will take a decade. Secondly, the number of confounding variables that must be considered to effectively answer a perioperative intervention-based study hypothesis is large and growing as successive retrospective studies are published.[51-54] Studies must control for age, patient comorbidities, underlying genetic predisposition, neoadjuvant chemo-radiotherapy, tumour staging and lymphovascular space invasion, clinical care providers, effective regional anaesthesia, blood transfusion, temperature control and a range of perioperative pharmacology. And thirdly, when analysing results of hypothesis-building retrospective studies, a cautious balance must be reached between the applicability of intention-to-treat analysis, the actual treatment effect, and the use of propensity analysis to interpret associations. The challenges in garnering an effective evidence base on which to apply a categorical assertion of benefit for a cancer patient are considerable.

A comprehensive review of the literature is beyond the scope of this article and can be found in excellent reviews by leading experts in the field of cancer anaesthesia.[3,7,55-58] However, several proposed therapeutic modalities of reduction in cancer recurrence are discussed below: the theoretical (and laboratory demonstrated) mechanistic basis for effect and how this relates to the immunosuppression pathways illustrated in figure 1. Incorporation of these modalities into daily clinical practice should be considered and refined as the evidence-base evolves over the next 10 years.

Opioid-based anaesthesia and regional techniques

There is growing evidence that opioid-based medications may deleteriously impact upon cancer survival. Immune suppressive results from opioid administration through polarisation of Th0 cells to a Th2 dominance.[59] In animal models, increased angiogenesis, tumour growth and metastatic rate are attributed to opioids.[60] Tumour implantation models demonstrate that tumours expressing mu-opioid receptors are more aggressive.[61] Specific mu-opioid receptor polymorphisms in patients with breast cancer are attributable to altered survival.[62] Given this developing body of evidence, there is a need to explore alternate dosing delivery (for example, neuraxial versus intravenous) of opioid administration or opioid-sparing anaesthetic and analgesic techniques.

Regional or neuraxial analgesia is the most frequently considered intervention implicated in reducing cancer recurrence in the perioperative setting. Regional analgesic techniques may confer beneficial cancer outcomes through an opioid-sparing effect,[63] through a reduction in the immune stress of surgery[64] or potentially through modulation of lymphatic flow from the surgical site.[65]

Mice studies have shown that neuraxial analgesia preserves Th1/Th2 balance (compared with general anaesthesia alone)[66] and, under conditions of sympathectomy, that tumour growth is dramatically reduced[67] due to lower lymphangiogenic hormone release (for example, COX, MMP, VEGF).[68] While alterations in surgical technique have been proposed to reduce CTC release,[23,29] neuraxial anaesthesia may, via reduction in lymphatic flow from the surgical site (unpublished data from authors), improve cancer outcomes.[69] Ultimately, the three currently recruiting prospective multicentre studies in breast cancer (paravertebral), lung cancer (epidural) and colon cancer (epidural) will address this question. Figure 1 illustrates that properly implemented regional anaesthesia through anxiolysis, opioid-sparing analgesia and reduction in HPA/sympathetic up-regulation is likely to reduce perioperative immunosuppression.

Nearly 20 retrospective reviews have been published reporting a variety of beneficial or equivocal outcomes, often restricted to subgroups. A recent meta-analysis has demonstrated an overall survival benefit in favour of epidural anesthesia compared with general analgesia alone (HR=0.84, P=0.013).[70] A significant positive association between epidural analgesia and improved overall survival was shown in the subgroup analysis for colorectal cancer (HR=0.65, P=0.045). However, no significant relationship was found between recurrent free survival benefit and epidural analgesia (HR=0.88, P=0.457). This association (overall survival) and lack of association (recurrence free survival) between epidural anesthesia and cancer control should be interpreted carefully given that most of the studies are retrospective and very large between-study heterogeneity was identified. This further highlights the need for large prospective randomised studies.

Beta-adrenergic receptor antagonism

Catecholamines shift lymphocytes to a Th2 dominance.[71] By the known mechanism of sympathetic deactivation, a role for perioperative beta antagonism in the reduction of immunological stress response from surgery seems probable. Through the expression of beta-receptors on the macrophage cell surface, beta-receptor antagonism and consequent reduction in M1 to M2 differentiation is an enticing therapeutic modality. Population studies, including neoadjuvant (perioperative) database analysis,[72] indicate that a generalised reduction in cancer development exists for those patients administered beta adrenergic antagonists (particularly propranolol).[73-76] Direct evidence of beta blockade's effectiveness in preventing cancer growth is well demonstrated in mice studies.[10,64,77,78] To translate this laboratory evidence to clinical practice, the shift away from the concerns of high-dose acute perioperative beta receptor antagonism will need to be put into perspective.[79] Patients presenting for surgery almost certainly have a degree of sympathetic up-regulation and, in enacting a cancer anaesthetic that minimises immune suppression, a lower threshold for judicious and timely beta antagonist administration may need to be adopted.

Anti-inflammatory adjuncts

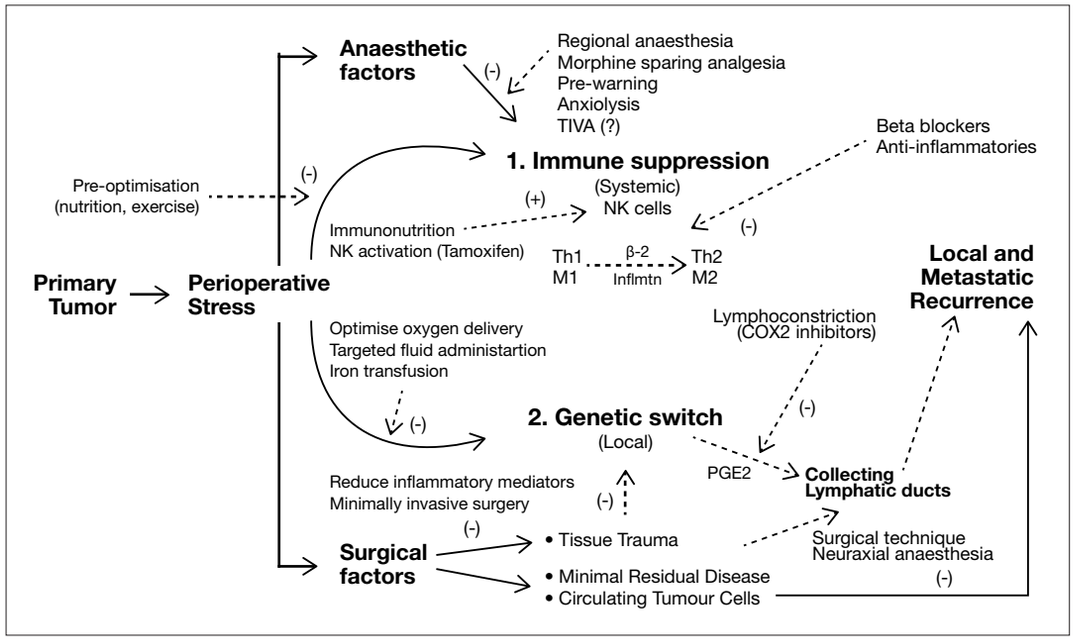
Prostaglandins are potent potentiates of cancer spread. Numerous articles relate a tumour's prostaglandin secretion with increased measures of invasiveness and metastasis; regardless of tumour type, patients with tumours that express COX are more likely to have reduced disease-free and overall survival.[80-84] Inevitably, COX is up-regulated at the time of surgical inflammation and is a key component of genetic switch, immune suppression and lymphatic dilation (figure 1). Retrospective studies of perioperative anti-inflammatory administration indicate beneficial improvement in cancer outcomes.[85,86] Mice studies have demonstrated that perioperative anti-inflammatory agents (particularly COX2 selective agents) reduce both tumour invasion[18] and cancer recurrence.[87,88] Interestingly, TIVA (with intrinsic COX inhibitory properties[89]) compared with volatile anaesthesia has been shown to prevent the shift to Th2 lymphocyte dominance in humans.[90] TIVA may also obviate the need for volatile anaesthetic agents that induce gene expression of pro-angiogenic pathways, for example hypoxia-inducible factor. Both as a therapeutic component of multi-modal analgesia as well as a potential anti-cancer therapy, preoperative loading and perioperative continuation of (COX2) anti-inflammatories seem justifiable in the absence of absolute or significant relative contraindications.

Other general perioperative immune-modulatory mechanisms

Perioperative hypothermia, blood transfusion (regardless of leukodepletion techniques) and hyperglycaemia increase immune suppression. Hypothermia suppresses NK cells and induces an IL-10 mediated shift to Th2 dominance.[91] In the laboratory setting this has been shown to increase the risk of metastasis.[92] Nearly half of patients receiving abdominal surgery are hypothermic and a third are still hypothermic in the recovery room.[93] Similar microvascular pro-inflammatory up-regulation (and genetic switch) occurs as a response to hyperglycaemia with associated immunosuppression.[94] The deleterious effects of blood transfusion and transfusion-related immunomodulation (TRIM) are well known to anaesthetists:[95] in animal models it has been shown that aged (compared with fresh) blood transfusion promotes metastasis through immunosuppression.[96] A Cochrane review found an association between perioperative blood transfusion and colon cancer recurrence.[97]

A summary of potential therapeutic and risk reducing components relevant to the care of the patient with cancer in the perioperative period is illustrated in figure 2 – a 'cancer anaesthetic'.

Figure 2. Potential components of a cancer anaesthetic



Abbreviation: TIVA – total intravenous anaesthesia

CONCLUSION

Cancer is an increasing major public health problem profoundly affecting our older population. This is a result of the aging baby-boomer population and longer life expectancies. Interest in perioperative aspects of anaesthesia technique affecting cancer outcomes is justified by the large volume of cancer resection surgery faced by anaesthetists, the enormous financial, health and psychological burden of cancer, as well as the high mortality rate associated with cancer recurrence. As the incidence of cancer and cancer survival grows, anaesthetists and other perioperative healthcare providers will need to better understand the impact of the perioperative period on cancer survival.

Surgical resection remains the primary means of reducing tumour burden in solid organ tumours. Strong mechanistic and laboratory evidence point to interventions available to anaesthetists in the perioperative period that may enhance our patients' cancer outcomes. Pre-conditioning, normothermia, anxiolysis, immunonutrition, beta-blockade, effective opioid-sparing analgesic techniques, attention to normoglycaemia, optimal fluid administration, choice of anaesthetic technique (inhalational, intravenous, regional), minimally invasive surgical techniques, judicious blood product administration and anti-inflammatory medication rapidly attain exaggerated importance in this context. While we wait for evidence from ongoing multicentre trials, in the meantime the emergence of a 'cancer anaesthetic' and its integration clinically may constitute good anaesthesia practice.

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Novel oral anticoagulants: Implications for the anaesthetist

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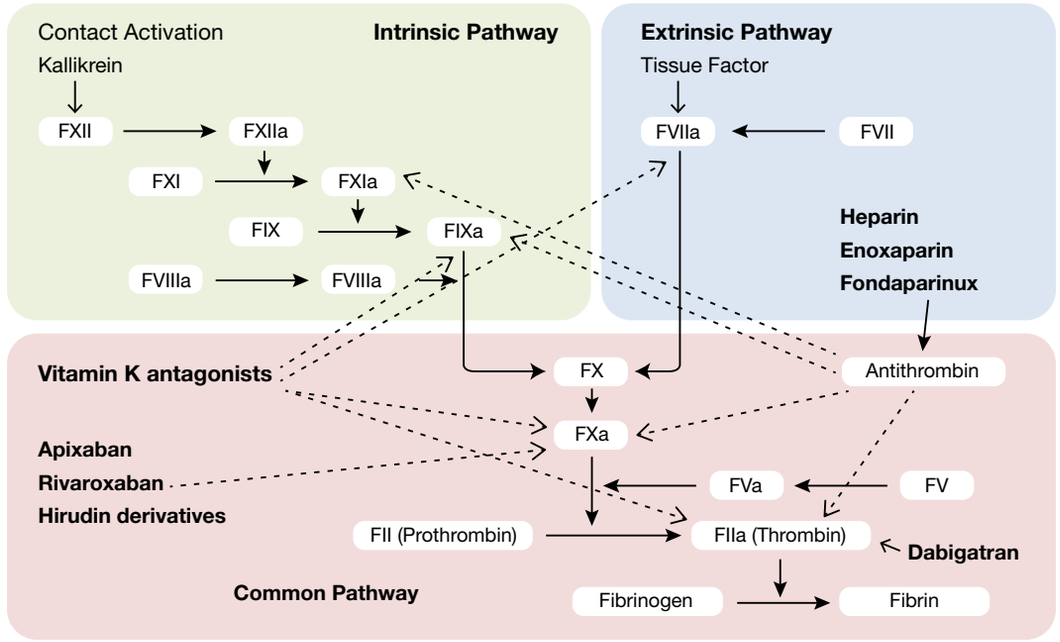
INTRODUCTION

Blood coagulation is an extremely complex process. In the presence of the requisite cofactors and substrates, sequential activation and amplification of enzymes (factors) ultimately leads to the deposition of large amounts of fibrin.[1] A perennial therapeutic theme has been manipulation of this complex system for the treatment and prevention of thromboembolic disease; however, the perfect medication has remained elusive. Despite decades of clinical use and familiarity, traditional anticoagulants demonstrate a range of pitfalls and drawbacks. Vitamin K antagonists, such as warfarin, require frequent monitoring, have delayed onset of action, suffer from multiple drug interactions and act in an indirect way to reduce the function of factors X, IX, VII and II. Heparin requires parenteral administration and when used intravenously requires frequent monitoring. It acts indirectly and requires the presence of anti-thrombin for its action. Low molecular weight heparins, such as enoxaparin and dalteparin, require parenteral administration, are dependent on anti-thrombin and lack full reversibility with protamine.[2,3]

Novel oral anticoagulants (NOACs) of two classes, the factor Xa inhibitors (for example, rivaroxaban and apixaban) and the direct thrombin inhibitors (for example, dabigatran) are the most recent answer to the long search for the ideal anticoagulant.[4] They are orally active direct inhibitors (Figure 1) and generally have stable and predictable pharmacokinetic and pharmacodynamic profiles and do not require regular monitoring (Table 1). However, they bring with them a new range of caveats and potential complications with which the anaesthetist will need to become familiar.

Figure 1. Simplified depiction of the coagulation cascade with sites of pharmacological inhibition indicated. Adapted from various sources.[5-7]



These new anticoagulants will have an impact across the whole spectrum of clinical anaesthesia including elective and emergency surgery but perhaps their biggest impact will be centred on the practice of regional anaesthesia, and more specifically neuraxial anaesthesia.

This article aims to give a concise review of the novel oral anticoagulants rivaroxaban, apixaban and dabigatran focusing on their pharmacology, monitoring and reversal. The intention is to equip anaesthetists with knowledge adequate to practice safe and effective neuraxial anaesthesia in patients receiving these agents.

Table 1. Summary of properties for the new oral anticoagulants[17, 26, 28, 31, 35-38, 43, 44, 47, 48, 51, 52, 63, 65, 67, 68, 70, 71]

	Rivaroxaban	Apixaban	Dabigatran
C_{max} (hours)	2	3	2
t½ (hours)			
Normal renal function	7.6	15	14
Mild renal impairment	8.7	Not available	16.6
Moderate renal impairment	9	17.6	18.7
Severe renal impairment	9.5	17.3	27.5
Protein binding	95%	87%	35%
Elimination	33% renal	33% renal	80% renal
	66 metabolism	33% metabolism	20% metabolism
		33% intestinal excretion	
Monitoring	PT or anti factor Xa assay	Anti factor Xa assay or PT	aPTT or TCT or Ecarin Clotting time

Cmax time to maximal concentration. t½ half-life.

ANTICOAGULANTS, BLEEDING AND NEURAXIAL ANAESTHESIA

Neuraxial anaesthesia is a common and effective technique with well documented analgesic benefits over systemic opioids in the post-operative setting, as well as more specific advantages including reduced hospital stay post major joint surgery.[8,9] The potential benefits must be weighed against the potential pitfalls, with neurological compromise due to neuraxial haematoma being foremost in mind. Thankfully, this complication is rare but studies are hence difficult to power, and robust evidence based recommendations are hindered. The exact incidence of this complication is unknown but several large studies shed light on the topic. A retrospective study in Sweden which examined over 1.2 million cases of spinal anaesthesia and 450,000 cases of epidural anaesthesia (including 200,000 epidural blockades for pain relief in labour) found 127 complications of which almost one quarter (n=33) were cases of neuraxial haematoma. The incidence of these spinal haematomata was one in 200,000 cases of neuraxial analgesia in obstetric patients, much lower than the one in 3600 incidence for women undergoing knee arthroplasty.[10] In another study, six cases of spinal haematoma were detected among 707 455 instances of neuraxial anaesthesia in a Royal College of Anaesthetists study.[11] A review analysing 1.1 million episodes of neuraxial anaesthesia in the obstetric population found six instances of epidural haematoma (95% binomial exact confidence interval two to 12 per million).[12]

The link between bleeding-related complications of neuraxial anaesthesia and anticoagulation is a logical one, though it is difficult to quantify precisely. A review by Vandermeulen found impairment of coagulation in 72% of the 79 cases of spinal haematomas investigated. Most of these were due to intravenous heparin but also implicated subcutaneous heparin, oral anticoagulants, thrombocytopenia, renal failure, alcohol abuse and pre-eclampsia.[13] Of note, 56% of haematomas occurred on epidural catheter removal. In Finland, all claims attributed to central neuraxial blocks and settled by the national no fault insurance scheme during the period 2000-09 were analysed. The incidence of neuraxial haematoma after spinal block was 1:775,000, for epidural block 1:26,400, and in the case of combined spinal and epidural, 1:17,800. Irrespective of the method of neuraxial technique, most patients suffering serious complications were the elderly having comorbidities.[14]

This is in accord with recent speculation that the incidence of neurological dysfunction resulting from haemorrhagic complications associated with neuraxial block may be increasing due to multiple clinical influences, including patient age and widespread use of anticoagulants for cardiovascular diseases.[15,16]

RIVAROXABAN

Rivaroxaban (XARELTO®, Bayer) 10mg, 15mg and 20mg tablets are registered by the Australian Therapeutic Goods Administration and New Zealand Medicines and Medical Devices Safety Authority.[17,18] Approved indications are venous thromboembolism (VTE) prevention in adults after major orthopaedic surgery of lower limbs (elective total hip, knee replacement); prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF) with at least one additional stroke risk factor; and treatment of deep venous thrombosis (DVT), or prevention of recurrent DVT or pulmonary embolism (PE).

Rivaroxaban is a direct factor Xa inhibitor that was first approved for clinical use in 2008 in Canada and Europe for DVT prophylaxis following total hip and total knee replacements with 10mg daily dosing on the basis of the RECORD studies.[19-22] These four large clinical studies included over 12,500 participants and found rivaroxaban was superior to enoxaparin in preventing venous thromboembolism with similar rates of adverse events, including bleeding. There were no reports of neuraxial haematoma among the 4086 patients in the rivaroxaban group of the RECORD studies who underwent neuraxial anaesthesia. This included 1141 patients who had epidural anaesthesia, 80% of whom had indwelling catheters, 2489 patients who had spinal anaesthesia and 1048 patients who had spinal plus another form of anaesthesia.[23] Rivaroxaban was generally started six to eight hours post-surgery. Indwelling epidural catheters were removed after waiting for at least two half-lives since the last rivaroxaban dose and there was at least a four-hour gap between catheter removal and subsequent dosing.[23] Of the 4090 patients who were in the enoxaparin group and who received neuraxial anaesthesia, a single case of compressive spinal haematoma occurred post epidural catheter removal in a 74-year-old woman with impaired renal function, which required laminectomy.[23]

Indications for rivaroxaban were subsequently expanded to include anticoagulation in non-valvular atrial fibrillation following results of the ROCKET-AF study.[24] This randomised, double blind study examined rivaroxaban 20mg daily (or 15mg daily in patients with creatine clearance 30-49 ml/min) versus warfarin treatment in 14,264 patients with non-valvular atrial fibrillation. There was a statistically significant reduction in the primary end point of stroke or systemic embolus which occurred at 1.7% per year in rivaroxaban treated patients and 2.15% per year in those patients treated with warfarin. Intracranial bleeding was less frequent in patients treated with rivaroxaban but gastrointestinal tract bleeding and bleeding requiring transfusion was more common when compared with the warfarin group.

Pharmacology

The pharmacological action of rivaroxaban is the direct inhibition of Factor Xa, the point of convergence of the extrinsic and intrinsic coagulation cascade and the rate limiting step in thrombin generation.[25] Rivaroxaban shows greater than 10,000 fold selectivity for factor Xa when compared to other biological serine proteases (Factor IXa, Factor VIIa, Thrombin, Factor XIa) and causes no prolongation of bleeding time at therapeutic levels.[26,27] Oral bioavailability is 80% and absorption is rapid with time to peak plasma concentration of two hours (range 0.5 – 2.5h) after a single 10mg dose.[28] It is highly protein bound, 92-95%, mostly to albumin.[17] Twice daily administration over seven days demonstrated a half-life of approximately 8 hours for both 10mg and 20mg tablet tablets, with no accumulation once steady state is reached.[26] The half-life increases to 12 hours in the healthy elderly population (mean age 65.5 years).[29]

Radiolabeled rivaroxaban studies show 33% of the dose was excreted unchanged in the urine. The remainder is metabolised via two major hepatic pathways with the involvement of the CYP3A4 system, 32% via the oxidative pathway and 14% via hydrolysis of amide bonds. These metabolites are inactive and rapidly cleared from the plasma via the renal and faecal routes.[30] The excretion of rivaroxaban is also at least partly dependent on the P-Glycoprotein transporter and strong inhibitors of this as well as the CYP3A4 system such as ketoconazole and HIV protease inhibitors may cause clinically relevant increases in plasma concentrations such that co-prescription is contraindicated.[17]

Worsening renal function is associated with increasing area under the curve concentrations (AUC) as compared to controls.[31] While the severity of renal impairment may have little impact on half-life (8.3 hours for controls and 9.5 hours for severe renal impairment) plasma levels may increase substantially in renal dysfunction, which may lead to an increased risk of bleeding. Australian and New Zealand prescribing guidelines recommend that rivaroxaban not be used at any dose in patients with creatinine clearance below 15 ml/min and the 10mg dose should be used with extreme caution in those whose creatinine clearance is 15-30ml/min while creatine clearance should be greater than 30ml/min for the 15mg and 20mg dosing regimens.[17,18]

Although mild hepatic impairment (Child-Pugh A) may not significantly impact rivaroxaban pharmacokinetic or pharmacodynamics, use in patients with either moderate or severe hepatic impairment is contraindicated due to significantly impaired drug clearance and possible underlying coagulopathy.[17,32]

Monitoring

Generally, regular monitoring of rivaroxaban is not indicated due to its stable and predictable pharmacokinetic and pharmacodynamic profile. Situations exist where being able to determine the level of anticoagulation caused by rivaroxaban might be desirable however this is complicated by the fact that there is no widely accepted standard assay for measuring its effect. Rivaroxaban causes a dose-dependent increase of the commonly used coagulation tests, aPTT and PT and has no or minimal effect on the thrombin time or ecarin clotting time.[33] It is widely held that the aPTT is unsuitable for monitoring due to a curvilinear response and reduced sensitivity.[33-35]

Effect on the PT is linear with a generally good correlation but inconsistent across different prothrombin reagent and conversion to an INR does not correct this as with warfarin monitoring. Converting PT results into rivaroxaban concentrations by the use of calibrators is suggested as a method of accounting for this variation.[35] Determination of rivaroxaban concentrations via chromogenic anti-factor Xa assays and standard calibrators has shown to be more sensitive and specific then using PT but is also more expensive and less available.[33,36]

The 2013 guidelines on rivaroxaban monitoring from the International Society on Thrombosis and Haemostasis indicate that a normal PT ratio with most reagents indicates an absent or minimal rivaroxaban effect and that further research into the optimum PT reagent and the use of reference samples is needed.[37]

APIXABAN

Apixaban (ELIQUIS®, Pfizer and Bristol-Myers Squibb) is another orally-active direct factor Xa inhibitor. This medication has been available in Europe since 2011 for DVT prophylaxis following hip and knee replacement surgery. Apixaban has since been approved for stroke prevention in non-valvular atrial fibrillation in Europe and America, however currently it is available in Australia in 2.5 mg tablets only for its DVT prophylaxis indication following lower limb joint replacement surgery.[38]

The efficacy of apixaban as DVT prophylaxis in post knee and hip surgery was investigated in the ADVANCE trials.[39-41] Of the 3195 patients in ADVANCE 1, almost 60% had spinal anaesthesia with no bleeding complications. Apixaban was started at a mean of 20 hours post-operatively. Over 60% of the 3057 patients recruited to ADVANCE 2 had spinal anaesthesia. Apixaban was started a mean 19 hours post-surgery and there were no spinal haematomas reported. This was the pivotal study examining apixaban against once daily enoxaparin in knee replacement patients and showed a significant reduction in the primary endpoint of all VTE and all cause death, 14.8% vs. 24.7%. The ADVANCE 3 trial demonstrated a significant reduction of all VTE and all cause death in 5407 patients undergoing hip replacement which occurred in 1.4% of the apixaban treated group and 3.9% in the enoxaparin group. Approximately 60% of the patients had a spinal anaesthetic with no bleeding related complications.

Pharmacology

Apixaban belongs to the same class of anticoagulants as rivaroxaban, with both working by reversible, highly -selective inhibition of factor Xa.[42] Apixaban is rapidly absorbed following oral administration reaching a peak concentration in three hours and is minimally affected by food.[43] The oral bioavailability is approximately 45% and plasma protein binding of 87%.[38,44] The half-life of apixaban is 11-15 hours in healthy adults.

Apixaban is eliminated via multiple routes. Almost 30% was excreted in urine, mostly unchanged.[44] Hepatic metabolism involving the CYP3A4 system accounts for just over 30% of apixaban clearance with metabolite profiles showing unchanged apixaban is the major circulating compound and O-demethyl apixaban sulfate the most abundant metabolite representing 25% of the apixaban AUC.[44,45] O-demethyl apixaban sulfate and its precursor O-demethyl apixaban are essentially inactive with regards to their ability to inhibit factor Xa.[46] A complex and incompletely characterised process of active intestinal excretion and reabsorption involving the P-Glycoprotein transporter and breast cancer resistant protein (BCRP) termed enteroenteric recirculation is thought to be responsible for the remaining approximate 30% of apixaban elimination.[47]

Severe renal impairment only marginally increases the half time from 15 hours (control group) to 17.3 hours.[48] The manufacturer indicates that although no dose adjustment is required in patients with mild or moderate renal impairment, care must be taken when using apixaban in patients with severe renal impairment and it is contraindicated in patients with a creatinine clearance < 15ml/min.[38] Mild and moderate hepatic impairment (Child-Pugh A and B) had minimal impact on apixaban protein binding, total apixaban exposure and maximum drug concentration in a single dose study, however apixaban is contraindicated in patients with clinically significant coagulopathy from hepatic impairment.[38,49]

Monitoring

Like rivaroxaban, routine clinical monitoring is not recommended for apixaban, but when monitoring is warranted it is again complicated by the lack of standardised testing. The 2013 International Society on Thrombosis and Haemostasis guidelines do not address apixaban monitoring.[37]

Of the routine coagulation tests used in the laboratory aPTT is least suitable.[50] The PT shows concentration-dependent prolongation; however, the inter-reagent variability is much higher than for rivaroxaban and this variability is exaggerated when converted to INR.[51] A modified PT test that includes addition of calcium chloride to the assay has shown a much greater sensitivity when compared to the standard PT; however this is not routinely available.[50] Standardisation with reference samples and expression of results in apixaban concentration as opposed to seconds might help compensate for inter-reagent variability.

Anti-factor Xa assays may show a strong linear correlation over a range of apixaban plasma concentrations including at very low levels, and if available such assays may be the current monitoring test of choice.[52]

DABIGATRAN

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim) in 75mg, 110mg and 150mg capsules, is the only therapeutically available orally active direct thrombin inhibitor after the withdrawal of ximeligatran from the market in 2006 due to liver toxicity (argatroban is also of this class, but requires intravenous administration).[53] Dabigatran is licenced in Australia, New Zealand, Canada and the European Union for DVT prophylaxis following hip or knee replacement and stroke prevention in non-valvular atrial fibrillation; and in America only for the latter indication. Dabigatran is not yet approved in Australia or New Zealand for treatment of DVT or PE outside the context of major orthopaedic surgery of the lower limb although results of the RE-COVER-1 trial comparing dabigatran and warfarin in patients with acute DVT showed similar efficacy and safety profiles.[54]

The RE-MODEL trial compared dabigatran with enoxaparin in 2183 patients undergoing total knee replacement.[55] Neuraxial anaesthesia occurred in 1055 patients in the study with no bleeding complications apart from one patient who suffered a bloody puncture prior to surgery and did not receive any subsequent trial drug.

Dabigatran as DVT prophylaxis post hip surgery was investigated in the RE-NOVATE and RE-NOVATE II trials.[56, 57] The first study randomised 3494 patients undergoing elective hip replacement to enoxaparin 40mg daily starting the night before surgery or dabigatran 220mg or 150mg once daily starting with a half dose four to six hours post-surgery. Both doses were non-inferior to enoxaparin with regards to the primary outcome (total VTE including asymptomatic VTE plus all-cause mortality) which had the same definition as the RE-MODEL studies (6.7% enoxaparin group, 6.0% 220mg dabigatran group and 8.6% 150mg dabigatran group). At least 1512 patients treated with dabigatran had neuraxial anaesthesia with no reports of neuraxial bleeding. The RE-NOVATE II trial compared the same enoxaparin regime against only 220mg of dabigatran daily in 2055 patients undergoing hip replacement. The primary efficiency outcome was the same as the previous trials and occurred in 7.7% for the dabigatran group and 8.8% for the enoxaprin group, which met the non-inferiority criteria. There was no difference in bleeding rates and there was no neuraxial bleeding among the 70% of patients who had regional anaesthesia (spinal, epidural, lumbar plexus block and other).

The biggest dabigatran trial, the RE-LY study, compared warfarin with dabigatran for the prevention of stroke and systemic emboli in 18,113 patients with atrial fibrillation.[58] The lower dose was non-inferior to warfarin with regards to the primary outcome (stroke or systemic embolism) and showed less major bleeding (3.36% for warfarin and 2.71% for 110mg of dabigatran). The higher dose had a lower rate of stoke or systemic embolism when compared to warfarin, 1.11% vs 1.69% and similar rates of bleeding although intracranial bleeding was more common with warfarin and gastrointestinal bleeding more common with dabigatran.

The safety and efficacy of Pradaxa in patients with prosthetic heart valves were evaluated in the European RE-ALIGN trial.[59] This phase II study was terminated early as patients taking dabigatran experienced significantly more thromboembolic events (valve thrombosis, stroke, and myocardial infarction) and major bleeding events than patients taking warfarin. Thus dabigatran etexilate is contraindicated in patients with prosthetic heart valves.[60.61]

Pharmacology

Dabigatran is a rapid, selective and reversible thrombin inhibitor that acts by direct binding to its target.[62] Due to a basic benzamidine group dabigatran is ionised at physiological pH and hence strongly hydrophilic making it unsuitable for oral dosing.[63] For this reason dabigatran is administered as a pro-drug, dabigatran etexilate in which two chemical moieties have been converted to esters to aid oral absorption.[64] This allows rapid absorption with time to maximal concentration around two hours and oral bioavailability of 6-7%.[63,65] Dabigatran etexilate is rapidly metabolised in the blood stream by non-specific serine esterases to the active drug dabigatran which is subsequently 35% protein bound.[63]

Half-life is eight hours after single doses in healthy adults and 14-17 hours after multiple doses and steady state is reached after three days.[65] Analysis of population pharmacokinetics within the RE-LY trial showed that age alone did not have a clinically relevant effect on dabigatran exposure.[66]

Renal excretion of the unchanged drug is the major elimination pathway for dabigatran accounting for 80% of the absorbed dose. A minor portion of dabigatran underdoes metabolism by glucuronidation. This metabolite has pharmacological activity similar to the parent drug and accounts for approximately 20% of total drug exposure.[63] Neither the conversion of dabigatran etexilate to dabigatran or its subsequent metabolism involves the cytochrome P450 system and dabigatran was found not to inhibit reactions involving the P450 system.[63] Additionally, analysis of the effect of P-Glycoprotein inhibitors amiodarone, verapamin and diltiazem showed only minor increases in dabigatran exposure which according to the study authors do not warrant any dosing adjustments, however the manufacturer recommendations in this area are inconsistent.[66,67] Treatment with amiodarone and verapamil warrants dabigatran dose reduction in patients being treated for DVT prevention post orthopaedic surgery but not in those receiving dabigatran for atrial fibrillation. Ketoconazole use is a contraindication to dabigatran treatment and concomitant dabigatran use with tacrolimus or cyclosporine is not recommended.

Renal dysfunction has a major impact on dabigatran pharmacokinetics. Half-life is increased from 16 hours in mild renal impairment, to 19 hours in moderate and 28 hours in severe renal impairment.[68] Dabigatran is contraindicated for use in patients with a creatinine clearance less than 30ml/min and reduced dosing is recommended for those with creatinine clearance of 30-50 ml/min.[67]

When compared to healthy controls, moderate hepatic impairment (Child-Pugh B) had minimal effect on drug absorption, half-life, total drug exposure and the resultant effect on anticoagulation as tested with aPTT, Ecarin clotting time and thrombin time.[69] Dabigatran is contraindicated by the manufacturer for the treatment of any patient with hepatic disease that is expected to impact on survival.[67]

Monitoring

As with the factor Xa inhibitors, direct thrombin inhibitors are used clinically without routine coagulation monitoring. Dabigatran causes a dose-dependant increase in aPTT, PT, thrombin time and ecarin clotting time but with a wide variation of sensitivity.[70,71] Across the range of expected therapeutic plasma concentrations, the PT and INR are insensitive to the effects of dabigatran and unsuitable for monitoring its effects.[70,71]

The aPTT shows a curvilinear concentration-response with a steep increase at lower concentrations and a flattened linear response above 400ng/mL.[70] The aPTT is recommended by the International Society on Thrombosis and Haemostasis as a good first line test to assess the level of anticoagulation of patients treated with dabigatran, but not for determining dabigatran plasma concentrations.[37] The manufacturer product information indicates an APTT greater than 2.5 times above reference range indicates likely over-coagulation.[67] The inter-laboratory variation for aPTT measurements is generally less than 10%.[71] Thrombin clotting time shows a linear and very sensitive response to the effect of dabigatran; however at concentrations higher than 600ng/mL the upper limits of the testing range are exceeded.[71] A normal thrombin clotting time can exclude a clinical dabigatran effect but the test does not provide good quantification in the setting of overdose. Ecarin clotting time, if available, also shows a strong linear correlation with dabigatran dose and can be used to determine drug concentration if used with calibrators.[37, 65] Anti factor Xa assays are unaffected by dabigatran.[37]

REVERSAL OF THE NOVEL ORAL ANTICOAGULANTS

A feature common to all the currently used novel oral anticoagulants and also one of the major drawbacks for these medications when compared to traditional anticoagulants is the lack of specific reversal agents in the event of haemorrhage or prior to an urgent procedure.

Early reports are emerging for potential reversal agents. A recombinant, enzymatically inactive FXa has been shown to reverse the anticoagulation caused by FXa inhibitors apixaban and rivaroxaban in vitro and in animal models.[72] Additionally, it has been shown that engineered antibodies to dabigatran are able to completely reverse the drug's anticoagulant properties in laboratory studies of human plasma and whole blood.[73] When, and if, these agents will reach clinical use is unknown.

The options available to the clinician are limited and without a solid evidence base. Studies focused on the reversal of the novel oral anticoagulants are largely restricted to animal models and laboratory studies of general haemostatic agents, prothrombin complex concentrates (PCC), activated prothrombin complex concentrates (aPCC) and recombinant activated factor VII (rFVIIa).

Haemodialysis is a valid option for acutely reducing dabigatran concentrations. It has been studied in pharmacokinetic studies in \which patients with end-stage renal disease received dabigatran before their usual haemodialysis treatment.[68] Published case reports also demonstrate the use of haemodialysis in clinical care.[74,75] Rivaroxaban and apixaban are not expected to be removed by dialysis due to their high protein binding.

Activated charcoal treatment of dabigatran has been investigated in a simulated absorption model.[76] The results may indicate activated charcoal could be used in cases of recent suspected or known overdose of dabigatran. The presence of active intestinal excretion and enteroenteric circulation of apixaban has implications in the use of activated charcoal. When given two and six hours post an oral dose of apixaban, activated charcoal showed no effect on maximal apixaban concentration or time to reach maximal concentration but reduced total apixaban exposure and half-life.[47] The manufacturer of rivaroxaban states that activated charcoal may be considered in case of overdose.[17]

Overall, there remains no compelling evidence to recommend any of the non-specific haemostatic agents for reversal of anticoagulation effect from the new direct oral anticoagulants. Furthermore the manufacturers provide no further specific advice regarding reversal of these drugs.[17,38,67] To address this evidence gap members of 10 organisations with special interest in anticoagulation including the American Heart Association, American Thrombosis and Hemostasis Network and Thrombosis Interest Group of Canada published a collaborative document "Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors".[77] Recommendations from this document include supportive care; fluid resuscitation, red cell transfusions, maintenance of renal function and surgical bleeding control as necessary; activated charcoal if drug ingestions was recent; and consideration of haemodialysis in dabigatran treated patients especially if they have impaired renal function. Of the reversal agents, greatest consensus was with the use of PCC in dire circumstance but this recommendation was not unanimous. No specific dosing was given.

INTERNATIONAL RECOMMENDATIONS FOR NEURAXIAL ANAESTHESIA

Multiple factors make the provision of strong evidence-based guidelines for neuraxial anaesthesia very difficult in the setting of anticoagulation with the new oral agents. Most notable among those is the infrequent occurrence of spinal haematoma and the limited clinical experience and patient exposure to the new agents. Nevertheless various anaesthetic societies have attempted to give guidance and recommendations for anaesthetic practice (Table 2).

Table 2. Summary of international anaesthetic guidelines regarding neuraxial anaesthesia[17, 38, 67, 78, 79, 81]

	Rivaroxaban	Apixaban	Dabigatran
American Society of Regional Anaesthesia and Pain Medicine			
Time between last dosing and puncture/ epidural catheter removal (hours)	Avoid	Not considered	Avoid
Time between puncture/epidural catheter removal and subsequent dosing (hours)	Avoid	Not considered	Avoid
European Society of Anaesthesiology			
Time between last dosing and puncture/ epidural catheter removal (hours)	22-26	26-30	Contraindicated
Time between puncture/epidural catheter removal and subsequent dosing (hours)	4-6	4-6	4-6
Scandinavian Society of Anaesthesiology and Intensive Care Medicine			
Time between last dosing and puncture/ epidural catheter removal (hours)	18	Insufficient data	Insufficient data
Time between puncture/epidural catheter removal and subsequent dosing (hours)	6	6	6
TGA product information			
Time between last dosing and puncture/ epidural catheter removal (hours)	18	20-30	Contraindicated
Time between puncture/epidural catheter removal and subsequent dosing (hours)	6	5	2

The 2010 guidelines from the American Society of Regional Anaesthesia and Pain Medicine take the conservative view that not enough is known about rivaroxaban and dabigatran and suggests avoidance of neuraxial techniques.[78] Apixaban is not considered.

The European Society of Anaesthesiology 2010 recommendations for regional anaesthesia and antithrombotic agents provide more specific guidelines.[79] Rivaroxaban treated patients should have a 22-26 hour dose free period before puncture or catheter removal and dosing can recommence four to six hours post puncture/removal. Apixaban treated patients require periods of 26-30 hours pre and four to six hours post puncture/catheter removal. The guidelines state that based on dabigatran half-life data, dural puncture or catheter removal should be appropriate with a 34-hour gap in dosing however it should be avoided as the manufacturer indicates neuroaxial anaesthesia and indwelling epidural catheters are contraindicated once dabigatran has been started. The recommended period before starting dabigatran after puncture or catheter removal is four to six hours. Manufacturer data published by the Therapeutic Goods Administration lists indwelling epidural catheters as contraindications to dabigatran use but recommends only two hours between puncture or removal of catheter and dabigatran dosing.[67] The equivalent New Zealand information does not list indwelling catheters as a contraindication and recommends a gap of only one hour.[80]

Finally, the 2009 Nordic guidelines from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine provide recommendation similar to, but distinct from the European counterparts.[81] Rivaroxaban is to be withheld for 18 hours before puncture/catheter manipulation and may be restarted after six hours following these actions. These guidelines state there is insufficient data to make recommendations on how long to withhold apixaban prior to neuraxial anaesthesia but indicate a six-hour period between puncture/catheter removal and subsequent dosing of apixaban. The recommendations for dabigatran are the same as for apixaban. All the Nordic recommendations are based on expert evaluation of pharmacokinetic data.

CONCLUSION

The introduction of novel oral direct coagulation factor inhibitors into clinical use has and will continue to influence anaesthetic practice. Expanding market penetration appears likely as new indications are established and more prescribers become comfortable with these new agents. This is evidenced by American data showing rapid growth of dabigatran use for anticoagulation in atrial fibrillation from 4% of patients in 2010 to 16.9% in 2011.[82] To provide safe and effective neuraxial anaesthesia in the presence of the newest generation of oral anticoagulants, anaethetists require a solid grasp of these agents' pharmacology and laboratory monitoring, as well as an acute awareness of the dangers of concurrent liver and renal dysfunction and the absence of simple reversal options for these increasingly commonly encountered drugs.

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Spinal ultrasound: The superior way?

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INTRODUCTION

The labour epidural technique requires advanced technical proficiency as it involves a complex set of tasks in order to successfully perform the procedure and avoid complications. Anaesthesia trainees are taught a surface landmark technique, which they practice throughout their careers. The technique involves the palpation of anatomical landmarks prior to targeting the epidural space with a blindly inserted 8cm Tuohy needle using a loss of resistance technique. The problem with a blind procedure is that anaesthetists may often be one or two lumbar interspaces higher than expected and therefore placing a Tuohy needle in close proximity to the spinal cord.[1] Furthermore, the anatomical landmarks may be difficult to palpate due to obesity or spine abnormalities. This presents a dual problem – a blinded approach and difficult palpable anatomy that may account for neuraxial technique complications.[2] Complications may include failed or difficult epidural placement, multiple punctures, traumatic insertions, nerve damage and dural puncture.

In an age where ultrasound advocates are arguing for its routine use in acute care anaesthesia and the technique is supported by the NICE guidelines, spinal ultrasound has the potential to be a game changer.[3,4] It presents the only technique that transforms a fundamentally tactile epidural insertion method into an ultrasound-assisted procedure.

The objectives of this article are to provide:

1. Evidence and rationale for the use of spinal ultrasound for labour epidural training.
2. Evidence for the use of spinal ultrasound by experienced practitioners in order to improve neuraxial procedural outcomes.
3. Evidence for the use of spinal ultrasound in patients with difficult anatomy.
4. The learning curves for spinal ultrasound.
5. A structured explanation of the pre-puncture spinal ultrasound technique.

EVIDENCE AND RATIONALE FOR USING SPINAL ULTRASOUND FOR TRAINING LABOUR EPIDURALS

The early introduction of spinal ultrasound to epidural training programs is important because it has been shown to improve the epidural learning curves of trainees.[5] Anaesthesia trainees experience high rates of technical difficulty especially during their first 20 procedures.[6] Their success rate during this period ranges from 60 to 70% [Table 1][6,7,8,9,10] and complication rates are high.[11] For beginners, significant improvement can only be demonstrated after 20 to 25 procedures,[6] but despite these relatively low success rates they progress to unsupervised practice after fewer than 10 epidurals in Australia.[12]

The initial learning improvement of the surface landmark technique is usually followed by an epidural learning curve plateau as the epidural catheterisation technique represents one of the most difficult anaesthesia skills in which to attain competency.[7] In order to reach competency at endotracheal intubation as few as 43 attempts is required in comparison to a minimum of 60 attempts for epidural catheterisation [Table 1].[6,7,8,9,10]

Therefore, we have to ask ourselves how we can help improve trainee epidural success rates? Spinal ultrasound presents a potential solution as it has been shown to decrease epidural failure rates in trainee anaesthetists.[13] The best evidence comes from a prospective, non-blinded, randomised controlled trial performed by Vallejo et al. on 370 parturients requesting epidural pain relief.[13] Patients were randomised to receive their epidural procedure by a first year trainee with or without prior determination of the depth to the epidural space via ultrasound. The ultrasound group had a significantly lower failure rate (1.6 vs 5.5%; $P<0.02$) and epidural placement attempts (1 vs 2; $P<0.01$) in comparison to the control group. Notwithstanding the fact that most obstetric anaesthesia module supervisors in Australia surveyed believe that ultrasound improves epidural learning curves and is widely available, it is not being used as a training aid in Australia (personal correspondence).[14]

Table 1: Observational studies determining trainee epidural proficiency

Author	Methodology	Key epidural proficiency results	Comments
Kopacz et al. 1996	Pooled cumulative success rate at groups of five attempts. Seven first-year anaesthetic trainees. Success defined as successful anaesthetic block. Acceptable failure rate not stated. Unacceptable failure rate not stated.	60% success after 20 attempts. 76% success rate at 60 attempts. Increase to 90% success rate after 60 attempts.	Initially learning steep followed by a trough.
Konrad et al. 1998	Monte Carlo procedure and least square fit model. 11 first-year anaesthetic trainees. Success defined as adequate technical performance of the procedure. Acceptable failure rate not stated. Unacceptable failure rate not stated.	After 20 cases 70% success rate. After 60 cases 70% success rate. After 80 cases approximately 80% success rate. 80% success rate after 90 attempts.	Epidural anaesthesia most difficult task of anaesthetic procedures evaluated. Initial learning quick; slower thereafter.
Naik et al. 2003	Cusum analysis. 13 first-year anaesthetic trainees. Success defined as independently placed epidural catheter that provided some degree of analgesia, without assistance from staff specialist. Acceptable failure rate 10%. Unacceptable failure rate 15%.	10 of 11 reached 15% acceptable failure rate. Median number required to reach competency was 57 (range 1-85). 75 attempts required by trainee 11 to reach competency.	More than 75 required for consistency.
Kestin et al. 1995	Cusum analysis. 12 first year anaesthetic trainees. Failure defined as inability to obtain satisfactory anaesthesia or analgesia. Acceptable failure rate 5%. Unacceptable failure rate 10%.	5 of 12 (41%) reached 5% acceptable failure rate between 29 to 185 epidurals.	Author suggested that acceptable failure rate might have been too stringent in context of study. Success not defined.
De Oliveira Filho 2002	Cusum analysis Success defined as successful surgical anaesthesia after location of epidural space via interspace first chosen. Acceptable failure rate 15%.	5 of 11 (45%) attained 15% acceptable failure after 20 epidurals.	Author concluded that that the wide interindividual variability in the number of procedures required to be performed before attaining acceptable failure rates suggests performance should be followed individually.

EVIDENCE BASE FOR THE USE OF SPINAL ULTRASOUND BY EXPERIENCED PRACTITIONERS IN ORDER TO IMPROVE NEURAXIAL PROCEDURAL EFFICACY AND OUTCOMES

Experienced anaesthetists can be sceptical about the utility of spinal ultrasound as they are very good at performing labour epidural procedures even in patients with challenging anatomy. This is the result of years of experience, a good understanding of spinal anatomy, repetitive performance of hundreds of procedures and good judgment. Would this suggest that spinal ultrasound would not increase the success rates of experienced practitioners?

To help answer this question it is important to evaluate the evidence from the systematic review and meta-analysis performed by Shaikh et al.[15] Their primary objective was to determine whether ultrasound imaging can reduce the risk of failed epidural catheterisations and lumbar punctures. After an exhaustive, pre-specified search of various databases, 14 randomised studies with a total of 1334 participants (647 patients assigned to the ultrasound group, 660 to the control group) were included in the analysis. It is of note that seven trials reported outcomes for obstetric patients in the labour and delivery suite and of those the procedures were performed by a staff specialist, that is an experienced anaesthetist, in five trials. The results for the primary outcome (failed neuraxial procedure) of the meta-analysis showed that six of 624 procedures conducted in the ultrasound group failed in comparison to 44 of 610 failed procedures in the control group. Ultrasound imaging reduced the risk of failed procedures (risk ratio 0.21 (95% confidence interval 0.10 to 0.43), $P<0.001$). The absolute risk reduction of failed procedures was 6.3%, resulting in a number needed to treat of 16 ultrasound guided procedures to reduce one failure. A large, multicentre randomised controlled trail is warranted to confirm these findings, however, the current evidence on spinal ultrasound suggests improved clinical efficacy even in the hands of experienced practitioners.

EVIDENCE FOR THE USE OF SPINAL ULTRASOUND IN PATIENTS WITH DIFFICULT ANATOMY

The ability of trainee anaesthetists to successfully identify the epidural space in parturients is influenced by four patient anatomical factors: abnormal spinal anatomy, an inability to palpate spinous processes; obesity defined by a body mass index (BMI) of more than 30 and an abdominal circumference more than 105cm.[16]

Analysing the context of these factors is important in order to understand its relationship to epidural procedural difficulties. First, obesity is an important population health issue as epidemiological studies in Australia have shown that up to 38% of women aged 25 to 44 years are overweight or obese.[17] In some obstetric populations there has been a two to threefold increase in women with class II (BMI ≥35 but <40) or III (BMI ≥40) obesity over the past decade.[18] This is worrying as patients with a high body mass index (BMI) are susceptible to complications such as inadvertent dural puncture, and failed neuraxial blocks. In patients who are morbidly obese the failure rate may be as high as 42%.[19]

Second, obesity on its own is probably not the most important cause of technical difficulty as some obese parturients have easy block placements. The key factors that influence technical difficulty in these patients are impalpable landmarks and inadequate back flexion.[20] Significantly, ultrasound depth estimates have been shown to be accurate in obese parturients, although less so at increasing depths due to underestimation of the needle depth by US.[21,22] Soft tissue compression in the transverse plane (TM) can contribute to this problem. Less compression will lead to more accurate estimates, but at the expense of image quality in the TM plane.

Sonograms are less distinct in the obese as the ultrasound beam has to travel greater distances causing exaggerated beam attenuation and phase aberration effects resulting from the uneven speed of sound as it passes through irregularly shaped adipose tissue layers.[23] Nonetheless, image quality of the ligamentum flavum-dura mater complex in the parasagittal oblique plane (SOP) is often superior to the transverse interlaminar view due to the larger size of the acoustic window.[24] Sahota et al. found that there is very good correlation between the US-determined distance to the epidural space in the PSO and the TM plane.[25] These estimates can potentially be used interchangeably for midline punctures in obese patients with poor visibility in the transverse interlaminar view.[25]

However, the question remains whether ultrasound can improve the efficacy of neuraxial procedures in a population of patients with difficult surface anatomy? Chin et al. performed a prospective, randomised study in 120 adults with difficult surface anatomical landmarks (moderate to severe lumbar scoliosis, poorly palpable spinous processes, BMI more than 35 or previous lumbar spine surgery) who presented for orthopaedic surgery under spinal anesthetic.[26] Participants were randomised to spinal anaesthetic by surface landmark-guided technique or preprocedural ultrasound marking of the needle insertion point. They found that the first attempt success rate in the ultrasound was double that of the landmark group (65% versus 32%, $P<0.001$). They concluded that ultrasound imaging facilitates spinal anaesthesia in adults with difficult surface landmarks. A similar study is required in order to confirm these finding in the obstetric population.

THE LEARNING CURVES FOR SPINAL ULTRASOUND

How easy is it for novices to attain the spinal ultrasound skill? Deacon et al. examined the learning curve of anaesthetists with no prior experience with spinal ultrasound.[27] Following standardised instruction and strict competency criteria the learning curves were determined using CUSUM-analysis. Trainees identified a lumbar intervertebral space relatively easily (Figure 1a; competent after nine scans), measured the depth to the ligamentum flavum with some difficulty (Figure 1b; competent after 42 scans), marked the ideal needle insertion point with difficulty (Figure 1c; 2 out of 5 trainees competent after 55 scans) and completed the tasks on average within three minutes (Figure 2).[22] The results suggests that competency with accurately measuring the US depth to epidural space can be attained after 40 scans.

Figure 1. Cusum analysis for tasks

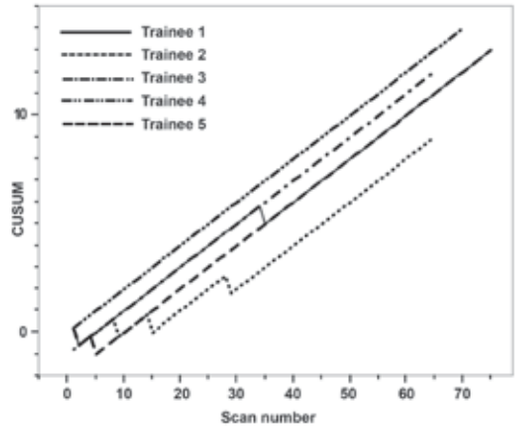


Figure 1a. Identification of random lumbar interspace – upward CUSUM trend indicates early competency for all trainees performing this task.

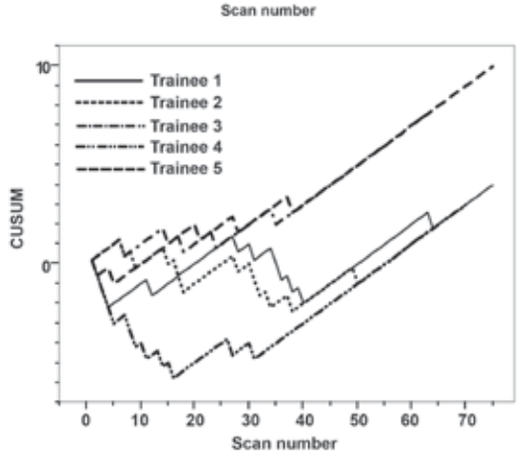


Figure 1b. Measurement of depth to ligamentum flavum to a tolerance of 5mm – a greater number of scans is required to produce horizontal or upward cusum trends indicating greater difficulty in attaining competency by all trainees.

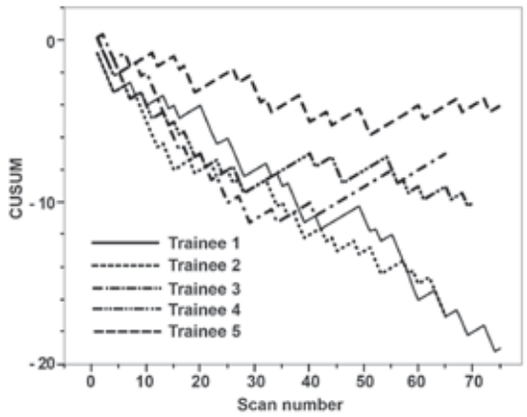
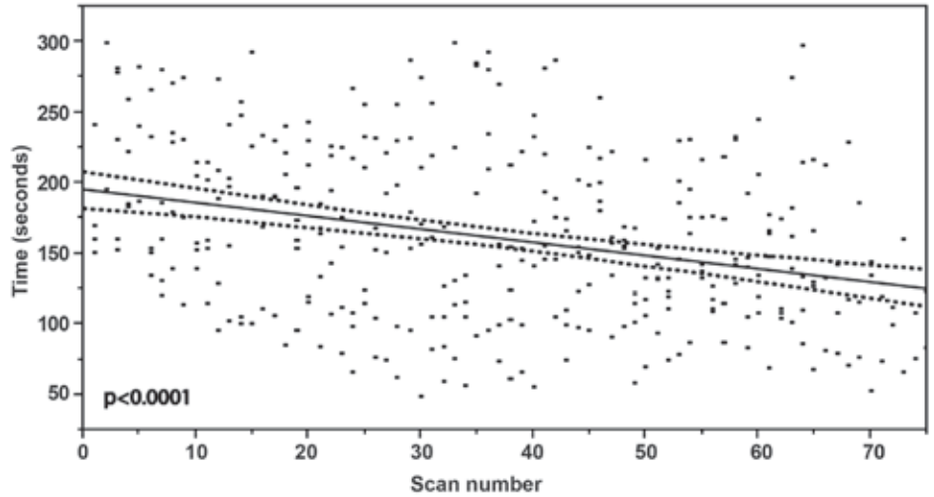


Figure 1c. Marking of ideal needle insertion point to a tolerance of 5mm – horizontal CUSUM trends indicating competency are achieved by only two trainees (3 and 5) while three trainees (1,2 and 4) were unable to reach competency as indicated by negative trends.

Figure 2. Time taken to complete all tasks

Scan time decreased by a mean of 0.96 seconds per scan (p<0.0001; 95% confidence intervals represented by the dotted lines above and below solid line).



STANDARDISED METHOD FOR PERFORMING A SPINAL ULTRASOUND GUIDED LABOUR EPIDURAL

The solution to effective spinal ultrasound learning is standardised teaching. Structured training for technical skills has been shown to be more effective than conventional non-structured training.[28,29] Palter et al., in a randomised controlled trial, showed that surgical trainees who underwent a structured training and assessment in the context of a workshop, developed superior technical and non-technical laparoscopic cholecystectomy skills in the operating room.[30] Similarly, a step-wise method of performing spinal ultrasound as described below is recommended:

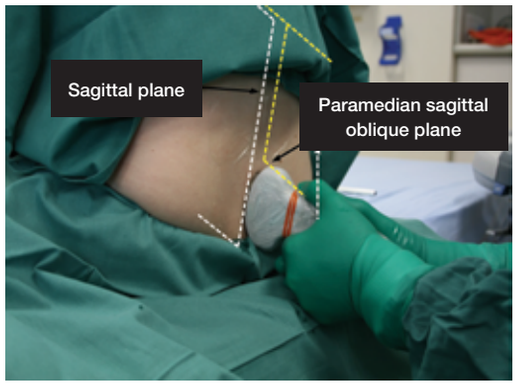
Step 1: Preparation for scanning

Position the patient in a flexed sitting posture. Select a low-frequency (for example, 2-5 MHz), curved-array ultrasound probe (Figure 3). Adjust the depth (between nine and 12cm) and gain settings on the ultrasound machine as needed. Warn the patient before applying the ultrasound probe.

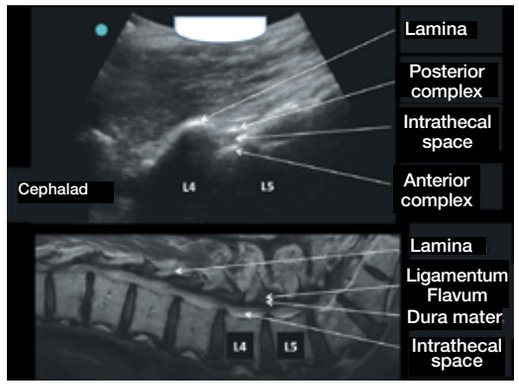
Figure 3. A low-frequency (for example 2-5 MHz), curved-array ultrasound probe is shown

Step 2: Paramedian sagittal oblique (PSO) view scan
Position the probe on the skin at the level of the sacrum, 2-3cm lateral to the midline, while tilting the probe towards the midline ensuring the signal enters the spinal canal through the widest diameter of the interlaminar space (Figure 4a). This represents the paramedian sagittal oblique plane. Following identification of the reflective surface of the sacrum, slide the probe cephelad, recognising and centring the L5-S1 interspace in the middle of the ultrasound screen. Its location will correspond with the midpoint of the probe's long side and can be marked on the patient's skin. Cephaled advancement of the probe reveals the "sawtooth" appearance of the laminae. Proceed by centring successive intervertebral spaces (L4-L5, L3-L4, L2-L3) on the ultrasound screen and marking it on the patient's skin (the 'counting-up' approach) (Figure 4b). A conclusive sonogram in the paramedian sagittal oblique plane will show an easily identifiable sacrum, lamina, anterior complex (ligamentum flavum and dura mater) and posterior complex (reflective surface of vertebral body).

Figure 4. Paramedian sagittal oblique views scan



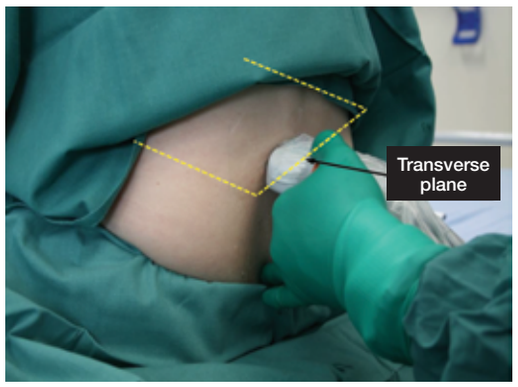
4a. The ultrasound probe orientation and associated anatomical planes is shown.



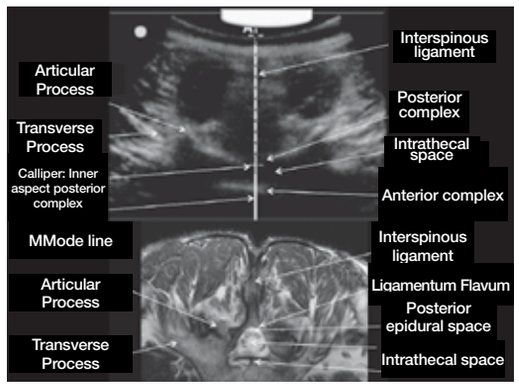
4b. A sonogram and corresponding MRI of the paramedian sagittal oblique view of the L4-L5 interlaminar space is shown to demonstrate important anatomical structures.

Step 3: Transverse interlaminar view scan (TM)
Rotate the probe 90 degrees into a transverse orientation and slide it cephalad or caudad as required to obtain transverse interlaminar views of the desired interspaces (Figure 5a). To optimise the view the probe may have to be tilted in either a cephalad or cauded direction. The corresponding sonogram has been described as having the appearance of a bat. This view includes articular processes ("ears of the bat"), the posterior complex (ligamentum flavum-dura mater; "top of the head of the bat"), the anterior complex ("the nose of the bat") and the transverse processes ("the wings of the bat") (Figure 5b). The required needle insertion depth can be estimated by measuring the depth from skin to the posterior complex using the machine's electronic callipers.

Figure 5. Transverse interlaminar view scan



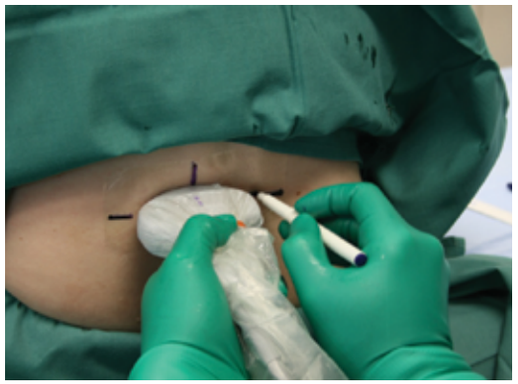
5a. The ultrasound probe orientation and associated anatomical planes is shown.



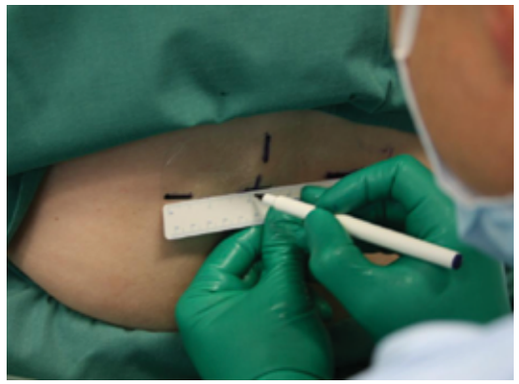
5b. A sonogram and corresponding MRI of the transverse interlaminar view of the L4-L5 interlaminar space is shown to demonstrate important anatomical structures.

Step 4: Mark needle insertion point for a midline approach
Centre the neuraxial midline on the ultrasound screen in the transverse interlaminar view and mark the midpoint of the probe's long and short sides (Figure 6a). The needle insertion point can be obtained by intersecting these three markings (Figure 6b).

Figure 6. Surface marking is performed to guide needle insertion



6a. The midpoint of the probe's long and short sides is marked first.



6b. The needle insertion point can be obtained by intersecting the three surface markings.

Step 5: Labour epidural procedure
Perform the labour epidural procedure using an aseptic technique.

CONCLUSIONS

ANZCA has developed a word-class anaesthesia training program to train world-class anaesthetists. This implies that in the pursuit of excellence we should keep striving for innovative methods to improve different aspects of anaesthesia training and practice. Evidence suggests that spinal ultrasound represents a novel and effective aid for teaching and performing obstetric epidurals. It is the superior way as it embodies the only procedure that gives anaesthetists real-time imaging windows through which to identify and assess lumbar intervertebral spaces in various anatomical planes prior to performing obstetric epidurals.

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Caesarean haemodynamics

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AN HISTORICAL PERSPECTIVE

In 1950 Nicolas Assali and Harry Prystowsky undertook a set of experiments that helped to characterise the haemodynamic changes induced by spinal anaesthesia during pregnancy. Their studies included investigation of the effects of high spinal anaesthesia in normal term pregnancy and severe pre-eclampsia.[1] The clinical variables they were able to assess were blood pressure, by auscultation using a mercury sphygmomanometer; heart rate, by palpation of radial or carotid pulse; and clinical observation of patient "condition". Twelve normal pregnancies between 33 and 40 weeks gestation, 15 pre-eclamptic or eclamptic pregnancies and five "healthy young normotensive non-pregnant females (medical students and paid volunteers)" were the subject of investigation. The spinal anaesthesia testing involved insertion of an intrathecal catheter at the L3 or L4 space via a 16-gauge Tuohy needle. The catheter was threaded cephalad to between the L1 and T9 level, then the subject was returned to the supine (un-wedged) position. Procaine 0.2% was administered in 2-5mL aliquots to achieve a sensory block above T2 level (range C3 to T2). No fluid was given and in cases where blood pressure fell to "dangerous" levels, raising the legs to 90 degrees was the only intervention performed. The normal pregnancy group not surprisingly demonstrated a significant decrease in blood pressure. From a baseline 120/79mmHg, a post spinal "floor" mean of 68/37 was documented. This was in stark contrast to the non-pregnant and pre-eclamptic groups in whom they noted "negligible" blood pressure decreases. In fact five of 15 subjects in the pre-eclamptic group subsequently received 1% procaine "in order to detect any difference in the effect of higher concentrations" resulting in hyperpnoea and motor paralysis of legs and arms without significant blood pressure fall. The pulse rate and clinical observations in the normal pregnancy group deserve special attention: in most cases they described an initial increase in the pulse rate at the onset of the blood pressure decrease, followed by a rapid fall to between 10-30 beats per minute below baseline levels. This was associated with side effects including vomiting, perspiration, hyperpnoea, cyanosis and other "signs of imminent collapse" in all patients.

The purpose of this review is firstly to explore the physiologic basis for the responses that Assali and Prystowsky, and many thereafter, have observed. Newer minimally invasive monitoring techniques have prompted further investigations into the physiologic effects of spinal anaesthesia during caesarean delivery, challenging some of the accepted lore. It is clear from Assali and Prystowsky's work that the physiologic differences between the term pregnant and non-pregnant state must explain the contrasting haemodynamic responses witnessed. Likewise, the observations in the pre-eclamptic group of an attenuated response to spinal anaesthesia demonstrates that there are different considerations in the anaesthetic management of this patient population.

Newer investigative techniques have allowed a greater insight into how our therapeutic interventions modify upon the physiologic derangements introduced by spinal anaesthesia. A review of these physiologic interactions caused by common therapeutic interventions in this situation is the second aim of this review.

HAEMODYNAMIC DIFFERENCES BETWEEN THE NORMAL PREGNANT AND NON-PREGNANT STATES

The cardiovascular and haematologic changes associated with pregnancy are well known: blood volume increases by 45%, associated with a mild physiologic anaemia. Systemic vascular resistance decreases by 20% as a result of the inclusion of a new low-resistance vascular bed, a decreased pressor response to angiotensin II, and the effects of the placentally derived hormones including progesterone and oestrogen (which increase vascular prostacyclin and nitric oxide production).[2] Cardiac output increases by 50%, with increased heart rate and stroke volume contributing equally to the higher flow. The hyperdynamic cardiovascular response in pregnancy is the result of an increase in sympathetic outflow above non-pregnant levels.[3] This finding however belies the ability of the sympathetic nervous system to respond to circulatory compromise.[3,4,5] Pregnancy impairs the arterial baroreflex, such that the sympathetic nervous system response to hypotension is impaired, the result being that pregnant women are more prone to orthostatic hypotension, and have an impaired ability to maintain blood pressure in the presence of vasodilation or haemorrhage. Interestingly, the adrenergic response of the uterine vasculature still exceeds that in the systemic circulation and may indicate a maternal protective mechanism preferentially sacrificing foetal flow.[6] The arterial baroreceptor response to hypertension is similarly blunted, heart rate does not decrease to the same extent as in non-pregnant individuals, and an exaggerated blood pressure response from circulating catecholamines results. Also it appears the baroreceptor response in pre-eclampsia is further attenuated predisposing to severe hypertension with adrenergic stimulation.[3]

The second major physiologic contributor to the disparate responses seen in normal pregnant and non-pregnant women following spinal anaesthesia is the effect of mechanical compression caused by the gravid uterus. Aorto-caval compression has been implicated in the supine hypotensive syndrome. Its incidence has been variably reported to be between 2.5 and 20% at term.[7] This discrepancy may have more to do with the difficulty authors have had in deciding on a definition rather than the actual prevalence of the condition, which is probably closer to 8%. Despite less than one in 10 being clinically symptomatic there is objective evidence of cardiovascular compromise and a compensatory autonomic response: Clark et al. demonstrated a decrease in cardiac output of 9% in moving from the lateral to supine position associated with an increase in HR of 30% and no significant change in mean arterial pressure.[8] Venous pressure in the legs is markedly elevated when in the supine compared with the lateral position, suggesting sequestration of blood in the periphery and reduced venous return.[7]

MATERNAL AND FOETAL MANIFESTATIONS OF MARKED CIRCULATORY COMPROMISE

For the mother, arterial hypotension is the cause of the unpleasant symptoms associated with spinal anaesthesia. Brainstem and gut ischaemia are thought to cause nausea and vomiting. Greater degrees of cerebral hypo-perfusion may cause dyspnoea and a "sense of impending doom" that precedes collapse.[9]

The determinants of foetal flow are more controversial, with maternal blood pressure and cardiac output favoured as the most important contributing factor by various authors.[10,9] Authors favouring pressure as the regulator of uteroplacental flow cite studies demonstrating it to be a widely dilated low resistance system, with little capacity to vasodilate further. As such the pressure gradient across it is the only determinant of flow. In contrast one of the few studies correlating cardiac output changes with umbilical artery pH (a presumed surrogate for uteroplacental flow) demonstrated a significant correlation with maximal cardiac output change but not with blood pressure drop. A deficiency of this investigation was the fact that hypotension was invariably present in all cases of severely decreased cardiac output. What is not disputed is the fact that there appears to be significant uteroplacental reserve under normal physiologic conditions. Uteroplacental blood flow may fall by as much as 50% before foetal oxygen uptake decreases and metabolic acidosis occurs. As alluded to earlier, adrenergic reactivity is preserved to a small degree, which may reduce flow.[6] In the case of the already compromised foetus, there is some concern that alpha-1 agonists might cause an increase in uteroplacental resistance. However in the presence of maternal hypotension this effect may be negated by the increase in pressure produced in the foetal-placental unit.

PHYSIOLOGIC BASIS FOR THE HAEMODYNAMIC EFFECTS OF SPINAL ANAESTHESIA

Much discussion has resulted from the findings of two investigators who have recently challenged the accepted wisdom pertaining to haemodynamic changes induced by spinal anaesthesia.[5,10-14] Traditionally, teaching has been that hypotension results from a decrease in cardiac output associated with a reduction in venous return and heart rate.

Using minimally invasive lithium dilution cardiac output monitoring (LiDCO), Langesaeter et al. and Dyer et al. each independently demonstrated a sustained increase in cardiac output following induction of spinal anaesthesia in elective healthy term patients for caesarean delivery.[11,12] This result contradicted the accepted dogma that preganglionic sympathetic blockade of the level required for caesarean delivery reduced cardiac sympathetic outflow (heart rate) as well as arterial, and to a greater extent, venous tone. Venodilation, it was assumed, should decrease venous return to the heart and cardiac output. Furthermore, both investigators demonstrated the observed increase in cardiac output was the result of both an increase in stroke volume and heart rate.

An adequate understanding of the interaction between venous compliance, capacitance and return to the right heart is required in order to come to terms with how this information might be explained physiologically. Reddi and Carpenter provide a simplified model for the interaction between cardiac output and venous return that can be applied in the case of spinal anaesthesia.[15] Their explanation revolves around a conceptual separation of arterial and venous determinants of cardiac output. On the arterial side they propose that the rate of arterial "volume accumulation" determines arterial pressure: volume entering the arterial systemic circulation is determined by the flow rate in (the cardiac output), and the rate at which it dissipates away, determined by the peripheral resistance. Accumulation of "arterial excess" volume results in increased blood pressure all else being equal, and this becomes a regulated variable via the baroreceptor response. The baroreceptor reflex induces a decrease in heart rate and contractility to reduce cardiac output and as a consequence the "arterial excess" volume. The venous circulation is defined by its capacitance (the volume of blood it holds), as well as its compliance (its distensibility), which serves to reduce or increase capacitance, depending on changes in the venous tone. The venous compliance determines the flow of blood returning back towards the right atrium where it accumulates as "venous excess" before being distributed by the right atrial contraction into the right ventricle where the distension produced will determine stroke volume and ultimately cardiac output.

According to this model, the expected arterial effect of ascending sympathetic blockade would be to reduce peripheral arterial resistance causing an "arterial deficit". To counter this there would be arteriolar constriction in unblocked segments, and the cardiac baroreceptor reflex should induce a rise in heart rate to increase cardiac output. Clearly these responses depend on some degree of intact sympathetic tone in the upper body and a functional baroreceptor response. It is not inconceivable that initially intact responses would progressively fail with time and ascent of sympathectomy. Progressive heart rate reduction has been confirmed with increasing duration of spinal anaesthesia suggesting a reduction in the sympathetic outflow from the cardiac accelerator.[10]

On the venous side of the circulation there would be increased venous capacitance as a result of the sympathectomy, so despite transfer of blood from the arterial to the venous circulation its effect on "venous excess" may, with ascending sympathectomy, become increasingly frustrated, tending to reduce cardiac output (after an initial, transient surge as a result of arterial deficit as described above).

So how do we explain the contradictory results produced by both Langesaeter et al. and Dyer et al.? There may be a therapeutic confounder, which has been underplayed in the aetiology of the purported sustained cardiac output increase associated with spinal anaesthesia; previous investigators that assessed cardiac output changes with spinal anaesthesia did not identify increases in cardiac output associated with spinal induction. Their investigations were methodologically different however[16,17] Langesaeter et al. and Dyer et al.'s studies incorporated a crystalloid coload (a rapid administration of fluid at the time of spinal induction), using volumes of between 750mL and 1.5L. Coloading was not a practice that was prevalent when the first studies suggesting cardiac output decreases with spinal anaesthesia were presented (preloading was still in vogue).[16] Tamilselvan et al. assessed cardiac output responses in 60 pregnant women having caesarean delivery when administered fluid preload using three different fluid regimens (1.5L crystalloid, 0.5L 6% hydroxyethyl starch (Voluven®), and 1L Voluven®).[18] Hypotension following spinal anaesthesia was treated with ephedrine bolus. All patients significantly increased their cardiac output following preload, but cardiac output continued to decline towards baseline values in all three groups following spinal anaesthesia. Teoh and Sia compared the effects of 15mL/kg Voluven® preload or coload on cardiac output changes with spinal anaesthesia in 40 caesarean patients. They used phenylephrine as rescue therapy for hypotension. They showed a significant increase in cardiac output following a preload, which was not sustained above the cardiac output increase induced by coloading at 10 minutes post spinal.[19]

COMMON THERAPEUTIC INTERVENTIONS FOR THE PREVENTION AND TREATMENT OF SPINAL INDUCED HYPOTENSION

1. Aorto-caval relief

Interestingly the introduction of fluid preloading was initially proposed as a method to help mitigate the effect of blood "trapped in the legs" as a result of aortocaval compression.[13] Leg compression was another method that was attempted in an effort to redistribute the supposed "trapped" volume into the central circulation, but with limited success. Finally, lateral tilt was advocated. L lateral tilt continues to be widely (but variably) applied. Unfortunately despite good evidence for the effects of aortocaval compression the methods described do not reliably prevent hypotension at caesarean delivery.

2. Fluid preload or coload

Fluid by preload or coload significantly increases cardiac output in the supine wedged position.[17,18] However, as sole therapy, fluid administration does little to reduce the rate of hypotension following spinal anaesthesia. Colloid is more effective as a preload fluid than crystalloid solutions, but even so the incidence of hypotension remains as high as 45%.[20] Coloading of fluid at the time of spinal induction is usually combined with vasopressor administration. In this setting is has demonstrated a reduction in vasopressor doses required to maintain blood pressure. There appears to be little advantage to coloading using colloid (Voluven® 1L) versus crystalloid (Hartmans solution 1L), in conjunction with a phenylephrine infusion.[21] In addition there is a potentially greater risk of adverse effects including allergy, pruritis and coagulation defects depending on the chosen colloid fluid.[22]

3. Vasopressor administration

Vasopressors are the most effective therapeutic intervention for combating spinal hypotension. As it is predominantly preganglionic adrenergic failure that is the cause of hypotension it is logical that peripheral activation of adrenergic receptors would reverse the spinal mediated effects. An appropriate balance, however, is difficult to achieve. As the sympathetomy ascends the relative contribution from both alpha and beta-adrenergic blockade may change. Similarly there may be region specific differences in vasopressor response in the blocked and unblocked areas potentially altering regional flows.

It is evident that alpha-1 agonists such as phenylephrine and metaraminol counter the effect of arteriolar vasodilation, and the consequent "arterial deficit" produced by the loss of arterial volume through a vasodilated arterial circulation. By increasing arteriolar tone they increase the arterial volume accumulation rate and restore blood pressure. Excess administration of vasopressor will cause an increase in the "arterial excess" volume and blood pressure. By the baroreceptor reflex this will induce a decrease in heart rate, which is commonly seen following pure alpha agonist administration.

The effect of isolated alpha-1 adrenergic stimulation on the venous circulation following spinal anaesthesia will depend in part on its capacitance (the volume in the venous reservoir). In the normal pregnant state a reduction in venous tone as a result of spinal blockade will increase the venous compliance and serve to reduce the volume of blood directed back towards the right atrium and thus the "venous excess" volume. Often this unmasks the effects of vena caval compression, further decreasing cardiac output. Increasing venous tone with alpha-1 agonists in a well-filled circulation will decrease venous compliance and serve to direct a greater volume of blood back to the right atrium increasing the volume of "venous excess". However, in the hypovolaemic state, alpha-1 stimulation will reduce the diameter of the veins but without any appreciable change to the compliance of these vessels (the tension in the vessel wall will not increase and therefore will not promote flow back towards the atria).

Furthermore, the venous contraction may increase venous resistance and reduce blood flow through the vasculature, compounding the decrease in cardiac output.

If rapidly treated, hypotension does not appear to have any appreciable effect on the unstressed foetus. However maternal symptoms are likely. Ephedrine is less effective than phenylephrine in reducing maternal symptoms. In addition it has been shown to reduce uterine artery pH, despite no appreciable difference in Apgar scores when compared with phenylephrine. It is probable that the difference in uterine artery pH relates to beta-adrenergic stimulation in the foetus induced directly by the drug crossing the placenta.[23]

Hypotension prophylaxis using a phenylephrine infusion currently appears to be the most effective therapy. Allen et al. assessed four different infusion rates, 25, 50, 75 and 100mcg/min in conjunction with a 2L crystalloid coload. The rates they thought demonstrated the best efficacy to side effect ratio (including the lowest rates of phenylephrine-induced reactive hypertension) were the 25 and 50mcg/min regimens. Stewart et al. performed a similar study using infusion rates of 25, 50, and 100mcg/minute but also assessed the effect on cardiac output.[17] Their protocol included a fluid preload of 500mL Hartman's solution between baseline testing and spinal. They demonstrated a significant cardiac output rise after fluid bolus, and a progressive decrease in cardiac output and heart rate (20% below baseline in the 100mcg/minute group). It has been suggested that during phenylephrine infusion heart rate change serves as a good surrogate for cardiac output deviations, and that titrating infusion to maintain a stable heart rate is appropriate.[10]

EXCEPTIONS TO THE RULES

1. Labouring women

Clark noted that hypotension was less likely to occur at caesarean in patients who had already started labouring.[24] In an observational study of 331 patients there was a 20% difference in the hypotension rate (61% in non-labour and 39% in labouring). The observation should be accepted with some caution as 247 patients had epidural anaesthesia as their mode of anaesthesia for caesarean, presumably some having been placed on the labour ward.

2. Pre-eclampsia

Unfortunately, the effects of spinal anaesthesia in pre-eclamptic patients demonstrated by Assali and Prystowsky were downplayed by their contemporaries. A number of subsequent investigators revisited vasopressor response in pre-eclampsia, demonstrating reduced ephedrine requirements.[25,26] Although the disease manifestations may vary, pre-eclampsia is associated with a failure of maternal-placental angiogenesis and there is endothelial dysfunction. The predominant physiologic derangement is the presence of an abnormally high vascular resistance, which is refractory to sympathetic blockade. Spinal anaesthesia is well tolerated, and is associated with less hypotension, and a blunted cardiac output response. Both systemic and uteroplacental responses to alpha-1 agonists may be exaggerated, and phenylephrine infusions potentially may reduce utero-placental flow and are discouraged.[9] Cautious fluid loading with 5-10mL/kg may augment cardiac output, but large volumes should be avoided given an increased risk of pulmonary oedema.

3. Bezold Jarish reflex

So far this summary has failed to address the aetiology of the dramatic cardiovascular collapse Assali and Prystowsky demonstrated in all of their normal pregnant subjects with untreated high spinal anaesthesia. The rapidity of the marked bradycardia and hypotension following a period of increased heart rate suggests a reflex response rather than a progressive change resulting from ascending spinal anaesthesia. At the time of a severe (40-50%) reduction in cardiac output a paradoxic decrease in heart rate, arteriolar resistance and blood pressure can occur. This is likely the result of mechanoreceptor stimulation caused by the vigorous contraction of an empty ventricle inducing a decrease in sympathetic outflow to the vasculature as well as a vagally mediated bradycardia. The result is fainting and circulatory collapse.[27]

A RECIPE FOR ELECTIVE CAESAREAN DELIVERY IN NORMAL PREGNANCY

One successful recipe based on the current evidence to offer practical anaesthetists attempting to prevent adverse maternal and foetal outcomes after spinal induction in the normal healthy elective caesarean delivery is as follows.

Immediately on spinal induction:

- Left lateral tilt to 15-20degrees.
- Rapid crystalloid coload of 500-1000 mL.
- Phenylephrine infusion with a starting rate of 25 to 50mcg/minute.

It is not uncommon to have an initially high post-spinal blood pressure and tachycardia due to the stress of the spinal procedure and the exertion of returning to the supine wedged position. But, starting the phenylephrine infusion immediately on induction is necessary as the onset of sympathetic blockade may be rapid, and it is essential that an adequate dose is administered by the time this occurs. Close observation of heart rate, and blood pressure measurement every minute thereafter should guide titration of the phenylephrine infusion. Ideally blood pressure should be maintained above 80% of the baseline measure, accepting that a heart rate reduction to the level of the unstressed preoperative baseline, or below, will occur. If hypotension does occur, further bolus administration of phenylephrine 50-100mcg is appropriate, unless heart rate is less than 60 beats per minute, in which case ephedrine is appropriate. Low heart rate (for example <60 beats per minute) associated with normotension or hypertension is usually a result of arterial baroreceptor activity and should respond to a reduction in the phenylephrine infusion rate.

It is important to recognise that the combination of a vasopressor and atropine in this situation may cause a severe increase in blood pressure, with one case report of myocardial infarction as a result.[28] Conversely abrupt reductions in heart rate (usually <50 beats per min), associated with severe hypotension are likely the result of inadequate cardiac output and activation of the Bezold-Jarish reflex. In this situation aggressive treatment including fluids, ephedrine and/or anticholinergic is required.

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Torrential peripartum haemorrhage

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INTRODUCTION

In many countries across Australasia, peripartum haemorrhage is one of the leading causes of maternal death. Yet, haemorrhage is the cause of maternal mortality and morbidity most amenable to forward planning and early, aggressive intervention.

The armamentarium for dealing with torrential haemorrhage in obstetrics is prodigious but there is great danger, especially among the inexperienced and uninitiated, to resort to exotic methodologies with poorer outcomes when simple, previously rehearsed methods are more effective. There are a handful of first line techniques which have very high yield in terms of positive outcome and which can be used in virtually every situation. These include:

- Massive transfusion protocol.
- Major obstetric haemorrhage drill training.
- Rational use of uterotonics.
- Haemorrhage control and containment.
- Aggressive volume resuscitation.
- Haemorrhage trolley or box.
- Protocol-driven management.
- Team approaches to early detection, rapid assessment and treatment of the cause(s) of haemorrhage.
- Repeated patient reassessment for multiple causes for the current episode of haemorrhage.
- Rapid deployment of appropriate levels of competent staff to deal with a bleeding emergency.

Other techniques and medications hold an important but supportive role in haemorrhage management. They include:

- Secondary devices, especially rapid infusers and blood warmers.
- Pharmacological methods, especially recombinant rFVIIa and tranexamic acid.
- Surgical interventions, especially uterine B-Lynch sutures, uterine compression, caesarean hysterectomy and vessel ligation.
- Haemodynamic monitoring, both non-invasive and invasive.
- Clinical interventions such as intrauterine balloon techniques.
- Supportive interventions, especially cell salvage.
- Interventional radiology, especially balloon tamponade of arterial blood supply.

While the incidence of major obstetric haemorrhage is steadily increasing, we are observing a lower mortality from haemorrhage. Also, there is a lowered morbidity from bleeding – post-haemorrhage pre-renal renal failure and Sheehan's syndrome are becoming uncommon. Pulmonary failure, pneumonia and sepsis following massive blood loss are also declining. Better still, future reproductive function is often being retained (by not resorting to caesarean hysterectomy too early) and there is a lessened reliance on radiological embolisation procedures to secure cessation of the haemorrhage. The rising incidence of haemorrhage stems from an escalating reliance on caesarean section (CS) for infant delivery and a steady increase in maternal age at delivery with assisted reproductive technologies widening the reproductive age window. Women above 35 years of age now make up more than 25% of those presenting for caesarean section. This doubling in caesarean rates from about 16% in the late 1990s to more than 35% in 2010 in most Australian hospitals, and higher in some, has a sting in its tail because, as a consequence, the incidence of placenta accreta has risen almost 10-fold in the last 40 years (for example, from 5% from 1965-1975 to 47% from 1996-2005, in Dublin, Ireland). Also, more women are on low molecular weight heparins, aspirin and other anti-coagulants in pregnancy.

'Torrential', 'massive', 'overwhelming', 'catastrophic', 'major', 'critical' or 'extreme' bleeding (or for that matter transfusion) are somewhat arbitrary, interchangeable terms but it is accepted that transfusion of a patient's entire red cell mass within 24 hours, that is transfusion of ~10 units of packed red blood cells (PRBCs) in adults/24 hours, is as good a criterion as any other. Haemorrhage can be so horrendous in obstetrics because, at term, the gravid uterus receives 15% of the maternal cardiac output (up from a pre-pregnancy 2%). This represents a uterine blood flow of >600ml/minute, that is a potential placental haemorrhage of >1 unit blood loss per minute. The low-resistance placental circulation also lacks auto regulation. Only effective uterine myometrial contraction can stop bleeding.

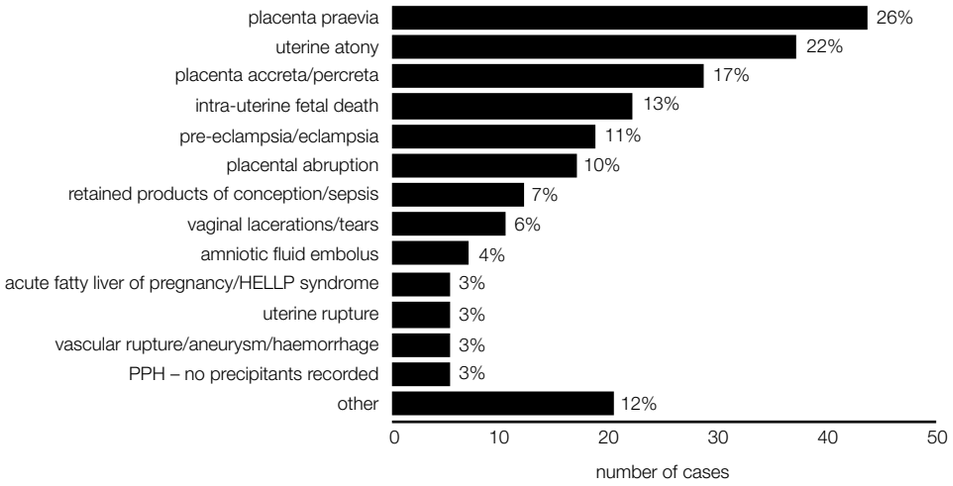
PATHOGENESIS AND AETIOLOGY OF MAJOR OBSTETRIC BLEEDING

The primary causes of obstetric bleeding are shown in the accompanying panel – 26% placenta praevia, 22% atonic uterus, 17% placenta accreta or percreta, 13% intrauterine foetal death, 11% pre-eclampsia/eclampsia and 10% placental abruption. It must be remembered that, regardless of the primary cause (for example, placenta accreta), there is very often more than one 'cause' of obstetric haemorrhage, so that, in postpartum haemorrhage (PPH), much of the torrential bleeding is also attributable to, to give but two examples: (1) placenta accreta + uterine atony + development of thrombocytopaenic coagulopathy; (2) pre-eclampsia + abruptio placentae + atonic uterus + disseminated intravascular coagulopathy (DIC).

It is usually easy, by asking a few questions, to determine the cause(s) of bleeding:

- Is the placenta delivered and is it complete or incomplete?
- Is the bleeding visible vaginally or is there concern that the bleed is concealed?
- Is the uterus soft or contracted?
- Is the uterus palpable? What is the uterine position?
- Is the bleeding accompanied by pain? Where is the pain located – abdominally or elsewhere (for example, at the shoulder tip)?
- Is there additional bleeding from other wound sites?

Number of cases by cause of obstetric bleeding (n=175) in the Haemostasis Registry



THE MASSIVE TRANSFUSION PROTOCOL

Universal availability and use of massive transfusion protocols (MTPs) is, arguably, the single factor that has had the biggest positive impact on mortality and morbidity in obstetric torrential haemorrhage. It is essentially a simple contractual arrangement between the blood banking/haematological services and the anaesthesia/obstetric teams. Once the protocol is activated (by a phone call), it will set in motion a pre-agreed delivery of blood products and haematological support services, which will continue unabated until the MTP is called off.

Many MTPs are unnecessarily complex and, in some ways, defeat the purpose of actively using such protocols when the torrential haemorrhage starts and "it is all hands to the pumps". These MTPs need to be as simple as:

On activation of MTP:

- Supply initial four units packed red blood cells (PRBCs).
- Supply MT pack I: four units PRBCs + four units FFP + four units platelets.
- Alternating with MT pack II: four units PRBCs + four units FFP + six units cryoprecipitate + 1amp rFVIIa.

Most protocols have additional features, such as:

Suggest additional:

- Platelets – if platelets <50 X 10^9/L.
- Cryoprecipitate – if fibrinogen < 1.0 g/L (and more recently, <2.0g/L)
- FFP – if PT, APTT prolonged and provided fibrinogen >1.0 g/L.
- PRBCs – if Hb <80 g/L.
- $CaCl_2$ – if Ca^{++} <2.0 mmol/L.

The criteria for identifying patients at risk of massive haemorrhage are relatively easy in obstetrics where haemorrhage is, in most cases, visible. If patients are likely to need replacement of their entire blood volume in 24 hours or have received > 3000mls (40mls/kg) crystalloid/colloid and four units of blood and have ongoing resuscitation needs, the MTP needs to be activated.

The team needs to go into damage control during resuscitation by minimising macro- and micro-vascular bleeding, the development of coagulopathy, and aim at avoiding hypothermia and acidaemia. Some modification of the MTP may be necessary in some situations but this is not often the case in obstetrics where patients are usually healthy before the bleeding starts. Blood component therapy may require 'tweaking', so the services of a haematologist, who will direct the appropriate coagulation monitoring and guide ongoing component therapy (for example in liver failure) is essential. Haematological and biochemical monitoring of replacement therapy and resuscitative efforts should be repeated approximately every 60 minutes during resuscitation. FBC, EUC, LFT, Ca^{++}, PT/APTT, fibrinogen, arterial blood gas, group and cross-match should be obtained initially. An FBC, EUC, PT/APTT, fibrinogen and ABGs are needed every 60 minutes during resuscitation and ionised calcium measurements also may be required. Point of care devices such as ROTEM and TEG have made this monitoring much easier.

The decision to cease the MTP is that of the consultant-in-charge, usually the anaesthetist, and must be communicated directly to the blood bank.

In pregnancy, coagulation factors are often reset at unusual 'normal' levels. Most coagulopathy in pregnancy is associated with thrombocytopaenia or hypofibrogenaemia or both. Platelets and cryoprecipitate (a good source of fibrinogen) are best started early in obstetric haemorrhage. Normally, platelets tend to approach inadequate levels only after transfusion of eight to 10 units of PRBCs but, in pregnancy, platelet consumption is high, especially in certain common conditions like pre-eclampsia (~8% of all pregnancies). Platelet function is affected by hypothermia and acidosis. Damage control resuscitation directed at minimising hypothermia and acidosis is therefore critical to survival. Also, once the APTT and/or PT are abnormal, there is probably close to only 30 – 40% of pro-coagulant factors present. It is, therefore, prudent to be aggressive with FFP early – rather than waiting for an abnormal result as a trigger to replace coagulation factors.

From the duty blood bank technician(s)' and the haematologist's point of view, the crux of the requirements of the MTP itself are: (a) to supply an initial four units PRBCs; (b) to ensure urgent grouping and cross-match of recipient's blood; (c) to ensure adequate thawing of frozen product (for example FFP takes 15 minutes to thaw); (d) to ensure urgent, rapid processing of haematological and coagulation parameters initially and during resuscitation by notifying specimen reception and the main lab of the MTP; (e) to advise the haematology consultant in charge of variances from haematological end points; and (f) to prepare and supply endless cycles of MTP packs I and II until the MTP is stood down as follows:

MTP I: four units PRBCs, four units FFP, four units platelets (in Australia, four units of platelets is usually presented as one pooled bag of thawed platelets) alternating with MTP II: four units PRBCs, four units FFP, six units cryoprecipitate.

RESUSCITATIVE END-POINTS FOR TORRENTIAL HAEMORRHAGE

The resuscitation team must aim at an INR of < 1.5, a PT of less than 16 seconds, an APTT less than 42 seconds, a fibrinogen greater than 1.0g/L, platelets higher than 50 x 10^9/L, a pH of 7.35 to 7.45, a core temperature higher than 35.5°C and a base deficit less than 3.0. Temperature < 34°C, base deficit > -6, pH < 7.1, a lactate > 4mmol/L and ionised calcium <1.1 mmol/L signify poor prognosis.

RECOMBINANT FACTOR VIIa (rFVIIA)

We should consider rFVIIa, eptacog alpha, in life-threatening obstetric haemorrhage. The surveillance monitoring ANZ Registry is now complete and shows that rFVIIa is most efficacious when every effort has been made to correct surgical bleeding, hypothermia and acidosis. rFVIIa will not stop bleeding when the source of the haemorrhage is a single large source (for example, a laceration of the vagina running into venous varicosities, or an arterial tear in the uterine pedicle). rFVIIa works at a number of points in the clotting cascade, so substantial levels of fibrinogen and platelets are needed to produce a strong, stable clot. For example, more than 79% of obstetric patients with pH less than 7.10 had no change in bleeding after rFVIIa administration. In particular, the patient pH should be >7.2 for reliable procoagulant effect. rFVIIa is to be considered at the 8-10 PRBC transfusion stage, that is, it is supplied with MTP Pack II. The dose of rFVIIa is 90mcg/kg, rounded to the nearest whole vial to minimise wastage. It is administered as an intravenous bolus. A second dose may be required two hours after the first.

The Australian and New Zealand Haemostasis rFVIIa Registry has shed much light onto the dose, appropriate time of administration, outcome, complications, successes and failures of administering rFVIIa to obstetric patients with major haemorrhage. In the 155 obstetric patients in whom there was accurate and reliable data on bleeding response, 28 (18%) stopped bleeding; 73 (46%) had reduced bleeding; and 57 (36%) had no change in bleeding after rFVIIa use. Patients reported as responding to rFVIIa were less likely to die than those whose bleeding remained unchanged (17% vs 62%, p<0.001). The worst response was in those in whom the rFVIIa was administered too late when acidaemia, platelet and procoagulant depletion and hypothermia had set in.

There is little/no increase in the risk of thromboembolic adverse events following the use of rFVIIa in the obstetric population. rFVIIa will continue to have a place in the armamentarium to deal with uncontrolled bleeding.

CELL SALVAGE AT CAESAREAN SECTION

Intra-operative red cell salvage is certainly feasible at caesarean section but only with the newer models of cell saver equipment.

There are three theoretical problems with cell salvage:

(1) Amniotic fluid embolism, which is not at issue when washed RBCs are reinfused. A leucocyte filter alone will remove most cellular components (foetal squames, lamellar bodies, hair, meconium, vernix) of amniotic fluid.
(2) Foetal red blood cells in the leuco-depleted re-infusion resulting in foeto-maternal alloimmunisation by foetal Rh-mismatched cells (correctable with anti-D immunoglobulin), ABO incompatibility (ABO antigens are not fully developed at birth) and other foetal red cell antigens. There is no evidence this incidence is higher than in pregnancy and follow-up at four to six months has shown that these women do not develop antibodies.
(3) Haemolysis. Using modern cell salvage techniques, haemolysis is negligible in obstetrics. Haemolysis is caused by the negative vacuum pressure, the washing/centrifuging process or the collection method. When plasma free haemoglobin (free Hb) levels are used as a marker of haemolysis, final post re-infusion product free Hb is 0.3 g/dL (range: 0.1-1.35 g/dL), which is greater than that for allogeneic blood at 0.14 g/dL (range: 0.02-0.48 g/dL).

Two real hazards to watch out for:

(1) In those with sickle cell disease (not trait), a high percentage of sickle haemoglobin could potentially result in a high percentage of red cell sickling in the cell saver reservoir, which could lead to a sickle cell crisis.
(2) In those with torrential vaginal bleeding cell salvage is considered impractical and may be a source of contamination.

The levels of 2,3-diphosphoglycerate (2,3-DPG) in salvaged blood are twice that of allogeneic blood and these salvaged RBCs have normal 24 h survival rates.

In those (for example, Jehovah's Witnesses) who prospectively advise or provide advanced directives that they will refuse blood transfusion for torrential obstetric haemorrhage, oral or intravenous iron (preferably as intravenous ferric carboxymaltose), erythropoietin, prophylactic internal iliac artery balloon catheters and cell salvage are potential management tools.

The introduction of cell salvage to an obstetric unit reduces allogeneic donor red blood cell red cell transfusion rates in those patients where its use is indicated.

CAESAREAN HYSTERECTOMY AND THE SURGICAL APPROACH TO OBSTETRIC HAEMORRHAGE

The surgical priorities for managing PPH include:

- Identify source of bleeding.
- Apply pressure to uterus.
- Control blood supply to uterus.
- Place uterine compression sutures.
- Perform hysterectomy.

Hysterectomy is often, though not always, the definitive treatment for severe PPH. Hysterectomy occurred in 89 (51%) of Haemostasis Registry obstetric haemorrhage patients. Of these, 62 hysterectomies (70%) occurred before the use of rFVIIa and 27 (30%) after. We have suggested that, prior to extirpation of a uterus to correct haemorrhage and especially in primiparae, young parturients or where there has been poor foetal outcome, at least one dose of rFVIIa should be administered.

Aggressive surgical haemostasis, fluid resuscitation and blood component therapy should be attended to prior to and *pari passu* with administration of rFVIIa.

TRANEXAMIC ACID

Tranexamic acid given intravenously before caesarean section decreased the intra- and post-operative blood loss and oxytocin requirements. When intravenous infusion of 1g tranexamic acid in 20mL of 5% glucose was infused prior to surgery, blood loss was halved as was the percentage of patients with blood losses of >1 litre. Tranexamic acid also reduces blood loss from the end of CS to two hours postpartum and from placental delivery to two hours postpartum. Fewer patients needed additional uterotonic agents. The number of thromboembolic events does not seem to increase in those who received tranexamic acid.

TRANEXAMIC ACID AND RECOMBINANT FACTOR VIIA COMBINATION

The use of combination therapies (for example, desmopressin-DDAVP + intermediate-purity VIII clotting factor concentrates (rich in VW Factor) + tranexamic acid is relatively common in patients with, say, Von Willebrand's disease, presenting for surgery.

Combination therapy with tranexamic acid + recombinant Factor VIIa + fibrinogen (as concentrate or as cryoprecipitate) for major bleeding is gaining traction but there is still no randomised, controlled trial (RCT) evidence that there is benefit in these combination treatments. It can be validly argued that, in torrential haemorrhage situations, there can never be ethics-approved RCTs. It has been shown in rigorous registry data that rFVIIa is efficacious. The same can be said for tranexamic acid in obstetrics. Fibrinogen will be needed if rFVIIa is to be effective. Will the combination of the three agents be better than the component parts when administered together at caesarean section?

UTEROTONICS

The uterus must be kept contracted if we are to stop bleeding. Over the past three years, some novel aspects of uterotonic use have come to light. The first is a realisation that using repeat doses of oxytocin will eventually 'whack out' the uterus so that additional doses, even at increased dosage, will not contract the uterus. This is especially so in those where an oxytocin infusion has been used to augment labour. The second is that there may be some indication for carbetocin (Duratocin), given that syntocinon is so short-acting [see Carbetocin chapter in this book]. The third is that once syntocinon becomes 'inactive', it may be better to add or swap to ergometrine or prostaglandins. Fourth, there is a great variability in patient oxytocin receptor density or response so that the response to oxytocics can be variable.

In most cases, uterine contraction can usually be achieved and maintained using syntocinon (synthetic oxytocin), carbetocin, ergometrine, syntometrine or prostaglandins used in a variety of fashions – IV bolus or infusion, IM, intramyometrially or as an intrauterine douche. All these agents have some side-effects and these deleterious effects are magnified in the hypotensive, acidaemic, bleeding parturient. A typical uterotonics medication escalation schedule is as follows:

Drug	Dose	Side effects
Syntocinon	5U slow IV bolus 30-40U in 1L titrated	Hypotension Reflex tachycardia/arrhythmias Weak ADH like effect
Ergometrine	250ug IM or 125ug slowly IV	Nausea/vomiting(common) Hypertension (can be severe) Coronary spasm/ ischaemic pain
Carboprost PG $F_2\alpha$	0.25mg intramyometrially or IM repeated to max 2mg	Nausea, vomiting, diarrhoea Hypoxia (altered pulmonary shunt fraction)

Once uterine contraction is achieved or whilst it is being achieved, large bore IV access and invasive monitoring (e.g. intra-arterial cannulation for arterial pressure, cardiac output and stroke volume measurement) plus blood cross-matching should be instituted so that immediate volume replacement, blood transfusion and blood component therapy (including rFVIIa, Prothrombinex, etc) can follow.

PROPHYLACTIC INTERNAL ILIAC ARTERY BALLOON CATHETERS FOR CAESAREAN SECTION

Prophylactic interventional radiological balloon catheterisation is a complex intervention and, while there are reports of success in its use, there are no large randomised trials to support its routine use in obstetrics when major blood loss is anticipated (for example, grade IV placenta praevia).

ASSESSMENT OF BLEEDING SEVERITY

Anaemia is becoming less common in many countries because it is diagnosed and corrected in the early and mid trimesters (for example, with intravenous iron as ferric carboxymaltose).

The clinical signs of haemorrhage can be delayed in the pregnant patient and early detection of ongoing haemorrhage is important. Also, during labour and delivery, quantitation of the extent of bleeding can be difficult especially if some of the haemorrhage is concealed or if the blood is mixed with liquor. Using clinical signs only, a fair rule-of-thumb assessment can be made:

500-1000ml loss	BP & appearance normal	HR usually fast, >100
1000-1500	SBP 80-90, pallor, sweating	HR >100, tachypnoea
1500-2000	SBP 60-80, clammy, u/o <30	HR >110, tachypnoea
2000-3000	SBP <50, anuria, unconscious	HR may be low, air hunger

(Key: HR = heart rate, SBP = systolic blood pressure)

ASSESSMENT IN SECONDARY POSTPARTUM HAEMORRHAGE

Clinical examination and transabdominal ultrasound assessment are both equally poor at assessing whether retained placental tissue is the suspected cause of bleeding, and both have limited diagnostic accuracy in secondary postpartum haemorrhage.

CONCLUSION

An action plan of management of torrential haemorrhage:

Torrential obstetric haemorrhage management includes: (a) an anticipation that severe haemorrhage will happen with some regularity, and that it will, with time, increase in both incidence and severity; (b) an understanding that it cannot be predicted with any degree of accuracy; (c) appreciating that the diagnosis of the cause of bleeding is usually simple but requires vigilance and awareness of confounders because it is often multifactorial; (d) management through team work and good communication; (e) securing help early; (f) applying simultaneously methods aimed at reducing bleeding using mechanical and pharmacological means; (g) stabilising and controlling the haemodynamic imbalance; and (h) stopping the bleeding.

Massive transfusion protocols, haemorrhage fire drills, large-bore IV access, the transfusion trolley or box, availability of blood banking facilities on site and rapid bulk blood product availability are all essential to an optimal outcome. Cell savers, rapid volume infusers, surgical and radiological bleeding-containment techniques, effective monitoring and its interpretation are all part of what is needed to resuscitate quickly and effectively. rFVIIa and anti-fibrinolytics are also useful but the preparedness, structure, competence and efficiency of the resuscitation team as a whole in rapid volume, blood and blood component replacement are even more important.

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Carbetocin in the prevention and management of post partum haemorrhage: A review of current evidence for obstetric anaesthesia

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INTRODUCTION

Uterotonic medications are routinely administered at the request of obstetricians to minimise the risk of postpartum haemorrhage (PPH) following childbirth. Though syntocinon is ubiquitously used, carbetocin is increasingly accepted as an effective, longer-acting alternative, its primary benefit being the practical advantage of not needing to sustain and monitor an infusion to maintain uterine tone. In the perioperative setting this may manifest as a reduced chance of drug or infusion error, as well as reduced workload for anaesthetist and perioperative staff.

Though the Australian Therapeutic Goods Administration (TGA) has licensed carbetocin for use for several years, its transition to mainstream use has been gradual. In response to escalating local use of carbetocin, this review has been formulated with the aim of compiling evidence relevant to the obstetric anaesthetist. Directions for future research will also be considered.

BACKGROUND

PPH remains the leading cause of maternal death worldwide,[1] and accounted for 22 deaths in Australia between 1997 and 2005.[2] Developed countries are not immune to the enormous social and community impact of preventable maternal death.

According to the World Health Organisation (WHO), PPH is defined as blood loss greater than 500mL within the first 24 hours of delivery. Blood loss greater than 1000mL is considered severe.[1] However, inaccuracies associated with estimating blood loss may result in significant underestimation. An alternate definition of PPH is a drop in haematocrit or haemoglobin of greater than 10%, although this value may not reflect the patient's current haemodynamic state.[3] Furthermore, the clinical signs of hypovolaemic shock are less reliable in pregnancy due to the physiological adaptations that occur. As a result, the recognition and subsequent treatment of hypovolaemia may be delayed and rapid deterioration may occur following decompensation.[4]

The incidence of PPH in Australia is estimated to be between 5-15%.[5,6] Australian[7,8] and international[9] data suggest a trend toward increasing rates of PPH. The underlying reasons for this rise remain uncertain but might include variations in the method of PPH reporting between hospitals and health jurisdictions and changes in the management of the third stage of labour.[7]

Inadequate uterine contraction, or uterine atony, is responsible for an estimated 70% of PPH cases.[10] PPH can often be anticipated and thus prevented. Active management of the third stage of labour has been shown to reduce the incidence of PPH due to uterine atony.[11] This involves the prophylactic administration of uterotonic drugs, early clamping of the umbilical cord and controlled cord traction to facilitate placental delivery. Built upon an established history of clinical use and efficacy, syntocinon is generally considered the first line uterotonic agent. Syntocinon will be introduced briefly before focusing on the pharmacology and clinical evidence that applies specifically to carbetocin.

SYNTOCINON

Syntocinon is the pharmaceutical analogue of oxytocin. Oxytocin is a naturally occurring peptide secreted by the posterior pituitary in response to nipple suckling, parturition or stress.[12] Its main physiological actions are the stimulation of uterine smooth muscle contraction during labour and the ejection of milk during lactation. Oxytocin mediates these actions by binding to G-protein coupled receptors located on myometrial and myoepithelial cells. This results in the generation of intracellular secondary messengers, a rise in intracellular calcium levels, and the activation of the myosin chain complex and subsequent initiation of muscle contraction.[13] As pregnancy progresses oxytocin receptor density in the myometrium gradually increases reaching a peak at the onset of labour. At this point, the uterus is maximally sensitive to the effects of oxytocin. Following delivery, oxytocin receptor numbers rapidly decline to baseline levels.[12] Syntocinon, the synthetic form of oxytocin, can be administered either intramuscularly (IM) or intravenously (IV). Syntocinon has a half-life of 30 to 60 minutes following IM injection and four to 10 minutes following IV injection.

Guidelines recommend syntocinon as the uterotonic agent of choice for the prevention and treatment of PPH following vaginal or caesarean delivery.[14,15] While the recommended dose of syntocinon following vaginal delivery is 10 IU IM[14,16], considerable debate surrounds the optimal dosage regime following caesarean delivery. Evidence is accumulating that syntocinon doses of less than five IU are as effective in maintaining uterine tone with fewer side effects.[17-19] Despite this, 73% of surveyed fellows from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) routinely request that 10 IU be administered by the attending anaesthetist. This bolus dose was routinely or selectively supplemented with a syntocinon infusion by 98% of respondents, despite a paucity of evidence supporting the practice.[20,21] When a syntocinon infusion is used, there is considerable variability as to the chosen regime with no evidence to support one regime over another. 68 different syntocinon infusion regimes were reported in the same survey of RANZCOG fellows with the most common being 40 IU in 1000mL over four hours (37%).[20]

SYNTOMETRINE

Syntometrine is an alternate uterotonic containing five IU syntocinon and 0.5mg ergometrine. Compared to syntocinon alone, syntometrine has demonstrated greater efficacy in the prevention of PPH. However, such benefits are largely outweighed by an unfavourable side effect profile meaning that syntometrine is usually reserved for second line treatment of uterine atony and prevention of PPH.[22]

CARBETOCIN

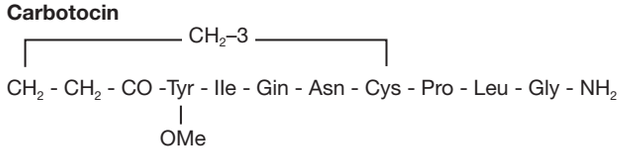
Carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties. In Australia, it is marketed as Duratocin® (Ferring Pharmaceuticals Pty Ltd). Approved by the Therapeutic Goods Administration in April 2004, it was launched commercially in August 2007.

The chemical synonym for carbetocin is 1-deamino-1-monocarba-[2-O-methyltyrosine]-oxytocin. The structural similarities between carbetocin and syntocinon are illustrated in figure 1. The specific differences of note in carbetocin are:

- Removal of N-terminal amino group.
- Exchange of the cysteine S atom in position one for a CH2 group.
- Substitution of –OH at tyrosine for a methylether group.

Figure 1. Illustration of structural similarities between carbetocin (above) and oxytocin/syntocinon. Carbetocin molecular formula: C45H69N11O12S; Molecular weight: 988.1

Carbotocin



Oxytocin

Carbetocin is presented in a clear glass ampoule for injection. Each ampoule contains 1mL of a colourless solution containing 100µg of carbetocin as the active ingredient. Carbetocin is stable for up two years when refrigerated between 2-8ºC in a light protected environment. Carbetocin can be administered either intramuscularly (IM) or intravenously (IV).

Carbetocin selectively binds to oxytocin receptors located within the myometrium with similar affinity to that of the natural peptide oxytocin. Via the activation of secondary messengers and a rise in intracellular calcium levels, carbetocin stimulates uterine smooth muscle contraction and increased uterine tone. Compared to syntocinon, these contractions are prolonged and more frequent.[23] The actions of carbetocin predominate in the pregnant and post-partum uterus, where oxytocin receptor density and sensitivity are at its greatest.[24]

In Australia, Duratocin is approved for use in the prevention of uterine atony and PPH following elective caesarean section under epidural or spinal anaesthesia.[25] Carbetocin is not to be administered prior to the delivery of the baby as this could induce uterine tetany, uterine rupture, a traumatic delivery, endangerment of foetal wellbeing and retained placental products. Carbetocin is also not advised for use in patients with known vascular disease, especially coronary artery disease.

The recommended dose of carbetocin is 100µg given as a single IV bolus slowly over one minute immediately following delivery. This dosage is based on the manufacturer's recommendations and follows an unpublished study of 18 women receiving IV carbetocin following caesarean section. An adequate uterine response did not occur in doses of less than 60µg, while five out of six women who received 100µg experienced effective uterine contraction.[26] Recently, a more robust study by Cordovani et al. attempted to establish the minimum effective IV dose of carbetocin required to produce adequate uterine contraction in 95% of participants following caesarean section. In a study

involving 80 women at low risk for PPH, it determined an optimal dosage range of between 80-120µg.[27] Clearly, further investigation is needed to establish the ideal dose of carbetocin in various populations and clinical situations. The suggested maximum dose of carbetocin is 200µg.[28]

Only 1.7-2.8% of the carbetocin dose is detectable in breast milk (N=5; IM injection of 70µg at seven to 14 weeks post partum).[29] This is unlikely to be of clinical significance given its rapid degradation by gastrointestinal enzymes.

PHARMOCOKINETICS

Absorption. Carbetocin demonstrates a rapid onset of action whether given IM or IV. IM carbetocin enters the circulation rapidly and reaches peak plasma concentration within 30 minutes.[30] The estimated bioavailability by this route is 80%.

Compared to syntocinon, carbetocin exhibits a prolonged contractile response in the post-partum uterus. IM carbetocin induces uterine contractions within two minutes, lasting 11 minutes, and is followed by rhythmic contractions for a further two hours. In contrast, IV carbetocin produces uterine contractions within two minutes, lasting six minutes, and is followed by rhythmic contractions for a further one hour. The prolonged duration of IM carbetocin compared to its IV counterpart is significant and is related to the time required for absorption from the IM site.[31]

Distribution. Carbetocin distributes beyond the plasma compartment with an estimated volume of distribution of 9L following IV administration.[30]

Metabolism. Deamination at the N-terminal aspect protects the molecule from aminopeptidase cleavage and replacement of the disulfide bridge by CH2 confers protection from disulphidase cleavage. These structural features in addition to its lipophilic properties result in a plasma half life of carbetocin equal to 40 minutes when given IV; this is four to 10 times longer than syntocinon. However, these characteristics also result in a potency equal to one-tenth that of syntocinon.[30]

Further studies have shown that carbetocin undergoes enzymatic degradation at its C-terminal end generating carbetocin metabolites I and II. The responsible enzymes remain unknown. Although these metabolites have antagonistic properties at the myometrial oxytocin receptor, it is not considered clinically important.[32]

Elimination. Only 0.7% of carbetocin is eliminated unchanged via the kidneys, suggesting non-renal routes of elimination.[30]

PHARMACODYNAMICS

Cardiovascular system

The haemodynamic effects of syntocinon have been well documented and are dose-dependent. Syntocinon induces systemic vasodilation and hypotension, followed by a compensatory increase in HR and cardiac output.[18,33] These changes are brief and more prominent when given as a bolus rather than an infusion[34] and continue to occur with repeated doses.[35]

It appears that carbetocin demonstrates a similar cardiovascular profile to syntocinon. Moertl et al.[36] studied 56 women deemed low PPH risk, undergoing elective caesarean section with spinal anaesthesia. The haemodynamic effects of an intravenous bolus of carbetocin (100µg) and syntocinon (5 IU) were compared using non-invasive methods (randomised, double blinded). The haemodynamic effects of carbetocin and syntocinon were found to be comparable with peak effects occurring at 40 seconds post drug administration. Following carbetocin administration, heart rate (HR) increased by 14.20 ± 2.45bpm and cardiac output rose by 17%, while mean arterial pressure and total peripheral resistance fell by 19.38 ± 2.12 mmHg and 32 ± 3.37% respectively. Values returned to baseline within eight minutes.

Another randomised study of women with at least one risk factor for PPH (N=32), reported similar findings when comparing a carbetocin bolus (100µg) to a syntocinon infusion (5 IU in 500mLs normal saline) following elective caesarean section under spinal anaesthesia.[37] The duration of the infusion was not specified. Parameters were derived from examination of aortic valve flow using Doppler ultrasound. Again, carbetocin and syntocinon demonstrated a comparable haemodynamic profile, although no change in HR was seen in either group.

The potential use of carbetocin in patients with hypertensive disorders such as preeclampsia appears promising. The risk of PPH (blood loss > 500mL) and severe PPH (blood loss > 1500mL) increases by 1.6 and two times respectively in the presence of preeclampsia compared to normotensive patients.[38] Syntocinon has traditionally been the preferred uterotonic in patients with preeclampsia since syntometrine is associated with hypertension[22] and is consequently contraindicated. In the normal population, carbetocin has been shown to reduce the likelihood of hypertension at both 30 and 60 minutes post-delivery compared to syntometrine.[39] Therefore, carbetocin may represent a suitable alternative to syntocinon in patients with hypertensive disease given its similar haemodynamic profile but with a reduced need for additional uterotonics.[40]

A recent study aimed to evaluate the safety and efficacy of carbetocin in women with severe preeclampsia following vaginal or caesarean delivery.[41] Participants (N=55) received either 100µg carbetocin IV or 20 IU syntocinon in 1000mL Ringer's Lactate over eight hours (randomised, blinded). Patients with HELLP syndrome, multiple pregnancy or blood coagulopathy were excluded. It was concluded that carbetocin was as effective as syntocinon with no significant difference in blood pressure, heart rate, the need for additional uterotonics or haemoglobin decrement.

Respiratory system
Though not specifically addressed in the literature, carbetocin, like syntocinon, is not expected to significantly affect respiratory system function.

Central nervous system
There are no reported cases of carbetocin affecting conscious level or altering seizure threshold.

The impact of carbetocin on pain perception was estimated using a visual analogue scale (VAS) in 55 women who underwent elective caesarean section with spinal anaesthesia.[42] Compared to syntocinon, carbetocin resulted in lower post-operative pain and analgesic requirements. The effect on pain scores persisted until day three following caesarean section, while the reduction in analgesic requirements only occurred on days 0 and 1.

Adverse effects
As expected by its mechanism of action, a 100µg dose of carbetocin may result in abdominal pain, headache, nausea, vomiting, and other non-specific symptoms such as facial flushing, a metallic taste, tremor and sweating. The reported incidence of these adverse effects is variable in the literature, but appears to reflect that expected with syntocinon.[39] When such symptoms do occur they are short lived, typically subsiding within 10 minutes.[30]

CLINICAL EVIDENCE

Vaginal delivery

Carbetocin versus oxytocin
Only one study has been performed comparing the efficacy of prophylactic carbetocin to syntocinon following vaginal delivery.[43] This was a double blind, randomised control trial involving 160 women with at least one risk factor for PPH. Participants received either a single 100µg IM dose of carbetocin or a 10 IU syntocinon infusion over a two-hour period. Overall, uterine intervention, specifically uterine massage, was required less frequently with carbetocin than syntocinon (44.6% vs 63.6%; p = 0.025 RR 0.70 95% CI 0.51-0.94).

Carbetocin versus syntometrine
Several studies have now concluded that carbetocin demonstrates similar efficacy to syntometrine in the prevention of PPH following vaginal delivery, with the benefit of less side effects. Four trials have performed a randomised, double blind comparison of standard doses of carbetocin (100µg) to syntometrine (5 IU syntocinon and 0.5mg ergometrine), each given intramuscularly following vaginal delivery, specifically anterior shoulder delivery.[44-47] Meta-analysis[39] of these trials (n=1030) showed no statistical difference between carbetocin and syntometrine in the reported incidence of PPH (blood loss > 500mL), severe PPH (blood loss > 1000mL) or the need for additional uterotonic agents. Overall, reported mean blood loss was found to be less in women who received carbetocin (-48.84mL; 95% CI -94.82 - -2.85), however variability existed between the analysed trials, which appeared related to the method used to estimate blood loss.

Instrumental delivery

Instrumental delivery is a strong predictor of PPH with 9.5% of such deliveries in 2002 resulting in PPH.[7] However, no study has performed sub-group analysis to assess the efficacy of carbetocin following instrumental delivery.[44,45,47]

Caesarean delivery

Six trials have compared the prophylactic use of carbetocin to oxytocin following caesarean delivery (n= 1442). A meta-analysis[39] of four trials (n= 1173) concluded that carbetocin reduces the requirement for uterine intervention, specifically, the need for additional uterotonics by 36% (four trials; n=1173; RR 0.64; 95% CI 0.51-0.81) and uterine massage by 46% (two trials; n = 739; RR 0.54; 95% CI 0.31 to 0.96). The reduction in additional uterotonic agent use persists regardless of PPH risk factor status.[40] Despite these outcomes, it appears unlikely that carbetocin diminishes the risk of PPH with the same meta-analysis[39] finding no statistical difference in the incidence of PPH (blood loss > 500mLs), severe PPH (blood loss > 1000mLs) or mean blood loss.

Similar findings were recently reported in a randomised control trial of 110 women who delivered via elective caesarean section under spinal anaesthesia.[42] Participants received either carbetocin (100µg) or oxytocin (10 IU bolus + 20 IU infused over 24hrs) intravenously. Although additional uterotonics were required less in the carbetocin arm (one case vs. eight cases), the remaining study parameters were equivalent.

In contrast, carbetocin showed no benefit in a retrospective study in which the outcomes of 159 women undergoing caesarean delivery were compared in the eight weeks before and after the introduction of carbetocin to clinical practice.[48] Compared to an IV bolus of 5 IU oxytocin post-delivery, no statistical difference was evident in the incidence of PPH, mean blood loss or need for additional uterotonics.

The ability to draw robust conclusions from the literature is hindered by substantial methodological heterogeneity (Table 1). As seen, various syntocinon dosing regimens are selected as the comparator to carbetocin with only two[40,48] reflecting international recommendations.[49,50] Although carbetocin is consistently administered as 100µg IV, only two studies[40,42] specify slow administration over 30-60 seconds as recommended by the manufacturer. Two studies give carbetocin as a single push, which is more likely to reflect everyday practice.[51,52]

Table 1. The varying syntocinon regimens used as a comparator to carbetocin

Study	Syntocinon bolus	Syntocinon infusion
Boucher et al.[51]	2.5 IU + rapid infusion 10 IU in 500mL Ringer's Lactate	20 IU over 16 hours in 2L 5% dextrose
De Bonis et al.[42]	10 IU	20 IU over 24 hours
Dansereau et al.[52]	5 IU	20 IU over eight hours in 1L Ringer's Lactate
Borruto et al.[53]	–	10 IU over two hours
Attilakos et al.[40]	5 IU	–
Higgins et al.[48]	5 IU	–

As expected by their similar mechanism of action, carbetocin and syntocinon demonstrate a similar adverse effect profile.[39,42,48] Larger trials and post-marketing surveillance will be required to reveal any subtle differences.

HEALTH ECONOMICS

Carbetocin versus syntocinon

At the time of publication, the cost of one ampoule of 100µg carbetocin is approximately A$29. This compares to A$4.40 for a 10 IU ampoule of syntocinon. No cost-effectiveness data relating specifically to the Australian healthcare system has been published.

In the United Kingdom, Higgins et al.[48] identified an increase in costs per patient following the introduction of carbetocin to low-risk women undergoing elective caesarean section from £80.21 (95% CI £71.36 – £114.80) to £98.73 (95% CI £88.73 – £122.90) (p = 0.01). The analysis captured the cost of staff per minute of care, use of analgesics, anti-emetics and other consumables from the time of delivery until transfer to the postnatal ward. This rise in costs (£18.51 per patient) was primarily attributable to the cost of carbetocin (£16.93 per patient).

In contrast, Del Angel-Garcia et al.[54] analysed the costs incurred by the Mexican Institute of Social Security based on reported resource use. Carbetocin resulted in a reduction in mean costs per patient of US$529 (US$3525 versus US$4054 for oxytocin; p < 0.0001).

Carbetocin versus syntometrine

Scant data exist comparing the economics of carbetocin to syntometrine following vaginal delivery. Su et al.[45] hypothesised that even though carbetocin is approximately 10 times more expensive than syntometrine in Singapore (S$39 vs. S$4), this cost differential could be offset by a reduction in staff and medication costs due to the reduced incidence of side effects associated with carbetocin. Length of hospital stay was not different between carbetocin and syntometrine groups (1.82 vs 1.81 days respectively; p = 0.936).

CONCLUSION

Carbetocin represents a legitimate alternative to traditional uterotonic agents in the prevention of post-partum haemorrhage. Based on the current literature carbetocin is an equally effective and safe alternative to syntocinon in the prevention of PPH following either vaginal delivery or an elective caesarean delivery performed under regional anaesthesia. Specifically, uterine intervention such as the use of additional uterotonics or uterine massage is required less frequently with carbetocin.

Similarly, carbetocin is as effective as syntometrine in vaginal delivery with no statistical differences in the incidence of PPH or the use of additional uterotonic agents. Although mean blood loss is reduced with carbetocin, measurement techniques are notoriously difficult. In comparison to syntometrine, the primary benefit of carbetocin is a lower incidence of side effects with significant reductions in the frequency of nausea and vomiting.

Practising obstetric anaesthetists will appreciate the practical advantages of carbetocin, which include the avoidance of error prone infusions[55], and a reduced need for uterine intervention. Collectively, these factors enable anaesthetic attention and labour to be re-directed to other aspects of patient care.

The increasing acceptance of carbetocin is best reflected by the recent decision of the Society of Obstetricians and Gynaecologists of Canada to recommend carbetocin as the uterotonic agent of choice following elective caesarean delivery to prevent PPH and reduce the need for additional uterotonics.[56]

Directions for future research may include evaluation in larger samples to verify the efficacy and safety of carbetocin across a broader range of possible obstetric comorbidities and scenarios. The value of carbetocin is yet to be established in hypertensive patients or following caesarean delivery performed under general anaesthesia or in emergent situations. Other useful areas of investigation would include verification of the minimum effective dose, and a comparison of carbetocin to the traditionally administered 10 IU IM bolus of syntocinon following vaginal delivery.

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Can I TAP that? Review of the use of transversus abdominis plane (TAP) block

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INTRODUCTION

Local anaesthetics and adjuvants are a part of analgesic regimes for abdominal and pelvic pain. The benefits of acute analgesia in the prevention of chronic pain are widely accepted.[1] The need to achieve adequate analgesia while reaching goals of early ambulation and shortened hospital stays has broadened the search for various analgesic techniques.[2] The concerns in relation to the benefits of neuroaxial techniques and complexity of management as well as issues regarding systemic opioid have continued the ongoing challenges to achieving adequate analgesia.[3,4] The transversus abdominis plane (TAP) block is aimed to be an analgesic adjuvant for patients undergoing surgery involving the anterior abdominal wall. This article aims to review the technique, its efficacy and its use in anaesthetic practice.

The TAP block was first reported in 2001 by Rafi.[5] It is described as a blockade of the nerves supplying the anterior abdominal wall to provide analgesia after abdominal surgery. Using a blunt nerve block needle and landmark based technique about 200 cases were noted with no adverse sequelae. The principle was to deposit local anaesthetic in the layer between the transversus abdominis and internal oblique in the anterior abdominal wall. This enables the blockade of the lower intercostal, ilioinguinal and iliohypogastric nerves as they traverse between the subcostal margin and iliac crest.

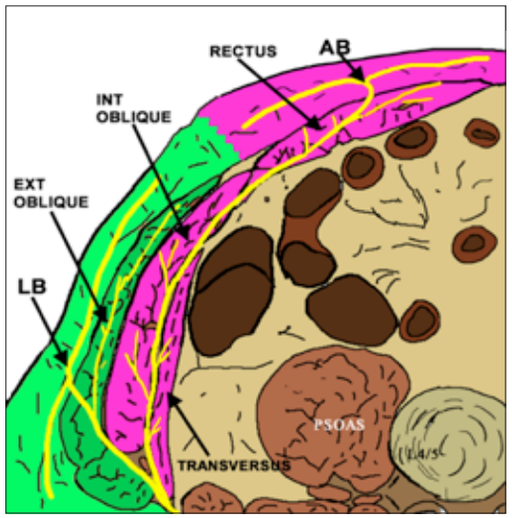
McDonnell et al in 2007 demonstrated using anatomical studies, the presence of the TAP in cadaveric models.[6] This was followed by contrast injections in healthy human subjects to demonstrate the presence and spread of marker in the TAP, with dye seen in nerves arising from T7 to L1. Using local anaesthetic as the injectate, they further demonstrated the presence, duration and spread of block. The ease and safety was further progressed with the use of ultrasound (USS) guided techniques. Tran et al used an ultrasound probe on the lateral abdominal wall to access the TAP on cadaveric models.[7] This achieved coverage of T11 to L1 nerves in 93-100% of cases. Contrary to McDonnell et al, no spread of dye above T10 was shown. Since then a large number of articles have been published in various patient groups for differing indications, with variable results as discussed below.

WHERE IS IT?

Muscles/vessels

The anterior abdominal wall consists of skin, fat, muscles and distinct demarcation of connective tissue. The muscles of wall consist centrally rectus abdominis, and laterally external oblique, internal oblique and transversus abdominis. Rectus abdominis is a band like pair of muscles, enclosed by the rectus sheath, which is formed by the aponeurosis of the other aforementioned muscles and accompanying fascia. The anterior reflection of the rectus sheath is formed mainly by the aponeurosis of external oblique while the posterior by the transversus abdominis. Contained within the rectus sheath are the superior and interior epigastric vessels as well as terminal branches of the spinal nerves.[8] The superior epigastric artery traverses the TAP before entering the rectus sheath. The deep circumflex iliac vessels travel laterally alongside the internal oblique and transversus abdominis muscles. The linea alba forms the midline of the anterior abdominal wall and is more distinct above the umbilicus compared to below. The muscles run in different planes to each other and have the role of supporting the viscera and movement of the trunk.

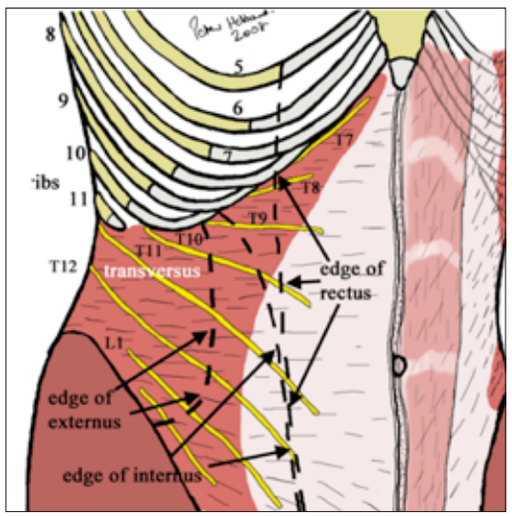
Figure 1.



The spinal nerve as it travels anteriorly in the area between internal oblique and transversus abdominis.

AB – Anterior branch.
LB – Lateral cutaneous branch.
(Image supplied by Dr Peter Hebbard.)

Figure 2.



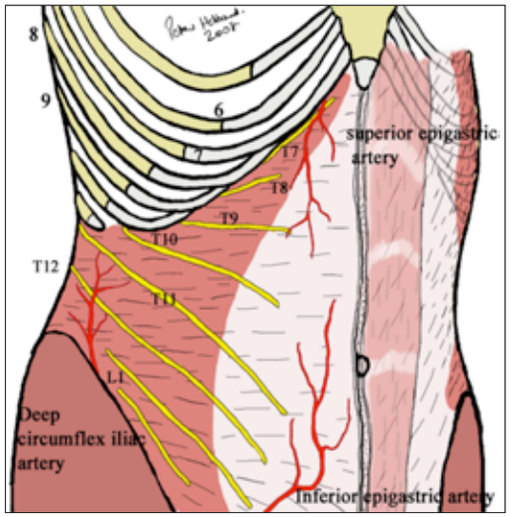
The spinal nerves of the anterior abdominal wall, superimposed with the muscles of the anterior abdominal wall.

(Image supplied by Dr Peter Hebbard.)

NERVE SUPPLY/DISTRIBUTION

The anterior abdominal wall is supplied by the lateral and anterior cutaneous nerves from thoracic spinal nerve six down to the top of the lumbar plexus (T6 to L1). The nerves leave the spinal cord and travel as mixed segmental nerves in the TAP, which lies between the internal oblique and transversus abdominis muscles. This plane, the consistency of the nerve course and relationship to blood vessels were demonstrated by Rozen et al by cadaveric dissection.[9]

Figure 3.



Nerves and blood vessels of the anterior abdominal wall.
(Image supplied by Dr Peter Hebbard.)

The parietal peritoneum consists of the lining of the abdomen, pelvis and inferior surface of the diaphragm. Its innervation including that for nociception is from the somatic nerves such as the intercostal, subcostal, ilioinguinal and iliohypogastric nerves. The visceral peritoneum has no sensory innervation.[10]

The nerves from T6-T7 supply the xiphisternum and T10 supplies the umbilicus. Barrington et al showed the nerves from T6 to T8 may enter the rectus muscle near the costal margin, therefore blocks more than 2-3cm medial to the costal margin may be insufficient.[11] Tran et al described variation in the course of the L1 nerve, often entering the TAP closer to the anterior superior iliac spine than the lower thoracic nerves.[7]

WHEN CAN I USE IT?

Unilateral: Open appendicectomy.[12]
Hernia repair.[13]
Hepatic, gastric, pancreatic and biliary surgery.
Renal surgery and transplant.[14]

Bilateral: Laparotomy.[15,16]
Caesarean section.[17,18]
Abdominal hysterectomy and gynaecological surgery.[19]
Abdominoplasty.[20]

Other indications where they have been used include diagnostic purposes, chronic abdominal pain and palliative pain control.[21,22]

WHEN SHOULD I NOT USE IT?

Absolute: Abdominal wall sepsis.
Patient refusal.
Lack of expertise/inability to place block.
Infection at the site of injection.
Allergy to local anaesthetic.

Relative: Proximity of block site to operative site.
Coagulopathy.
Poor images on ultrasound.
Abdominal wall oedema.

WHAT SHOULD I INJECT?

There are no studies currently comparing the efficacy of different doses, volumes or concentrations. Analgesia achieved by greater than 15mL appears to be better than that with less than 15mL.15 The concentrations used also are varied, with both dilute and concentrated blocks achieving analgesia.[23,24] Currently underway is a trial comparing the difference between 0.25% and 0.75% ropivacaine.[25] The addition of clonidine was not shown to have analgesic benefit, however this was limited to a small study.[26] The use of other additives such as adrenaline and opioids, which have been used in other blocks, have not been studied in TAP blocks.

The dose calculated takes into account the toxic dose of the particular agent, as well as organ function, particularly liver and kidney. When catheters are used, the dose at initial injection needs to take into account the ongoing infusions. No cases of local anaesthetic toxicity are reported to date. An observational study using 3mg/kg of ropivacaine showed venous plasma concentrations, which were potentially toxic. In this study due to the general anaesthetic there were no neurological signs of toxicity noted. Similarly high levels of plasma ropivacaine were noted in infusions, although no adverse sequelae were reported.[27] It is likely however, similar to the intercostal areas; the highly vascular abdominal wall is more likely to have high intravascular concentrations of local anaesthetic compared with distal limb blocks.

The use of lignocaine for ongoing analgesia is limited due to the rapid metabolism as well as tachyphylaxis in slow infusions, while ropivacaine and bupivacaine are more acceptable options. Bupivacaine is now available in a new formulation attached to liposomal carrier (Exparel®) for local infiltration. Exparel® is not yet available in Australasia. The peak plasma half life is proposed to be 36 hours, suggesting a much longer duration of action.[28] We await further trials before making conclusions, however if successful it might remove the need to place catheters for ongoing analgesia.

While the concept of safety with local anaesthetic injections is apparent, only some practitioners use a test dose in a TAP block.[29] Negative aspiration up the needle or catheter is not a reliable test,[30] although ultrasound imaging of the needle tip and local spread confers some benefit in the prevention of systemic toxicity.[31] Some authors advocate the use of markers such as adrenaline prior to injection of large volumes of local anaesthetic to exclude intravenous injections.[32] Changes in heart rate, blood pressure and T wave morphology are validated though limited in their use.

WHAT DO I NEED?

- Full resuscitation equipment and medications including Intralipid®.
- Monitored environment meeting requirements for invasive procedures.[33]
- Intravenous access.
- Skilled assistance.[34]
- Aseptic skin preparation.
- Sterile gown, gloves, mask and drapes for catheter techniques.
- Ultrasound with high frequency probe (6-13MHz), and a curvilinear probe in obese patients.
- Coupling gel and sterile ultrasound guard.
- Short bevelled echogenic block needle (23-30 degrees) or Tuohy needle.
- Extension set for injection.
- Infusion pumps.
- Documentation and audit process.

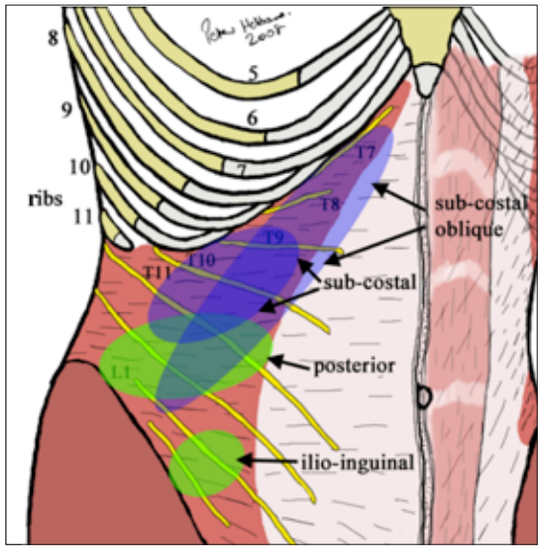
When using catheters, securing can be performed using stitches, glue or tunnelling techniques to prevent dislodgement. Concerns regarding catheter migration exist where the loss of position leads to inadequate pain relief. There are also concerns that the catheter may enter blood vessels or the peritoneum. The only reported case of a catheter in the abdomen was in a nephrectomy case where the tip of the catheter was found in the abdomen without visceral damage.[35]

Infusion pumps for the catheter techniques include electronic, elastomeric and spring-loaded devices. The Food and Drug Administration recommends an error of up to 15% deemed to be safe and acceptable for commercial use. These need to be accounted for in smaller patients, children, critically unwell patients and those showing signs of toxicity. The costs involved include that of the pump and connections, staffing to connect, administer, monitor patients and oversee the process as well as ongoing servicing of the devices. Options for catheters include intermittent or continuous regimes, patient controlled or regular boluses. In the presence of bilateral catheters, safe access and management including the use of patient-controlled bolus buttons need to be considered.

HOW CAN I DO IT?

A variety of techniques are described including the landmark-based technique, ultrasound guided and surgical. A highlight of the ultrasound guided technique that the fascial plane appears to be the same irrespective of the probe orientation. The TAP block is considered to be a relatively easy block to learn, although this is certainly not always the case.[36] The catheter techniques require a higher skill set due to requirement of using and managing sterility as well as securing of the catheters.

Figure 4.

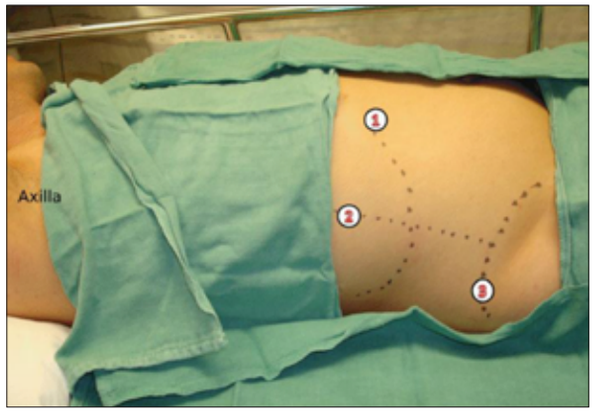


The potentially different approaches for the TAP, with underlying nerves, which may be blocked. (Image supplied by Dr Peter Hebbard.)

HOW DID THEY FIRST DO IT?

The early landmark techniques involved the use of local anaesthetic in the Triangle of Petit, which is bordered by the lattisimus dorsi, external/internal obliques and the iliac crest. McConnell describes a “double pop” technique using a blunt nerve block needle, with the first pop traversing the external oblique and second the internal oblique.[6] This group showed 85% efficacy with using this technique. However, Jankovic et al showed that the Triangle of Petit is more posterior than previously thought, and not all relevant nerves traverse this area.[37] This may account for the variability in results in this technique of performing the block. The advantages of the landmark-based technique are the relative ease of performance, speed of block placement, and reduced requirement for equipment including ultrasounds. However these are countered by malpositioned deposition of the local anaesthetic, and intraperitoneal injections in a proportion of patients. McDermott terminated a study early due to an 18% peritoneal injections rate in a landmark-based technique.[38]

Figure 5.



Landmarks of the abdominal wall:

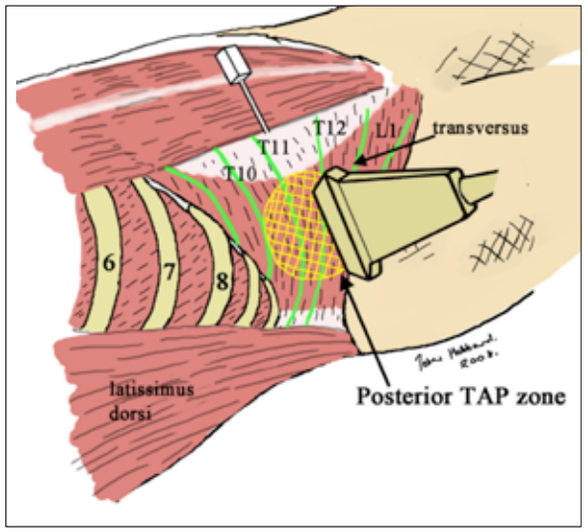
1. Costal margin.
2. Midaxillary line.
3. Iliac crest.

WOULD AN ULTRASOUND HELP?

More recently, with the availability of ultrasound technology as an aid to performing the block, use of TAP blocks have increased significantly. Hebbard et al described a technique using the ultrasound oriented transversely on the anterolateral abdominal wall where the muscle layers are more distinct.[39] With the patient laying supine, the needle enters anteriorly and is advanced posteriorly until the TAP is reached with the ultrasound probe nearly perpendicular to the needle. Once the needle reaches the TAP, a characteristic elliptical shaped appearance is seen (see figure 8). If the needle is in external oblique or transversus abdominis, a partial ellipse shape may be seen and a partial block may be anticipated.

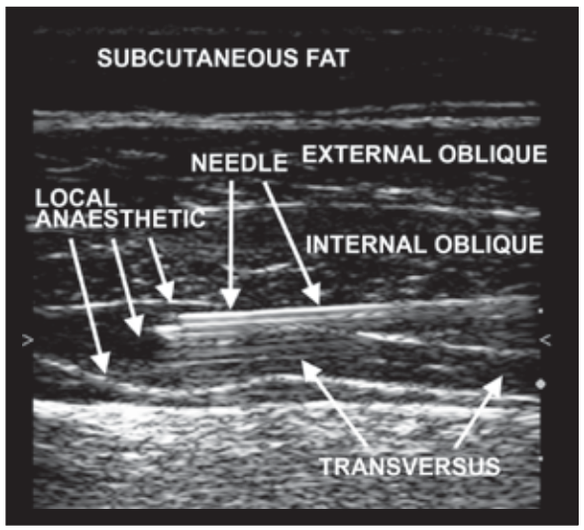
Hebbard also described the subcostal TAP block.[40] For the subcostal block the local anaesthetic can be deposited either as a single bolus, medial or lateral to the edge of the rectus or along the oblique subcostal line. This is performed using a long needle placed near the xiphisternum, with hydro-dissection. The insertion point is medial to the linea semilunaris. Identification of the superior epigastric vessels is recommended to avoid inadvertent injection and haematoma. After identification of the TAP at the junction of the rectus abdominis and the transversus abdominis muscles, the plane is distended using local anaesthetic. The needle is then further advanced to ensure spread of local anaesthetic along the plane. Effective analgesia in the supraumbilical region (T7-T10) was reported. It has been shown in cadaveric studies that oblique subcostal injections with hydro-dissection increased spread to more nerves compared with those without hydro-dissection.[11]

Figure 6.



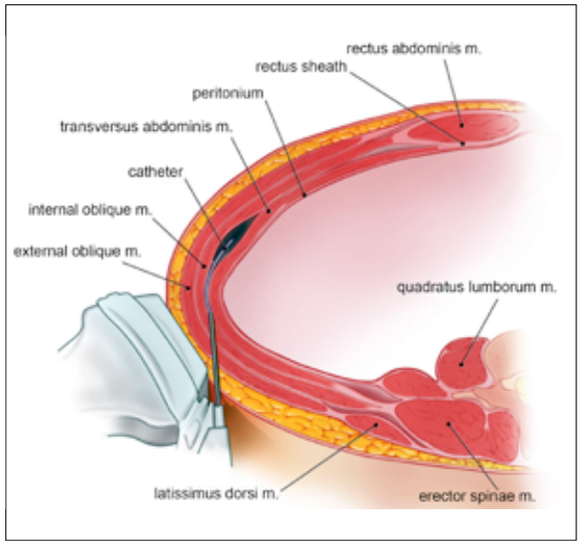
Approach to the posterior TAP block. (Image supplied by Dr Peter Hebbard.)

Figure 7.



Sonograph of TAP block with the different muscle layers. The needle has deposited local anaesthetic into the TAP. (Image supplied by Dr Peter Hebbard.)

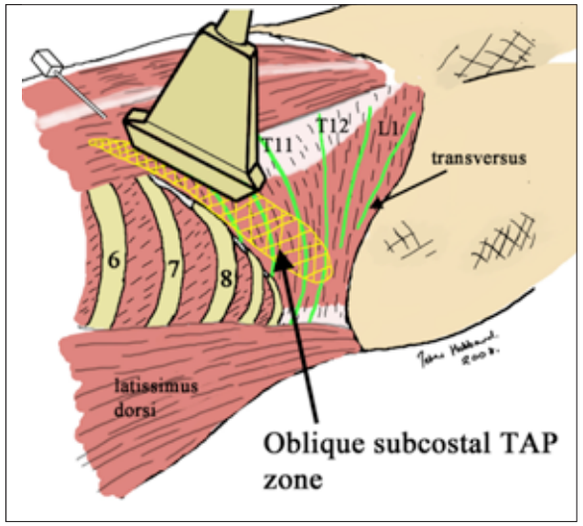
Figure 8.



Catheter placement in the TAP.

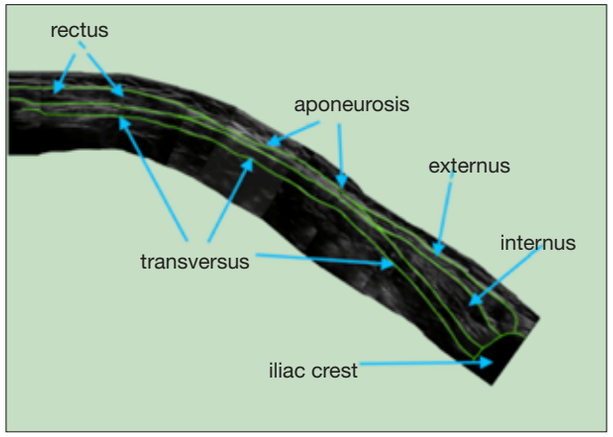
The different techniques have different results although no overwhelming advantage of one over the other has been demonstrated. MRI studies showed minimal communication of injectate from the lateral injections to the upper abdomen suggesting minimal spread of the TAP block using large volume injections, although the hydrodissection described by Hebbard et al will ensure better spread of local anaesthetic.[11,40,41] However, another study showed that the posterior and landmark based techniques had much higher spread into the thoracic paravertebral space, while the anterior and mid-axillary injections were limited to the lower abdomen.[42] It is unclear if the spread to the paravertebral space given the faint signal reported would be sufficient to provide anaesthesia.

Figure 9.



Subcostal TAP block. (Image supplied by Dr Peter Hebbard.)

Figure 10.



Sonograph of the subcostal TAP block. (Image supplied by Dr Peter Hebbard.)

HOW GOOD IS THE TECHNIQUE?

The proposed benefits of TAP blocks include adequate analgesia, reduction in opioid use and minimisation of side effects and complications. The analgesic benefit has been shown in a large number of studies.[15,43] However these are balanced by a number of studies where there was no notable benefit.[15,16,43] A recent meta analysis of abdominal surgery used eight trials, showed a non significant trend towards reduction in pain scores.[43] Reduction in opioid use has been studied, with a significant decrease noted.[15,43] When comparing the timing of the use of breakthrough opioids an increased time gap was noted in those having TAP blocks.[44] The reduction in opioid-related side effects is also studied, with a number of studies showing a decrease in nausea and vomiting and pruritus.[15,43] There were no obvious differences in sedation scores.[43] The heterogeneity of the institutions, patient groups, surgical groups and varied techniques all make generalisations difficult.[16] In surgery involving major visceral resection there is still considerable need for opioid use. There are no studies comparing the use of pre-incisional and post-incisional TAP blocks. In a meta analysis, there was more benefit in reduction of opioids in the group with pre-incisional blocks.[15] However, this will decrease the duration of action of the TAP block, thus minimising some of the benefit gained from the block.

WHAT ABOUT OBSTETRICS?

The addition of TAP blocks as part of multimodal analgesia for post-caesarean section pain decreases opioid requirements significantly over the first 24 hours, as well as decreasing the incidence of opioid induced side effects,45,46 although not unanimously.[18] However, when comparing TAP blocks with intrathecal morphine, the use of breakthrough opioid use wasn't different.[47-49] Of the opioid-related side effects only nausea was notably decreased in the TAP group, while pruritus, which is of notable concern with intrathecal morphine, wasn't different. There was considerable heterogeneity in these studies and none deposited the local anaesthetic near the anatomical location of L1. Due to the lowered threshold for toxicity from local anaesthetics in pregnancy, we do need to be aware of doses of local anaesthesia, particularly if large volume blocks are being performed. When patients underwent general anaesthesia for caesarean section, TAP blocks did have lower pain scores and increase the time to requiring breakthrough analgesia.[50,51]

The other major concern in the parturient group is the transfer of opioids in breast milk. However in the first few days after caesarean section milk production is mainly low fat colostrum, thus very little transfer of opioids.[52] Therefore it is unlikely that the use of TAP blocks in this context would add any value. This is, however, different in the mother who is been on long-term opioids, prescription or otherwise. These are a heterogeneous group of patients who will need multidisciplinary planning and management to ensure safety of the mother and baby, and to deliver safe analgesia. TAP blocks and catheters might be a useful adjunct in these patients.

CAN WE GET THE SURGEONS TO DO IT?

Deposition of the local anaesthetic in the correct planes by an amenable surgeon would also succeed in achieving a similar end effect. Chetwood et al described a series using a laparoscopic approach noting the visible bulge of the local anaesthetic.[53] Also possible is direct injection from the interior aspect of the abdominal wall or alternatively surgical dissection directly to inject on to the TAP under direct vision.[24] There are no major studies comparing the efficacy of surgical and anaesthetic placement of TAP blocks. It is worth noting that surgeons under direct vision are safer in injection compared to the blind technique, however the only reliable way of getting local anaesthetic into the TAP is ultrasound-guided technique.

HOW CAN I GET IT TO WORK FOR LONGER?

In cases where prolonged post-operative pain where neuroaxial techniques contraindicated, the use of the TAP block is essentially limited by the pharmacological property of the agents. Carney et al used a mid axillary approach to place a catheter using a Tuohy needle deep in the TAP, followed by continuous infusion of levobupivacaine, with effective analgesia.[54] Hebbard et al also placed catheters using the subcostal technique reported above.[40] These are performed with full sterile technique to minimise the risk of infection as well as avoiding contamination of the surgical site. The published used of TAP catheters is limited to a few cases series as well as three trials including a variety of ultrasound-guided techniques.[55-58] These include posterior, oblique subcostal and mid axillary for differing pathology. Included also is a series in the combat zone, in an attempt to minimise intensive care resources.

The three prospective trials on TAP catheters use very different techniques, which make them inappropriate to combine. TAP catheters led to a decrease in pain scores, and supplemental opioid use limited to day one and two when used as a continuous infusion.[57] By day three there were no differences and neither group had any major adverse effects. When using intermittent boluses as part of a multimodal technique, early mobilisation on the day of surgery was achieved.[58] In a study comparing subcostal catheters using intermittent boluses and thoracic epidurals, there were no differences in reported pain scores.[56] This suggests TAP catheters to be a reasonable alternative to epidurals in appropriate cases. Currently underway is the SUSTAIN for pain trial: subcostal ultrasound-guided transversus abdominis plane infusions for pain relief of abdominal incision. We await the results to make further conclusions regarding the benefit of these TAP catheters.[59]

HOW SAFE ARE THEY?

The reported complications of TAP blocks are very rare, and are limited to case reports only. Farooq et al reported blunt liver trauma based on a landmark-based approach to the TAP block.[60] They recommend for further cases, percussion of the liver to access the inferior border before placing this block. When using the TAP technique for blocking of the ilioinguinal/iliohypogastric nerves, cases of bowel haematoma and femoral nerve palsy have been reported. The tranversalis fascia deep to the rectus abdominis is continuous with fascia iliaca.[61] Therefore, a theoretical potential for obturator, femoral and lateral cutaneous nerve all having some blockade need to be considered although no cases have been reported with TAP blocks. Peterson et al showed no adverse effects on pulmonary mechanics due to the local anaesthetics in the TAP.[62] Using ultrasound Lancaster et al reported a laceration of the liver, showing that use of ultrasound alone isn't a fail-proof technique of safety.[63] An abdominal wall haematoma has also been reported.[64]

The implications of both the haematoma and abscess are significant. Similar lesions in a tight epidural space may render notable and permanent neurological damage to the spinal cord. While any complication is undesirable, the presence of an abdominal wall abscess or haematoma is likely to be easier to diagnose, easier to manage, and the consequences of delayed diagnosis and management less debilitating for the patient. The main concerns with bleeding at the peripheral site compared with neuroaxial include the volume of blood loss, risk of infection, and proximity to surgical site rather than the neurological consequences.[65]

WHAT ABOUT THE COAGULOPATHIC PATIENT?

TAP blocks have been advocated in cases of abnormal coagulation.[55] While there is minimal evidence to suggest that deranged coagulation tests are likely to predict bleeding risks, many guidelines still use relatively conservative guidelines for neuroaxial compared to peripheral nerve techniques.[66] The patients who have bleeding problems after peripheral nerve blockade are varied, making it very difficult to form conclusion about the risk factors. In the presence of abnormalities in traditional tests the use of the thromboelastogram may useful for performing TAP blocks.[67] Further studies in this area will be useful to assess its use in predicting bleeding risk in the periphery.

CONCLUSIONS

The goal of the TAP block is to provide satisfactory analgesia for the patient with minimal adverse effects and maximise the ability to recover. There are sufficient studies to show some analgesic benefit to the technique with reductions in side effects. The TAP block appears to be a relatively simple and safe technique for providing analgesia. The choice of any technique need to take into account the variables related to the patient and the perioperative factors including the conduct, management and post-operative analgesic regime. In well-selected patients with a trained experienced perioperative team in a good clinical context, TAP blocks techniques appear to be a useful adjunct in achieving effective analgesia.

ACKNOWLEDGEMENTS

We would like to thank Dr Peter Hebbard (Clinical Associate Professor, University of Melbourne and specialist anaesthetist, Northeast Health, Wangaratta) for his considerable work into this area and his review of the manuscript. We also appreciated the artwork and images from his personal collection.

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Acute compartment syndrome and anaesthesia

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INTRODUCTION

Acute compartment syndrome (ACS) is a rare but potentially severe complication following surgery or trauma. Compartment syndrome was first described in the medical literature by Volkmann in 1881.[1] It can be defined as a condition in which increased pressure within a limited space compromises the circulation and function of the tissues within that space.[2] The most important determinant of outcome is the time from diagnosis to treatment because late recognition has a higher risk of serious morbidity and mortality.[3] Concern regarding a missed diagnosis may influence the surgical and anaesthetic preference for post-operative analgesia in patients who are felt to be at risk of developing an ACS.

AETIOLOGY AND INCIDENCE

The compartments most commonly affected by ACS are the leg and forearm, where the size of the compartments is partly limited by a thick inter-osseus membrane between two bones. It has also been reported in the thigh, upper arm, buttock, foot and hand. A more recent addition is the abdominal compartment syndrome, defined within the last 30 years[4], which is beyond the scope of this article.

The most common cause of acute compartment syndrome is trauma. In an audit of compartment syndrome cases in a large trauma centre, approximately 36% of these occurred after fractures of the tibial shaft, 23% were caused by soft tissue injuries without fracture, and 10% by a fracture of the distal radius.[3] The incidence of ACS in tibial shaft fractures was 4.3%, and the group at highest risk was males under 35 years of age. The incidence of ACS in distal radius fractures was 0.25%. In the setting of vascular trauma, injuries to the popliteal artery and proximal lower leg are associated with the highest incidence of ACS.[5]

Other causes of ACS are also shown in table 1[6].

Table 1. Causes of acute compartment syndrome

Orthopaedic	Fractures and fracture surgery
Vascular	Arterial and venous injuries
	Reperfusion injury
	Haemorrhage
	Phlegmasia cerulea dolens
Soft tissue	Crush injury
	Burns
	Prolonged limb compression
Iatrogenic	Puncture in anti-coagulated patients
	Use of pneumatic anti-shock garment
	Casts and circular dressings
	Pulsatile irrigation
Occasional	Snakebite
	Overuse of muscles

Poor positioning during prolonged surgical procedures, particularly in the lithotomy position, may also lead to the development of ACS in the lower limb (well leg compartment syndrome), predisposing to it in several ways. Elevation of the lower limbs will reduce perfusion, and this may be compounded by intraoperative hypotension or hypovolaemia. Poorly applied leg holders, direct pressure from personnel or equipment, vasoconstriction due to hypothermia and drugs, and surgical compression of pelvic blood vessels all contribute.[7] The incidence of ACS complicating pelvic surgery is reported to be one in 3500 cases[8], and its incidence may be increasing with the increasing complexity and duration of pelvic urological surgery.[9]

PATHOPHYSIOLOGY

There are a number of theories regarding the microvascular changes that occur in the acute compartment syndrome, but the most popular is based on the arteriovenous pressure gradient theory proposed by Matsen.[2] Ischaemia begins due to either remote perfusion failure or increased resistance to flow through the compartment itself. See Table 2.[10]

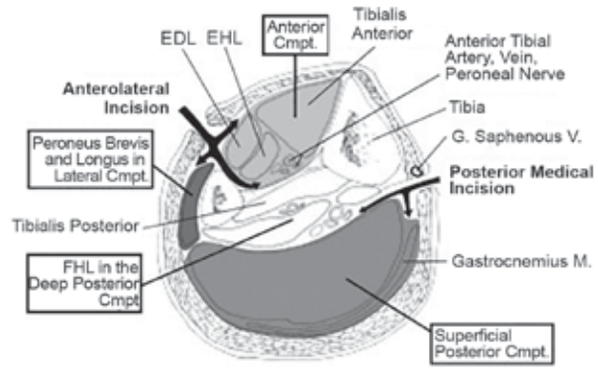
Table 2. Causes of ischaemia in acute compartment syndrome

Remote perfusion failure	Vascular obstruction
	Systemic hypotension
Increased compartmental resistance	Decrease in compartment size
	• Constriction by tight dressings or casts
	• Tight repair of surgical wounds
	• Local pressure
	Increase in compartment volume
	• Bleeding and coagulopathies
	• Increased capillary permeability
	– Reperfusion oedema
	– Exercise, seizures, eclampsia
	– Trauma and burns
	– Intra-arterial drugs
	• Increased capillary pressure
	– Exercise
	– Venous obstruction
	• Decreased oncotic pressure
	• Infiltrated infusions
	• Muscle hypertrophy

This ischaemia, followed in some cases by reperfusion, causes depletion of intracellular energy stores, cellular swelling and disruption of capillary walls, allowing extravasation of vascular contents into the surrounding tissues. This leads to elevated compartmental pressures and with this a rise in intraluminal venous pressures. A reduction in arterio-venous pressure gradient ensues, further compromising tissue perfusion. As interstitial tissue pressure rises further, venous drainage and subsequently lymphatic drainage are obstructed and a vicious cycle of worsening oedema and ischaemia follow.[11] Muscle necrosis and irreversible neural damage are the result of this ischaemia.[12]

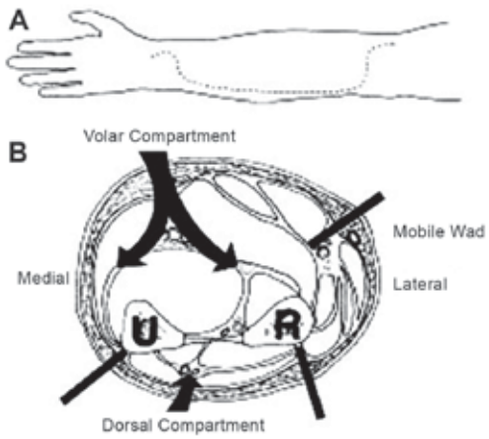
The lower leg is the part of the body most commonly affected by ACS. It consists of four compartments – anterior, lateral, deep posterior and superficial posterior. See Figure 1.

Figure 1. Compartments of the lower leg
(Image courtesy of the Journal of Surgical Education, Elsevier Publishing)



The forearm is the next most commonly affected compartment. There are also four compartments to the forearm – the superficial volar, deep volar, dorsal and mobile wad compartments.[13] See Figure 2.

Figure 2. Compartments of the forearm
(Image courtesy of the Journal of Surgical Education, Elsevier Publishing)



PRESENTATION AND DIAGNOSIS

A high index of suspicion is necessary in order to make a diagnosis of compartment syndrome because the earliest signs are often subtle and most often neurological. The condition may often be misdiagnosed as deep vein thrombosis or neuropraxia.[9] The clinical features are classically described as the "five Ps", and are shown in Table 3.

Table 3. The five Ps of ACS

Pain – out of proportion to injury, worse on passive movement.
Paresthesia – in distribution of nerve passing through compartment – see tables 4,5.
Palpable tension.
Paresis.
Pulselessness.

Pain at rest, and on passive movement, remains the earliest and most sensitive symptom of ACS. However, all of these indicators have their drawbacks.[11] Pain can be a very variable and subjective symptom, and is likely to be present to some degree due to recent trauma. It can only be assessed confidently in a fully conscious patient and will be unreliable at extremes of age and in patients following substance abuse or CNS compromise.[6] Sensory changes may be due to an isolated nerve injury. Muscle weakness is difficult to assess in acute trauma patients and its presence usually a late sign. Pulselessness is an uncommon and late sign – experimental studies have shown distal pulses can still be felt even when intracompartmental pressures are as high as 80mmHg.[14] The absence of signs and symptoms may be of more use in ruling out the diagnosis than in confirming it.[15]

Table 4. Contents of the lower leg compartments

Compartment	Muscles	Vessels	Nerves
Anterior	Tibialis anterior	Anterior tibial artery	Deep peroneal Nerve
	Extensor hallucis longus	Anterior tibial veins	
	Extensor digitorum longus		
Lateral	Peroneus longus		Superficial Peroneal nerve
	Peroneus brevis		
Deep posterior	Tibialis posterior	Peroneal artery	Tibial nerve
	Flexor hallucis longus	Peroneal vein	
	Flexor digitorum longus	Posterior tibial artery	
		Posterior Tibial vein	
Superficial posterior	Gastrocnemius		
	Soleus		
	Plantaris		

Table 5. Contents of the forearm compartments

Compartment	Muscles	Vessels	Nerves
Superficial volar	Flexor carpi ulnaris	Ulnar artery	Ulnar nerve
	Flexor carpi radialis		
	Palmaris longus		
	Flexor digitorum superficialis		
Deep volar	Flexor digitorum profundus	Anterior	Anterior
	Flexor pollicis longus	Interosseus artery	Interosseus nerve
			Median nerve
Mobile wad	Brachioradialis	Radial artery	Radial nerve
	Extensor carpi radialis longus		
	Extensor carpi radialis brevis		
Dorsal	Extensor carpi ulnaris		Posterior interosseus nerve
	Extensor digiti minimi		
	Extensor digitorum		
	Abductor pollicis longus		
	Extensor pollicis longus		
	Extensor indicis		

More objective means of measuring compartment pressures exist. There is some debate regarding the most accurate technique, but they include needle (see Figure 3.) and catheter techniques, the latter providing continuous monitoring for up to 24 hours. Both require a bubble-free column of saline, and tissue or blood can occlude the tip causing inaccuracies, although this can be improved with slit catheter and side-ported needle techniques.[16] Transducer-tipped probes avoid these problems but are not in widespread use. They all require accurate placement of the system, and all compartments at risk need to be measured separately. Many hospitals lack the equipment to easily perform compartment pressure monitoring.[6] The value of continuous monitoring has not been proven; some studies have shown no difference in outcome or time delay to fasciotomy even with this in place[17], while a recent article claimed high sensitivity and specificity for the technique.[18] Experimental studies in healthy volunteers have shown little correlation between absolute pressure and clinical signs, nerve function measured by EMG, or muscle tissue oxygen levels6.

Figure 3. Stryker Intra-Compartmental Pressure Monitor

Normal pressure in the muscle compartments is 10-12 mmHg. The critical pressure for tissue damage is in the range of 30-50 mmHg with a large degree of inter-subject variability. A commonly used threshold for surgical intervention is a differential pressure between the compartment and diastolic pressure of 30 mmHg[6,17], although the specificity of this measurement has recently been challenged for generating a high number of false positive results.[19]

Near infrared spectroscopy monitoring shows some promise in offering a non-invasive technique for directly measuring tissue oxygenation. It has been shown to be sensitive and specific for picking up early reversible nerve conduction defects.[20] Its limitations currently are the 3-4cm depth of monitoring achieved, which is not enough to reach the deep posterior compartment of the leg or more superficial compartments in obese or oedematous patients. Tonometry, as an objective measure of hardness has been shown to be less accurate than direct pressure measurement.[21] Pulsed phase-locked loop ultrasound analysis is a further non-invasive technique, which has been used experimentally but has not become established clinically.[22,23] While magnetic resonance imaging can show tissue changes of established ACS, it cannot differentiate swelling and oedema of soft tissue injury from an imminent compartment syndrome. Creatine phosphokinase levels will be elevated in established muscle necrosis and may lead to a diagnosis in a clinically unapparent compartment syndrome, but it does not aid in early diagnosis.

TREATMENT

If left unchecked, irreversible nerve and muscle damage begin after three to six hours.[12,17] Initial management on suspecting ACS is to remove all circumferential dressings, maintain normotension, and avoid elevation of the affected limb to maintain perfusion.[6] If compartment pressure measurement exceeds the threshold for surgical intervention, fasciotomy should be performed as an emergency. The longer the delay to fasciotomy, the worse the outcome, and a delay of more than 12 hours invariably leads to catastrophic outcomes, including amputation, muscle contractures and nerve palsies. Without treatment the pattern of injury will otherwise progress to include myoglobinuria and renal damage, fluid and electrolyte disturbances, local and systemic infection, and eventually multi-organ failure and death.

ANALGESIA AND COMPARTMENT SYNDROME

As anaesthetists, one of our primary roles in the post-operative period is adequate pain control. Our options in cases of moderate to severe pain include multi-modal systemic analgesia, single shot or continuous peripheral nerve blockade, and epidural infusions. Differences in attitude toward analgesia exist between anaesthetists and surgeons[24], as well as among surgeons within and between surgical specialties. A review of the medical literature shows no randomised trials comparing the relative risk of compartment syndrome between the different modalities. Case studies, several case series and a large prospective audit have all reported episodes of compartment syndrome occurring in patients using patient-controlled opioid analgesia (PCA), peripheral nerve blocks and epidural analgesia. A summary of these reports follows. The results of a survey of UK surgeons and anaesthetists published in 2004[24] do raise the possibility that many more cases have gone unreported, with almost a third of orthopaedic surgeons responding that they had seen cases of compartment syndrome that had been "delayed by the analgesic regime used". This survey included cases involving PCA opioids, epidural analgesia and peripheral nerve blocks, but no details of any individual case are given. A further survey of UK anaesthetists[25] reported that 17% of consultants and 9% of non-consultants had seen ACS masked by regional anaesthesia – predominantly epidural.

PATIENT-CONTROLLED ANALGESIA

Five published papers report on eight patients who had patient-controlled analgesia in the context of an acute compartment syndrome.[26-30] A case series of four patients[26] with tibial shaft fractures suggests a delay associated with PCA. However, all four young healthy patients received less than one mg/hr or morphine, implying that severe pain was not a feature of their symptoms. No mention of frequency of observation or pattern of morphine use within the post-operative period is made. Two papers[27,28] report on the same patient who developed muscle necrosis after IM nailing of the tibia, and the delayed diagnosis of ACS was attributed to the use of PCA. Again the pattern of PCA pump requests was not described, and of note high compartment pressures were never documented either preoperatively or intraoperatively. A posterior tibial artery thrombosis was found at surgery, complicating the diagnosis of ACS. The surgical authors suggest that intermittent IM opioid would be a safer way to deliver analgesia, increasing nursing contact with the patient and highlighting increased analgesic requirements. A further paper[29] reports on another patient with a tibial shaft fracture who had high compartment pressures unexpectedly found at a planned wound closure. The patient had high morphine requirements both before and after his initial IM nailing, but again no description of his pattern of PCA use is given. At exploration all muscle groups were viable and he made a full recovery, suggesting that the diagnosis was not critically delayed. Finally, and in contrast, a report of two paediatric cases[30] of upper limb compartment syndrome describe situations where increasing PCA demands were noted by nursing staff leading to prompt surgical review. In neither of these cases was surgery expedited immediately, and both resulted in minor but long-lasting disability. This highlights one of the advantages of PCA analgesia in enabling hour-by-hour recording of analgesia demand, made easier by the graphical displays of modern PCA pumps.

PERIPHERAL NERVE BLOCK

The first case in the medical literature of compartment syndrome associated with a peripheral nerve block came in 1996.[31] The case again described a tibial shaft fracture treated with IM nailing. A single shot 3-in-1 block was administered with 0.5% bupivacaine at the end of surgery. The patient did not complain of any post-operative pain, but reported variable loss of sensation over his foot and leg. Forty eight hours after surgery his paraesthesia persisted and he could not extend his big toe. A diagnosis of compartment syndrome was made, and at fasciotomy all his anterior compartment muscles had necrosed. His symptoms were initially ascribed to the nerve block, despite the fact that even the saphenous portion of a femoral 3-in-1 block would not have provided anaesthesia in the distribution of the affected muscle compartment and would have worn off well before the diagnosis was made. A case of foot compartment syndrome[32] has been reported after forefoot arthroplasty with ankle blockade. Within the first 12 hours post-operatively severe pain was described, leading to diagnosis and fasciotomy. No muscle necrosis or residual deficit entailed, suggesting sufficiently prompt diagnosis. A femoral nerve block was also involved in a case report of thigh compartment syndrome.[33] He initially reported significant pain requiring systemic opioids only four hours after a single shot block using 0.75% ropivacaine, and while diagnosis was only made 16 hours later, the patient made a full functional recovery.

The first of three case reports[34-36] involving continuous peripheral nerve blockade (CPNB) was published in 2011.[34] A 15-year-old boy underwent distal femur and proximal tibial osteotomy under general anaesthesia, with continuous femoral and sciatic nerve blocks post-operatively. On the second post-operative day and despite effective regional anaesthesia he developed severe pain resistant to nerve catheter bolus and intravenous opioids. A diagnosis of ACS was made, an emergency fasciotomy performed, and at subsequent re-exploration some of the anterior and lateral compartment muscle had to be removed. The second case report[35] described a femoral nerve catheter placed for analgesia following a total knee replacement. The patient was comfortable throughout post-operative day one, allowing a prolonged period of continuous passive motion (CPM) physiotherapy, but that evening reported increasing pain and reduced range of movement. Anterior thigh compartment syndrome was diagnosed and treated with fasciotomy, and the patient suffered no long-term sequelae. Although the femoral catheter was implicated for allowing excessive time in a CPM machine, it does not seem to have delayed the diagnosis of ACS. Finally a case of likely compartment syndrome is reported in the setting of an ambulatory patient who was discharged with a continuous popliteal block after foot surgery.[36] The patient developed increasing pain in her foot despite a previously satisfactory sensory block and re-presented to the emergency department where the pain was immediately relieved by splitting the patient's cast. On cast removal four weeks later there was evidence of well-healed, full thickness skin ulceration on the anterior aspect of her ankle.

EPIDURAL ANALGESIA

William Strecker, an orthopaedic surgeon, published an article in 1986 entitled "Compartment syndrome masked by epidural anesthesia for postoperative pain"[37]. Since then a number of other case reports and case series have reported compartment syndrome occurring in the presence of epidural analgesia, with some authors stating that their patients had suffered a delayed diagnosis and others asserting that epidurals had no adverse impact in their cases. Mar et al[38] conducted a comprehensive review of all published cases up until 2008, and after analysing each report considered that classic signs and symptoms, including pain in 18 cases, had been present in 32 out of the 35 patients. There were, however, three reported cases where epidurals resulting in dense bilateral motor blocks had led to a delayed diagnosis with no breakthrough pain at all. In two of these cases the authors specified a long-term adverse effect. Of the 32 cases where signs and symptoms were present, at least 15 patients experienced a significant delay to surgery suggesting that while epidural anaesthesia may not have been implicated in the missed diagnosis, it might have been a confounding factor.

Three more recent cases have been published since. Two case reports describe leg pain reported by patients in the early post-operative period leading to prompt diagnoses of ACS.[39,40] The other describes an unusual case of chronic incomplete compartment syndrome of the leg in a patient undergoing breast reconstruction surgery in the supine position.[41] The patient had complained of leg discomfort from the time of theatre recovery despite highly effective surgical analgesia, so the symptoms of ACS cannot be said to have been masked.

The National Paediatric Epidural Audit[42] undertaken in the UK from 2001-05 found four cases of compartment syndrome occurring in children with epidurals. All four cases reported pain in the affected limb, two of these despite excellent epidural blocks, and no delay to diagnosis occurred. The National Audit of Central Neuraxial Blocks also performed in the UK and published in 2009 unfortunately did not investigate any link between epidural or spinal anaesthesia and compartment syndrome.

There are no reports in the medical literature of single shot spinal or epidural anaesthesia in association with a diagnosis of compartment syndrome, delayed or otherwise.[43]

DISCUSSION

Pain relief after surgery is a basic human right. A search of the medical literature reveals that both systemic opioid and regional anaesthesia have been reported in association with delayed diagnosis of ACS, but a causative link has only been demonstrated in a handful of cases involving epidurals with dense motor blocks.

The paucity of published literature probably hides the true situation. Despite the lack of conclusive evidence many anaesthetists either avoid or provide regional anaesthesia based on surgical preference. There will undoubtedly be a degree of under-reporting of cases where anaesthetic technique may have been associated with complications. Randomised controlled trials would probably meet a high degree of resistance from surgical colleagues, and would need very large numbers due to the rarity of ACS even in at-risk cases. If our surgical colleagues have evidence from their own departmental audits of cases of ACS occurring in patients with regional anaesthesia in place, their publication would be a useful addition to the debate.

The dangers of dense motor blocks are highlighted in relation to epidurals, and despite the lack of case reports implicating CPNB in delayed diagnosis of ACS this danger seems likely to apply here as well. Other disadvantages of dense motor block include increased risk of falls, delayed rehabilitation and discharge from hospital, and delayed diagnosis of spinal cord or cauda equina injury. Differing local anaesthetics, concentrations and volumes have been used to try and minimise blockade of A alpha motor nerve fibres while allowing blockade of A delta and C pain fibres. The total dose of local anaesthetic has been shown to be more important than the concentration or volume.[44,45] Very low concentrations (for example, ropivacaine 0.1%) make it difficult to give a sufficient volume to provide acceptable analgesia[46], but the lowest concentration at the lowest rate to give adequate pain relief should be used. Modern patient-controlled regional anaesthesia infusion pumps may overcome the problem of inter-patient variation, and as with opioid PCA pumps they may provide evidence of increasing analgesic requirements in the context of ACS if properly monitored. Use of CPNB is increasing, and has been shown to provide superior postoperative analgesia to opioids in a meta-analysis for all catheter locations.[47] Several case reports demonstrate that the pain of ACS can become apparent even with an effective CPNB.

Regardless of which analgesic regime is used, effective post-operative monitoring systems should be in place for patients at risk of ACS and a high index of suspicion maintained. These patients should be flagged up by the treating surgical and anaesthetic staff, and close attention paid to pain scores, analgesic requirements, neurovascular observations, and swelling. Variations should prompt urgent surgical or acute pain service review. The fact that this may have staffing implications should not mean that patients have to accept inferior analgesia.

Anaesthetists need to be aware of the potential for lower limb compartment syndrome following prolonged surgery in the lithotomy position. It is our responsibility to ensure correct placement of the legs during surgery, maintain adequate blood pressure, and ensure that a dense motor block is not present post-operatively.

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Pre-filled emergency drugs: The introduction of pre-filled metaraminol and ephedrine syringes into the main operating theatres of a major metropolitan centre

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INTRODUCTION

The safe administration of drugs to patients lies at the core of anaesthetic practice. Anaesthesia is unique as a medical specialty where a single doctor routinely prescribes, dispenses, prepares then administers multiple medications,[1–5] often within an urgent or emergent time scale. Compound this with the fact that many of the medications used are potentially life threatening if given erroneously, it becomes clear that medication safety is fundamental to modern anaesthesia.

Metaraminol and ephedrine are the most common vasopressors used in anaesthesia in Queensland. Both require preparation by drawing out of a glass ampoule and diluting to an appropriate concentration for intravenous administration. This preparation takes valuable time, in situations where vasopressors are required urgently. It is therefore common anaesthetic practice in Queensland, and internationally,[6,7] to routinely draw up metaraminol and/or ephedrine for the case or list regardless of the likelihood of use. These "pre-drawn" syringes are usually discarded unused at the end of the list.[7,8]

The quantities of metaraminol, ephedrine, atropine and suxamethonium that were wasted in such a manner were investigated in an audit conducted at the Royal Brisbane and Women's Hospital (RBWH) in 2009 and published as an extract in the *ANZCA Bulletin* 2009.[8] It demonstrated metaraminol was the emergency or contingency drug most commonly pre-drawn (213 in 276 sessions audited), with half (50.2%) of the syringes discarded unused.

Ephedrine was pre-drawn approximately half as frequently as metaraminol (124 in 276 sessions). Two thirds (66.1%) of pre-drawn ephedrine syringes were discarded unused. Of interest, discard rates for suxamethonium and atropine were even higher, at 90.9% and 91.5% respectively.

Cost

The cost associated with these two vasopressors is not insignificant (metaraminol 10mg/1mL and ephedrine 30mg/1mL, both subject to price fluctuations but both consistently greater than $12 per ampoule), thus minimisation of wastage was deemed beneficial. The suitability of instituting sterile, pre-packaged, pre-filled syringes with an extended shelf life ("pre-filled syringes") was therefore assessed. It was hoped the cost associated with hospital pharmacy preparation of pre-filled metaraminol and ephedrine syringes ($26.72 per syringe) would be more than offset by a reduction in wastage, thus allowing for overall cost saving.

Safety

In addition to potential cost benefits, it has been argued that instituting a model of pre-filled vasopressor syringes increases patient safety by reducing medication errors.[9–11] The current method in which anaesthetists draw up and administer injectable drugs in Australasia is relatively error prone.[12,13] It has been suggested that pre-drawing syringes outside of the operating theatre has a safety benefit by reducing the risks of drug administration, dose calculation or dilution errors.[4,9]

Interim data analysis from the ANZTADC webAIRS (web-based anaesthetic incident reporting system) database reveals that of 59 "syringe swap" and "drug given in error" cases reported since the database started in 2009, 10 have involved ephedrine or metaraminol (interim database analysis May 2013). This translates to approximately 17% of such errors, arguably an over-representation relative to other drugs when it comes to syringe swap and wrong drug administration errors. It must be noted these rates would under represent the true incidence of such medication errors in Australian and New Zealand anaesthetic practice, as webAIRS is a relatively new and growing system with voluntary reporting.[14,15] A retrospective survey of New Zealand anaesthetists showed that 26.5% of responding anaesthetists admitted to a syringe swap or wrong drug error in the past, specifically related to pre-drawn drugs.[6]

A review of publications on medication errors and medication safety[2] showed the key factors resulting in drug administration errors have remained relatively unchanged for over two decades. Distraction, inattention and production pressure predominated, along with label checking and communication errors. It is argued then, that the time pressures that exist when rapidly diluting vasopressors increase the likelihood of a drug administration error. The six most common drug classes involved in error were muscle relaxants, opioids, antibiotics, vasoactive agents, inhalation agents, and local anaesthetics.[2,3,13] Multiple clinical and logistical issues exist in approaching the breadth of anaesthetic drugs with such a model, thus focusing on commonly used vasopressors in this study was deemed the most appropriate.

The manner in which anaesthetists prepare and administer medications is arguably quite error prone. In standardising concentrations of vasopressors in pre-filled syringes it has been proposed that medication administration errors will be reduced.[9,10,12,16] In recognition of this, the Australian and New Zealand College of Anaesthetists (ANZCA) makes recommendations in College document PS51[5] that such preparations should ideally be used or at least considered. In 2010 the Anesthesia Patient Safety Foundation (APSF, USA) formed a set of consensus recommendations following a summit of 100 stakeholders from various anaesthetic and pharmacy backgrounds. Among a number of specific and system-based recommendations, it was recommended vasopressors be available in standardised concentrations prepared by pharmacy in a pre-filled syringe.[4] A systematic review of evidence-based strategies to reduce medication errors by Jensen et al in 2004[9] came to similar conclusions, in that, such drugs should be presented in pre-filled syringes (where possible) rather than ampoules. Following incident analysis, this recommendation was considered to outweigh a conflicting statement, that drugs should be drawn up and labelled by the anaesthetist who will administer them.[9]

Erroneous labelling and the misreading of labels are implicated in medication administration errors.[9,17,18] It has been argued that supply of pharmacy labelled pre-filled syringes would potentially reduce drug administration errors by increasing the likelihood that labelling is accurate, and by reducing the steps involved in medication preparation and administration.[18]

Furthermore, it has been shown variability exists in the intended drug concentration and the actual (measured) concentration of drugs used in anaesthetic practice. A study by Stucki et al[19] showed 29% of evaluated syringes contained drug concentrations outside the designated range of acceptability (±10% of the targeted concentration). Of concern, 18% of preparations deviated from the declared dose by ±20% and 4% deviated by ±100% (implying calculation or preparation error rather than technique error). The nature of preparation of ephedrine and metaraminol lends these drugs to such concentration variations. It has not been shown that pharmacy preparation is more or less accurate than anaesthetist preparation, though the lack of time pressure in the non-theatre environment is likely to equal or improve upon in-theatre dilution accuracy.

Further benefit of a system of pre-filled syringes is likely to exist at a departmental level, where such syringes would be readily available to all anaesthetists, not just those that routinely pre-draw vasopressors.

INTRODUCTION OF PRE-FILLED METARAMINOL AND EPHEDRINE SYRINGES INTO THE MAIN OPERATING THEATRES OF A MAJOR METROPOLITAN CENTRE

In response to the points raised above, we planned to introduce and study the use of pre-filled metaraminol and ephedrine syringes at the Royal Brisbane and Women's Hospital (RBWH) over a 14-week period. This proposal included a comparison of data to the usage of ampoules alone over a similar period from the previous year. Cost implications, considerations of safety risks to patients and the responses of anaesthetists to the implementation are examined. Conclusions are drawn as to whether it is appropriate to continue the use of pre-filled metaraminol and ephedrine syringes in the long term in this institution. Furthermore, the presentation and preparation of the pre-filled syringes themselves is audited with a view to ongoing improvement. It is argued that the results would be applicable to similar institutions in the state and potentially further afield.

DESCRIPTION OF THE INTERVENTION

Several options to attain the metaraminol and ephedrine pre-filled syringes were investigated. Data on the longevity and stability of prepared metaraminol and ephedrine in syringes was not readily available, in keeping with correspondence in the international literature.[7] Queensland Health Central Pharmacy therefore proceeded to perform stability tests and subsequently provided adequate quantities of pre-filled syringes for use in the trial at RBWH. This data remains unpublished, though it can be reported that early in the trial, a 30-day shelf life was assigned, and this was extended to 90-days as further stability data became available.

Both pre-filled metaraminol and pre-filled ephedrine were provided in 20mL syringes. The provision of ephedrine in a 10mL syringe was desired but unavailable. Each syringe contained a volume of 10mL of medication. The concentration of ephedrine was 3mg/mL and of metaraminol was 0.5mg/mL. These concentrations were clearly labelled on the syringes. Both were presented in an opaque black plastic bag, clearly labelled on the outside (Figure 1).

Figure 1. Single metaraminol pre-filled syringe in labelled black packaging

Figure 2. One of each pre-filled syringe available in the anaesthetic drug trolley

One of each of the pre-filled syringes was placed in each anaesthetic trolley in all operating theatres (Figure 2). Instructions for use were detailed at a departmental meeting, via email and by a laminated sign on the top of each anaesthetic trolley.

Anaesthetists were instructed that pre-filled syringes were to be used in the setting of significant time pressures. Otherwise, if time permitted, metaraminol and ephedrine were to be drawn up from ampoules as per standard practice. This principle highlights that the cost saving and safety benefits are realised or maximised when using pre-filled vasopressor syringes in an urgent or emergent situation, replacing routinely pre-drawn syringes.

The usage of the pre-filled syringes was prospectively analysed over a 14-week period. These were a new stock item and numbers collected for data interpretation are absolute and accurate.

The usage of ampoules of metaraminol and ephedrine used in the main operating suites was determined via pharmacy stock delivery records during the trial period, and an equivalent period 12 months earlier. Initially, it was planned to correlate these pharmacy purchasing and usage statistics with actual drug administrations data recorded in the Anaesthetic Automatic Record Keeping system (AARK), which is ubiquitous in the main operating suites. Unfortunately, such clinical data from the AARK was unable to be analysed to an acceptable level of accuracy at the time of investigation. Therefore, analysis relied upon the outright deliveries of metaraminol and ephedrine to the anaesthetic department that occurred within this 14-week period. This means of analysis could introduce potential errors. If theatre stock levels were to increase or decrease significantly over the trial period, this would artificially skew the usage data (as pharmacy stock deliveries do not necessarily equate to clinical usage). Stock levels were analysed and were found to remain within 2% (ephedrine) and 10% (metaraminol) of baseline stock levels.

The RBWH increased its elective theatre sessions by 12.5% between the 2011 pharmacy data audit period (1467 sessions) and the 2012 trial period (1650 sessions). This proportional increase was applied to the analysed values.

The cost of pre-filled syringes from Central Pharmacy was static at $26.72 per syringe. It must be considered that any pre-preparation of a medication by a third party has an associated manpower and consumable item cost associated with it, in addition to the underlying medication cost. In this trial, one ampoule of metaraminol 10mg/1mL was used to prepare two syringes each containing 10mL of metaraminol 0.5mg/mL. This improves the cost benefit margin significantly, and is unlikely to be of any clinical significance. The cost of ephedrine and metaraminol ampoules was subject to variation over the trial period(s). The cost ranges for ephedrine were $12.21 to $13.58, and for metaraminol were $13.45 to $15.83. Prices were noted to increase, not decrease, over the 2011 to 2012 trial periods and into the 2013 analysis period. A conservative assumption for data analysis purposes was made that each ampoule (metaraminol or ephedrine) cost at least $12.

User satisfaction with the pre-filled syringes themselves was assessed via a questionnaire that was completed by a significant number of anaesthetists in the department.

RESULTS OF THE INTERVENTION

Usage

The total number of ampoules used in the 2011 period (based on pharmacy records) was 2145 metaraminol and 1040 ephedrine ampoules (Table 1). Applying the adjustment for the increased rate of theatre sessions, usage expected in 2012 would be 2413 and 1170 ampoules respectively. The actual number of ampoules used in the 2012 trial period was 1835 (metaraminol) and 760 (ephedrine). Hence ampoules of metaraminol and ephedrine were used (including both pre-drawn and dedicated use) less frequently in the trial period, leading to a reduction in delivery of 578 metaraminol and 410 ephedrine ampoules to theatres than would have been expected. The numbers of pre-filled syringes used in the trial period were 182 pre-filled metaraminol syringes, and 157 pre-filled ephedrine syringes.

Table 1. Deliveries of metaraminol and ephedrine from Central Pharmacy

Drug	Metaraminol	Ephedrine
Number of ampoules used in 2011 trial period	2145 amps	1040 amps
Expected usage in 2012* trial period	2413 amps	1170 amps
Actual number of ampoules used in 2012 trial period	1835 amps	760 amps
Reduction in ampoules delivered	**578 amps**	**410 amps**
Number of pre-filled syringes used	**182 syringes**	**157 syringes**
Ratio of ampoule reduction to pre-filled syringe use	3.18	2.61

* Expected usage based on figures in 2011 plus 12.5% to account for increased number of theatre sessions

A simple ratio of the number of ampoules not used to the number of pre-filled syringes used, facilitates comparison to the cost difference between an ampoule and a pre-filled syringe. For both metaraminol (ratio = 3.18) and ephedrine (ratio = 2.61), the reduction in ampoule use was more than two times the increase in pre-filled syringe use over the trial period. Such a ratio allows a department to predict whether implementation of pre-filled syringes will be cost beneficial or not, based on the cost difference between single ampoule and single pre-filled syringe.

Cost savings were calculated based on values itemised in the methods section. A conservative value was decided upon for ampoule cost in data analysis, in order to account for significant price fluctuations. Thus, it can be confidently said that the following are absolute minimum cost savings. Metaraminol ampoule savings amounted to $6936, and pre-filled syringe costs amounted to $4836.04, a net saving of $2072.96. Ephedrine ampoule savings amounted to $4920, and pre-filled syringe costs amounted to $4195.04, a net saving of $724.96.

Satisfaction

A questionnaire was circulated within the department with the intention of collating anaesthetists' experiences and opinions with the newly introduced pre-filled syringes. The response rate for the questionnaire was 45% (57 completed surveys of 127 recipients), which is close to the mean response rate for surveys sent to medical professionals (of 54%).[20]

Respondents generally agreed that the syringes were easy to use (84%), were labeled (87%) and packaged (78%) satisfactorily. The concentrations (87%) and volume (85%) were satisfactory or ideal. When administered, the drugs worked as expected (98%). It was felt that the syringes improved the safety of administering emergency drugs in anaesthesia (80%) and should continue to be available beyond the trial period (86.5%).

DISCUSSION

The implementation of pre-filled metaraminol and ephedrine syringes to the main operating suites of the Royal Brisbane and Women's Hospital was associated with significant cost savings over a 14-week trial period.

Cost savings

The ratio of measured use to cost difference (ampoules versus pre-filled syringes) allowed the department to determine whether implementation would be beneficial. For both metaraminol (ratio = 3.18) and ephedrine (ratio = 2.61), the calculated reduction in ampoule use was more than twice the increase in pre-filled syringe use over the same period. It follows that, if pre-filled syringes could be supplied for approximately double the cost of an ampoule, then the introduction of pre-filled syringes would be at least cost neutral in this institution. It is acknowledged that this cost saving would apply only to anaesthetic locations where metaraminol and ephedrine are pre-drawn as a routine at the start of a list. Off-floor and remote anaesthetic locations were not included in this study and inferences cannot necessarily be drawn to those budgets.

Findings of cost savings have similarly been published in the international literature.[21,22] One study highlighted that contingency drug costs would actually increase if discard rates were less than 50%.[22] These conclusions are based on pre-filled syringes costing approximately twice the cost of an ampoule (similar to our study). The authors note that any safety benefit may indeed outweigh an increased cost if discard rates were low.

Suggestion of cost detriment has also been made, including a UK study where it was concluded that the weekly cost of ephedrine would more than double with the introduction of pre-filled syringes.[23] This postal survey estimated usage rather than measured it, and extrapolated this to calculate costs. The associated reduction in ampoule use due to the availability of pre-filled syringes (as shown in our study model) was not estimated by this manner. The authors noted that as behaviours change, usage and thus costs would also change.

Potential savings

A number of important considerations, examined below, could improve the margin of cost saving from that measured in this RBWH study.

During the analysis period there were verbal reports that pre-filled syringes were being used even when no time pressure existed. This was despite anaesthetists being informed that the pre-filled syringes were only to be used when they were required urgently, and standard ampoules were to be diluted when time was not a factor. Additionally, metaraminol and ephedrine were sometimes pre-drawn as contingency drugs when no pre-filled syringes were stocked in the anaesthetic trolley. Both of these behaviours resulted in a reduction of the saving margin, and could be improved with further education and greater familiarity. Over time as cultural changes occur, a maximising of cost saving margins would be realised.

It was predicted that, as pre-drawn ephedrine wastage was high (66%),[8] this study would show a greater cost saving for ephedrine than metaraminol (discard rate 50%). The opposite was measured. The main reason identified for this was the pending expiry of a large number of pre-filled syringes part way through the trial, leading to an otherwise unwarranted surge in their use. The initial syringes were given a 30-day shelf life, later extended to 90 days as pharmacy stability data were confirmed. The authors suspect that this surge affected ephedrine to a greater extent. Therefore poor initial stock level management of ephedrine and its lower use compared to metaraminol[8] led to stock accumulation and contributed to the increased cost observed. As departmental stock level requirements are clarified over time and shelf life issues resolved, this cost would be minimised and ephedrine would have the potential to match metaraminol in cost saving margins.

The measured cost saving margin for pre-filled metaraminol syringes could also be improved. The price of an ampoule of metaraminol 10mg/1mL has continued to increase into 2013, currently costing more than $25 per ampoule. Furthermore, it seems clinically reasonable to allow splitting of one metaraminol ampoule into two pre-filled syringes, as previously described, thus potentially saving significantly. Negotiation with individual hospital pharmacies or third-party industry providers could be undertaken to find the most cost effective means of supplying pre-filled syringes.

The likely cost savings related to decreased disposable syringe and needle use in theatre was not examined in this study. The cost of these consumable items was factored into the pharmacy cost per pre-filled syringe.

Future applications

Following our lead, a number of anaesthetic departments across our network (SWAPNET) have started stocking and using pre-filled metaraminol and ephedrine syringes.

Since our implementation of pre-filled vasopressor syringes, other critical care departments at our institution have begun ordering stock. The intensive care unit (ICU) at RBWH now stocks pre-filled metaraminol syringes from the hospital pharmacy. ICU staff at RBWH pre-draw an emergency metaraminol syringe for most intra-hospital patient transfers. This contingency syringe is even less likely to be used than one pre-drawn prior to an anaesthetic list and as such, incurs a high wastage rate. Furthermore, given that metaraminol is a relatively unfamiliar drug in intensive care units (as compared to theatre cases), a safety benefit could be argued in that having pre-filled syringes with standard dilutions may be less likely to result in incorrect dilution or incorrect dose error.

It is felt that emergency departments might also benefit from the use of pre-filled syringes for many of the same reasons as the ICU. A recent emergency department incident report of incorrect dosing of metaraminol, stemming from unfamiliarity with the need to dilute the drug, highlights the safety argument for pre-filled syringes.

User satisfaction

Results of the questionnaire showed 86% of anaesthetists wanted to see the continued availability and use of pre-filled vasopressor syringes. No respondents to the survey believed that the syringes were inadequately labelled or that significant potential harm existed with the introduction of pre-filled syringes. These results, together with cost savings and potential advantages to patient safety make a strong case for the overall acceptance of the product by anaesthetists in our department.

One of the main problems identified with the pre-filled syringes was that the packaging was sometimes difficult to open. In some circumstances, scissors were needed to open the black packaging (see Figure 1), which is clearly inadequate for a product designed for emergency use. Twenty% of anaesthetists found the bags difficult to open, accounting for most of the negative feedback regarding packaging (11% “they could be improved” and 3.5% found syringes difficult to use). Supplying the packaging with a pre-cut “slit” at one end allowed for rapid tearing open of the packaging. Improving the packaging is clearly important if pre-filled syringes are to continue to be used at the RBWH.

No responding anaesthetists indicated they believed a different concentration should be used in the pre-filled syringes. It had been hoped to obtain metaraminol in 20mL syringes and ephedrine in 10mL syringes, as this was the most common syringe size for it to be drawn into, and would add another visual clue, aiding medication safety. Unfortunately ephedrine could only be supplied in a 20mL syringe. The survey revealed a lower satisfaction with the volumes supplied and many requests for the ephedrine to be supplied in a 10mL syringe.

The two issues of inadequate packaging and non-ideal volumes have been addressed as a result of this feedback and the availability of a new supplier.

Safety

The next most common theme in the comments section of the questionnaire was a strong desire for pre-filled syringes to be available in all anaesthetic areas, that is, including gastroenterology, cardiology, angiography suites and other off-floor locations. For this reason, pre-filled syringes will be available in such areas in the near future. It is felt that the safety benefit of pre-filled syringes will be significant in the remote anaesthetic environment, where crises may eventuate even more frequently than in theatre, and where skilled assistance and resources are often less readily available.[24–27]

ANZCA published position statement *PS51 Guidelines for the Safe Administration of Injectable Drugs in Anaesthesia* in 2009, and it is worth noting that pre-filled vasopressor syringes would satisfy these recommendations[5]:

“3.6 Wherever practicable drugs should be purchased in concentrations that avoid the need for dilution prior to administration. Certain drugs are particularly dangerous when undiluted and these should ideally be supplied in bags of fluid, pre-diluted to concentrations suitable for safe administration.

3.7 Consideration should be given to supplying selected drugs for intravenous use in pre-filled and pre-labelled syringes rather than in ampoules. Relevant factors include the frequency of use of the drug in routine anaesthesia, the availability of stability data supporting an adequate shelf life, data identifying particular drugs with frequent error and patient harm, and the cost-effectiveness of pre-filled syringes for drugs which may be routinely prepared for emergency use but often discarded.”

Arguments against the increased safety of pre-filled syringes have been made in the anaesthetic literature in the form of case reports from the UK, where multiple manufacturers prepare pre-filled anaesthetic syringes. Similar (blue) labelling between suxamethonium and fentanyl syringes has been repeatedly commented upon.[28,29] A reported failure of reconstituted thiopentone to have a clinical effect has also been made.[30] A brand of pre-filled syringe has been shown to have poor dosing graduation calibration; this has clear implications for vasopressor preparations.[31] These reports are invaluable in highlighting potential weaknesses or areas for improvement in a system of pre-filling syringes, and should be encouraged in order to optimise the model over time.

It must be kept in mind, however, that in a prospective assessment of the safety of pre-filled syringes (implemented among other interventions in keeping with the recommendations of the 2010 APSF summit and the 2004 systematic review by Jensen et al),[4,9] a 21% reduction in drug administration errors was shown.[10]

CONCLUSION

The introduction of pre-filled metaraminol and pre-filled ephedrine syringes in the RBWH main operating theatres has been highly successful. It has resulted in a decreased overall cost of these drugs to the department, with further improvements in the cost saving margins expected. User satisfaction was high, and changes in response to feedback could be used to further refine the system. The intervention was readily adopted and accepted into practice, and a desire to have continued and extended availability was expressed in user feedback. This simple intervention translates evidence-based recommendations on reducing error in medication administrations into practice and is of likely benefit to the safety of patients undergoing anaesthesia.

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Increasing efficiency through an evidence-based framework of volatile agent use

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INTRODUCTION

Ideal healthcare depends not only on how much money is expended, but on how effectively the money is allocated for a given resource.[1] In anaesthesia, isoflurane, sevoflurane and desflurane are the most commonly used volatile agents accounting for largest expenditure in the operating room (OR) pharmacy budget.[2] Operational costs of these volatile agents are determined by their respective acquisition costs, the fresh gas flow (FGF) rate used for agent delivery, and the number of volatile agent general anaesthetic hours. These determinants represent an opportunity to deliver significant cost savings through pharmacoeconomic modeling.

In order for institutions to maximise cost efficiencies of these volatile agents, we present a framework taking into consideration the clinical, economic and environmental cost. Pharmacoeconomic modelling is used to link volatile agent choice with important endpoints such as operating room and recovery times, and time to home readiness. Key clinical economic outcomes including volatile agents expenditure, overtime labour costs, and time to home discharge are also considered. This review also discusses the impact of volatile agents on the environment and on clinician satisfaction.

FACTORS INFLUENCING THE CHOICE OF VOLATILE AGENT

There are numerous factors influencing clinician choice of volatile agents in anaesthesia practice. These not only include the specific acquisition and operational costs, but the effects of each agent on time taken to extubation, time to follow commands, home readiness and hospital discharge. In addition, overtime labour costs, clinician satisfaction and environmental impact are important factors influencing choice of each agent.

1. ACQUISITION AND OPERATIONAL COST OF VOLATILE AGENTS

In current anaesthesia practice, running costs are primarily affected by the choice of volatile agent. This choice directly impacts on the: i) cost per mL which varies between institutions and their negotiated contract prices directly with the supplier in Australia (Abbott, Botany, NSW, Australia for isoflurane and sevoflurane; and Baxter, Old Toongabbie, NSW, Australia for isoflurane, sevoflurane and desflurane); ii) dialled vaporiser concentration based on the agent's minimum alveolar concentration (MAC); and iii) FGF rate (sevoflurane is associated with higher FGF rates).[3]

Over the past 10 years isoflurane has remained the cheapest volatile agent.[2] Sevoflurane is currently the second cheapest volatile agent, but prior to its patent expiration in 2005, was the most expensive.[2] Desflurane with its patent expiration occurring recently in 2012, still remains the most expensive.[2] It is also important to take into account a volatile agent's MAC in cost analysis, as desflurane with the highest MAC, utilises more vapour proportionately per minute than sevoflurane and isoflurane for a given MAC and flow rate.

The primary reason for using higher FGF with sevoflurane is the concern about

potential renal toxicities associated with its by-product Compound A4.[5] Use of low fresh gas flows with sevoflurane remains contentious, with Australia and Canada recommending flow rates not less than 2 L/min, the US recommending not to exceed two MAC•hours for flow rates between 1-2 L/min, and countries such as New Zealand, the United Kingdom, Japan and most of Europe having no recommendations on minimum fresh gas flow rates.[6] These limitations have been challenged and a shift to using sevoflurane-inert CO2 absorbents should allow for safe low flow anaesthesia using this volatile agent.[7]

General anaesthesia often involves an induction phase with face mask ventilation using high FGF to administer anaesthetic vapour prior to intubation.[8] A significant amount of vapour is utilised during this phase, and cost savings can be generated by turning FGF to low flows.[8] With the availability of gas monitoring in modern anaesthesia machines, low FGF between 0.5-1 L/min should also be employed during the maintenance phase whilst not compromising patient safety with concerns of under-delivering volatile agents or oxygen.[9] It is however associated with an increase of workload affecting compliance.[10] potential solution lies in technology such as automated control which can manage these complexities and increase participation in low flow anaesthesia.[10]

2. OPERATING ROOM RECOVERY TIMES

Surrogate markers of OR recovery times reported in literature are time to extubation and time to following commands. Compared with isoflurane, desflurane reduces the mean OR recovery times by 34% and the variability of OR recovery times by 36%;11 and sevoflurane reduces the mean by 13% and variability by 8.7%.[11] Desflurane reduces the mean and variability by 20-25% when compared with sevoflurane.[12] The weighted mean differences in OR recovery times between isoflurane, sevoflurane and desflurane are approximately two minutes.[13-15] While this may not appear to be clinically significant, these differences become larger for patients expected to have longer than the average expected OR recovery times.[11,12] These times are primarily affected by surgical duration.[11] Other possible factors can be extrapolated from studies in fast-track cardiac surgery and include: elderly, type of procedure, stroke, renal failure[16] and obesity.[17]

3. TIME TO HOME READINESS

"Time to home readiness" refers to the time when patients are ready to be discharged home as assessed by a standardised scoring system. When using desflurane, the weighted mean difference in time to home readiness is 6.4 min compared with isoflurane,[14] and 2 min compared with sevoflurane.[14] Sevoflurane reduces this mean difference by 5.1 min compared with isoflurane.[14]

However, it is more practical to consider "time to home discharge" which is the actual time patients leave hospital.

4. TIME TO HOME DISCHARGE

Several non-medical factors beyond choice of anaesthetic used affects time to home discharge (actual time patient leaves the hospital).[14] These confounding factors include availability of an adult to accompany the patient home or waiting for discharge medications. It is therefore difficult to associate a reduction in either the mean or variance of time to home readiness by using sevoflurane or desflurane over isoflurane, to a significant economic saving by reducing time to home discharge.

The requirements of post-operative care after ambulatory surgery in Australia, is also different to that in the US. Recommendations in Australia require all patients who have undergone sedation or general anaesthesia to be recovered in the post-anaesthesia care unit (PACU) before being transferred to the second stage of recovery prior to discharge.[18] In Australia it is acceptable practice to recover post-operative patients with supraglottic devices in situ in the PACU.[19] Practice in the US does however allow for patients with minimal post-anaesthetic care requirements to bypass PACU and be admitted straight to the second stage.[20]

5. OVERTIME LABOUR COSTS

The primary measurable clinical economic benefit of reducing OR recovery times is through the reduction of overtime labour costs.[12] This will vary among institutions and is dependent on: i) the incidence of prolonged extubation;[11,12] ii) number of lists where OR recovery times affects caseload;[21] iii) number of lists where there is scheduled overtime or more than eight hours of staffing planned.[11] and iv) OR overtime labour costs, which are generally stepped (15 to 30 minute increments) at 1.5 times the regular rate.

6. ENVIRONMENTAL IMPACT

Volatile agents are strong greenhouse gases,[22] with desflurane having the greatest environmental impact.[23] This is commonly assessed by its global warming potential (GWP) measured as CO2 equivalents over short, medium and long-term time horizons (20, 100 and 500 years). Over a 100 years, the GWP per bottle of desflurane is 893kg; sevoflurane 48kg; isoflurane 191kg.[10] The same principles that modify the running cost of agents: MAC and FGF, also apply in its calculations of their respective environmental impact. This will be discussed further in our modelling below.

An approach to price carbon is through the use of a carbon tax. This is not perfect as it can only estimate what the true marginal cost of emitting one extra tonne of CO2 at a given point in time.[24] It does, however, allow for an agent's environmental impact to be factored into clinical economic decision making. In 2012-13, the price of carbon in Australia is set at $23 per tonne.[1]

7. CLINICIAN SATISFACTION

This outcome is harder to quantify in tangible economic terms. Prolonged changeover times from increased OR recovery times can lead to frustrated surgeons leaving the surgical suite and not promptly returning to start the next case further adding to delays.[25] This can also lead to delays in starting times for ORs with another surgeon to follow with scheduled cases.

PRACTICE PLAN TO INTRODUCE AN EVIDENCE-BASED FRAMEWORK FOR VOLATILE AGENT MANAGEMENT

Based on the evidence discussed above, our two major assumptions for a framework of volatile agent use are: i) overtime OR labour costs and clinician dissatisfaction are expensive, and should be avoided by using either desflurane or sevoflurane over isoflurane to reduce OR recovery times; and ii) OR recovery times for general anaesthetics requiring a supraglottic device are independent of volatile agent choice as they can be recovered in PACU.

Therefore to maximise cost efficiencies, an ideal ratio of volatile agent use is to use the cheapest volatile agent (commonly isoflurane) for all supraglottic cases and desflurane for all cases that will lead to prolonged OR recovery times (had either isoflurane or sevoflurane been used instead). This minimises costs associated with overtime labour and clinical dissatisfaction, and maximises the utility of the cheapest volatile agent where clinical benefit is marginal.

To implement this framework into clinical practice, we designed a 10-step process outlined in Table 1.

Table 1. Steps to introduce an evidence-based framework of volatile agent management into clinical practice. (LMA: laryngeal mask airway; ETT: endotracheal tube; PACU: post-anaesthesia care unit; FGF: fresh gas flow)

Step 1	Prospectively audit your department's volatile agent costs and surgical hours over a set period of time. Divide cases into LMAs and ETTs. This data can also be estimated retrospectively by extracting data from pharmacy and the hospital information system.
Step 2	Audit the incidence of prolonged OR recovery time over a set period. Consider anaesthetic (especially choice of volatile agent and type of airway), surgical and patient factors.
Step 3	Audit the percentage of LMAs that are recovered in PACU.
Step 4	Estimate what potential savings could be generated by introducing an evidence-based framework for volatile agent usage. The ideal ratio of volatile agent use will depend on the ratio of LMA: ETT workload, as well as the incidence of prolonged OR recovery times and their respective average surgical duration. Appendix 1 describes how to calculate this.
Step 5	Educate your department on the evidence and potential savings.
Step 6	Trial a strategy of using isoflurane (or if this is not available, sevoflurane) for all surgical cases requiring LMAs and desflurane for all cases associated with prolonged OR recovery times. Use a maintenance FGF ≤ 1 L/min whenever possible.
Step 7	Re-audit volatile agent costs and surgical hours.
Step 8	Re-audit the incidence of prolonged OR recovery time. If this has increased, consider why? If this has not changed or decreased, then savings are being generated from volatile agent choice and low FGF without affecting clinical outcomes.
Step 9	Re-audit the percentage of LMAs that are recovered in PACU. Has this lead to issues such as inadequate staffing or delayed discharge leading to bed block? If so, then review these incidences. Isoflurane may need to be replaced by sevoflurane in some cases.
Step 10	Present these finding to the department to reaffirm how these changes are making a difference. Continue to also audit and educate practice at regular intervals to ensure accountability.

LIMITATIONS

Similar to other systematic reviews and meta-analyses comparing endpoints between volatile agents, the pharmacoeconomic framework does not consider the effects of nitrous oxide and bispectral index (BIS) on OR recovery times.[11-15] Use of nitrous oxide has been shown to increase the speed of emergence[26] and OR recovery times are also reduced with the use of BIS.[27] Both factors have unique considerations to take into account during a cost-benefit analysis. In addition, nitrous oxide is associated with clinical[28] and environmental costs[22] and BIS requires the use of a module and disposables. Ongoing research is needed to quantify their economic benefits.

CONCLUSION

A pharmacoeconomic framework for volatile agent choice and FGF rates can increase the technical and allocative efficiency of the delivery of anaesthesia, compared to current clinical practice. The degree of savings will be institution dependent where its true value is dependent on staffing, remuneration, organisational efficiency and caseload. Hospitals can apply the principles of the presented framework to derive an optimal ratio of volatile agent use applicable to its own unique parameters.

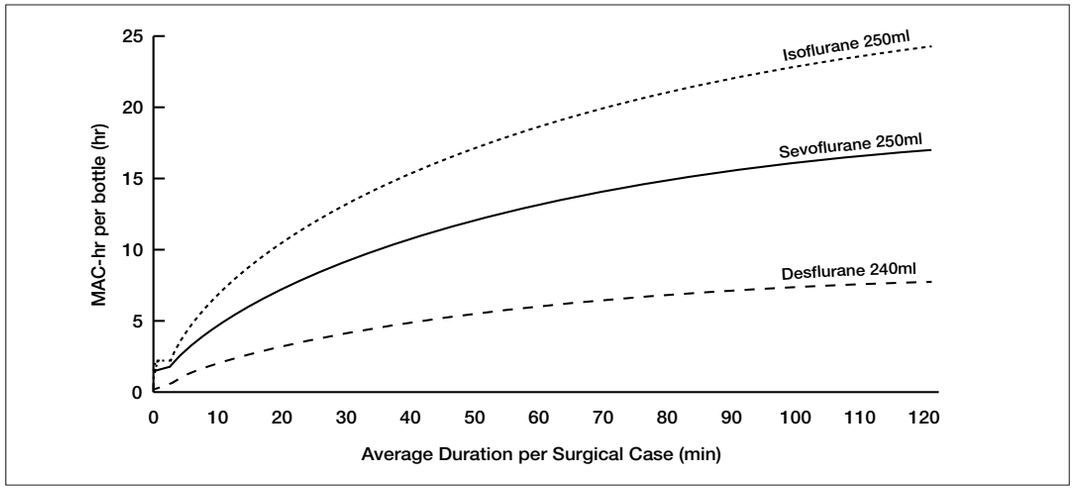
APPENDIX 1

To calculate the optimal ratio of volatile agent use, we need to consider the ideal MAC-hr per volatile agent bottle. MAC-hr per bottle is the number of MAC hours that can be performed with the volume contained in one bottle of volatile agent (isoflurane: 250mL; sevoflurane 250mL; desflurane 240mL). Our ideal MAC-hr per bottle is quantified using the following conservative assumptions: i) induction phase FGF rate of 8 L/min at a MAC of 1.3 for 3 min reflective of standard practice of using high FGF to administer anaesthetic vapour prior to intubation or surgical stimuli; ii) FGF of 1 L/min at a MAC of 1.0 during the maintenance phase; iii) the different blood:gas solubilities of the volatile agents which affects the ratio between the inspired fraction concentration (Fi) to the dialled fraction concentration (FD), and the ratio between the alveolar fraction concentration (FA) to the inspired fraction concentration (Fi).

To account for these variables, we ran simulations on Gas Man Understanding Anesthesia Uptake and Distribution Version 4.1 (Created by James H. Philip, Brigham and Women's Hospital, Harvard Medical School; Med Man Simulations, Chestnut Hill, Massachusetts, USA), using a semi-closed circuit on a 70kg patient with a minute ventilation and cardiac output of 5 L/min. During the induction phase, we used a FGF of 8 L/min for the first three minutes, aiming to reach a MAC of 1.3 by 2.5 minutes. During the maintenance phase, we lowered the FGF to 1 L/min while aiming to maintain a MAC of 1.0. We recorded volatile agent used in mL every minute for the first five minutes, and then in five minutes intervals thereafter up to 120 minutes. We repeated this scenario five times for each volatile agent: 15 simulations in total. Our results are presented graphically in Figure 1. From here, one can estimate the MAC-hr per bottle of isoflurane, sevoflurane and desflurane depending on average surgical duration. The ideal number of bottles for a given volatile agent can therefore be calculated by dividing the total surgical time for LMA (laryngral mask airway), ETT (endotracheal tube) and prolonged OR recovery cases by the appropriate MAC-hr per bottle.

Figure 1.

MAC-hr per bottle versus average surgical time for (-----) isoflurane, (_____) sevoflurane and (-----) desflurane. MAC-hr per bottle is influenced by the FGF and MAC of the volatile agent. The rate of change of the MAC-hr per bottle is reflective of the saturation of the peripheral compartments (vessel rich group, muscle and fat) based on its various interface partition coefficients and time. Shorter surgical case durations are therefore associated with lower MAC-hr per bottle because of the initial saturation of the vessel rich group. Longer surgical durations are associated with higher MAC-hr per bottle because the vessel rich group is now saturated and FA starts to approximate Fi; with the difference reflective of the uptake in muscle and fat and its hepatic metabolism. The induction phase FGF rate was 8 L/min at a MAC of 1.3 for 3 min followed by a maintenance phase FGF rate of either 1 L/min at a MAC of 1.0.



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Cardiopulmonary exercise testing for preoperative assessment of surgical risk

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INTRODUCTION

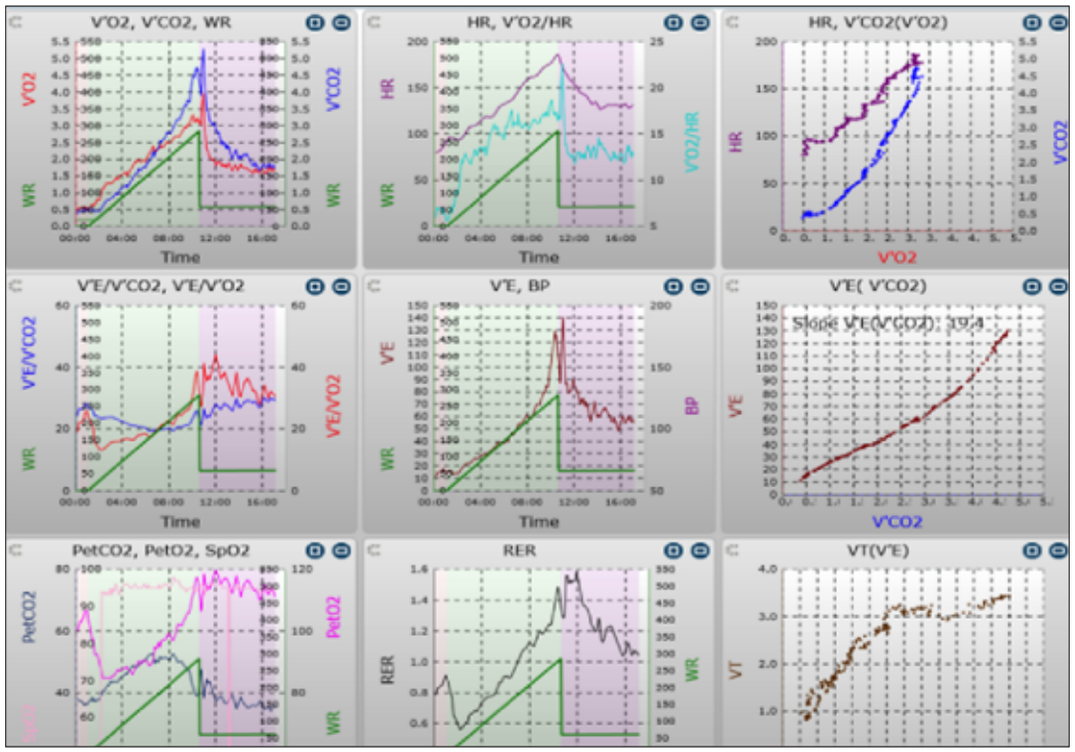
Cardiopulmonary exercise testing (CPET) is used to assess the ability of the cardiovascular and respiratory systems to support the increased metabolic stress of exercise and surgery.

The cardiovascular, respiratory and metabolic stresses of exercise are recorded during exercise and displayed, graphically in a nine-panel plot of the physiological responses to increasing work rate exercise.

Karlman Wasserman, at the Los Angeles Biomedical Research Institute of the Harbor-UCLA Medical Centre, the University of California at Los Angeles (UCLA) developed the test in the 1960s as a non-invasive test for cardiorespiratory assessment to exercise. Paul Older et al were the Australians who introduced cardiopulmonary exercise testing for pre-assessment.

Currently, CPET is available in over 40% of National Health Service Trusts in the United Kingdom for patient preoperative assessment.[1]

Figure 1. 9 Panel Plot (2012) from Cortex Biophysics CPET display



Preoperative assessment of patients undergoing major surgery allows identification of low and high risk patients for morbidity and mortality.[2,3,4,5,6,7,8]

Various risk stratification indexes are limited by the study cohorts and index algorithms, and most fail to objectively assess individual functional capacity as part of the risk assessment.[9,10]

Major surgery stimulates the inflammatory response resulting in increased postoperative O2 consumption and poor cardiorespiratory reserve may result in the inability to cope with the increased metabolic demand resulting in patient morbidity and mortality.[11-15]

Age, American Society of Anaesthetists physical status (ASA) classification, acute admission, low serum albumin, inflammatory response, acute and chronic kidney injury are risk factors associated with poor outcome in patients undergoing non-cardiac surgery.[16,17,21]

The ageing population is estimated to increase by 25% by 2020 with four times the intervention rate of a standard population.[18,7] A "good practice" of care as assessed by the National Confidential Enquiry into Patient Outcome and Death is at best 58.5% for elective surgical admissions[1] and 37.5% in patients aged 80 years or greater.[19] A high-risk surgical population accounts for 83.3% of deaths but only 12.3% of surgical procedures, yet fewer than 15% of high-risk patients are admitted to intensive care or high dependency unit facilities. The highest mortality rate of 39% occurred in those patients admitted post-operatively to a standard ward later requiring transfer to an intensive care unit.[20] A single post-operative complication is associated with a reduction in median survival by 69% independent of preoperative patient risk.[21]

CPET has the potential to improve patient outcome by identifying high-risk physiological parameters, optimisation of prehabilitation, modification of surgical procedure and appropriate post-operative care based upon individual cardiorespiratory reserve.

PERIOPERATIVE OUTCOME

Exercise capacity is probably the most important predictor of perioperative outcome.[22,6- 9,12-15,23-28] The number and severity of co-morbidities, surgical procedure and perioperative care influences patient survival.[29,3-10,12-17,20-28] Asymptomatic medically stable patients scheduled for major non-cardiac surgery are able to proceed directly to surgery if they are able to perform four METS activity.[6] Patients' self reporting the ability in climbing two flights of stairs or walk greater than four blocks are considered to have good exercise tolerance and associated with fewer perioperative complications in major non-cardiac surgery.[8]

5939 patients attended an anaesthetic preadmission clinic within two months of elective non-cardiac surgery. Metabolic equivalents (METS) were estimated and electronically documented based upon the ACC/AHA Guidelines and the Duke Activity Status Index (DASI) and were assigned an ASA classification I-V by the attending anaesthetist. 94 patients (1.6%) had cardiac complications, 16 (0.27%) died and 38% of complications occurred following vascular surgery. Both age and ASA classifications were highly significant predictors but estimation of METs was not a significant predictor of post-operative cardiac complications or death.[30]

Perioperative mortality and morbidity may be predicted using stair climbing capacity in major cardiac and thoracic surgery as the studies quoted for non-cardiac surgery included thoracic patients in their cohorts,[31] and stair climbing correlates with MVV, peak VO2 and FEV1, and predicts perioperative mortality and morbidity in patients undergoing lung resection surgery for cancer.[32-35]

A good performance with the incremental shuttle walk test (ISWT) correlated well with CPET, however a significant number of poor performers with ISWT achieved a satisfactory peak VO2 and AT with CPET.[36]

110 patients were assessed with the six-minute walk test and CPET prior to major non-cardiac surgery. Patients walking greater than 563m would be considered fit for surgery, while those walking less than 427m would require further evaluation. A distance less than 440m with the six-minute walk test will likely be achieved by approximately 6.6% of patients with an AT> 11mls/kg/min. A distance greater or equal to 440m will likely be achieved by 25% of patients with an AT < 11mls/kg/min.[37]

CARDIOVASCULAR DISEASE AND CARDIOPULMONARY EXERCISE TESTING

62 patients aged 19 to 79 years with New York Heart Association (NYHA) chronic stable Class I-IV heart failure were exercised on a treadmill and classified into functional classes according to their peakVO2:

A >20ml/kg/min, B 16-20ml/kg/min, C 10-15ml/kg/min and D <10ml/kg/min.

43 patients from functional classes B, C and D underwent a second exercise test with radionuclide ejection fraction and pulmonary artery catheter studies.

Upright hemodynamic data at standing rest and maximal exercise

Table 2. Values are mean+/- SD

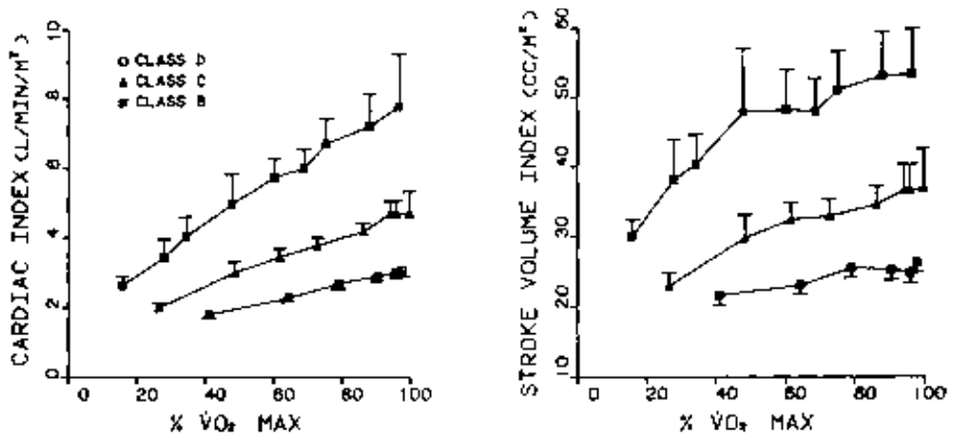
	CI (l/min/m²)		SVI (ml/m²)		LVFP (mm Hg)		O_2 Ext %	
Class	R	E	R	E	R	E	R	E
B (n = 4)	2.23 ± 0.24	7.8 ± 0.95	26 ± 3	49 ± 5	8 ± 6	23 ± 12	33 ± 8	75 ± 2
C (n = 11)	2.01 ± 0.41	4.68 ± 1.1	23 ± 6	36 ± 11	19 ± 6	37 ± 9	39 ± 9	71 ± 5
D (n = 25)	1.81 ± 0.51	3.04 ± 0.48	22 ± 7	26 ± 4	24 ± 7	40 ± 11	48 ± 10	75 ± 8

CI = cardiac index; SVI = stroke volume index; LVFP = left ventricular filling pressure from pulmonary wedge or diastolic pressure; Os Ext = oxygen extraction; R = upright standing rest; E = maximal upright exercise.[38]

Exercise induced cardiac output in functional class B and C was achieved by increases in stroke volume and heart rate, whereas class D patients were unable to increase stroke volume and where reliant on increase in heart rate for their increase in cardiac output. Resting O2 extraction varied but there was no difference in O2 extraction with increasing exercise between classes B, C and D. Maximal O2 extraction(≥ 70%) occurred at 80% of peak VO2 peak.

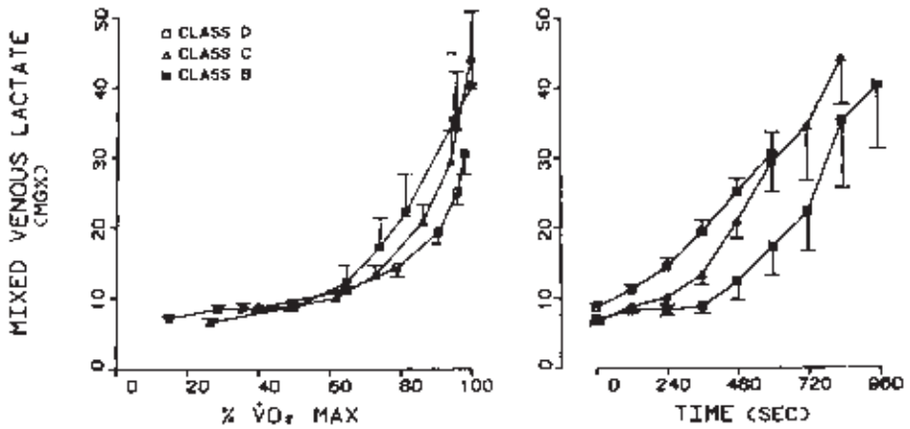
During treadmill exercise, patients were limited by cardiac output rather than high pulmonary venous pressure, as patients did not stop exercising because of breathlessness. Poorly compliant lungs and elevated wedge pressure may be more important factors in the supine position or in prolonged exercise for symptomatic limitation.

Figure 4. The response in cardiac function and systemic O2 extraction as a function of normalised work (% maximum O2 uptake, % VO2 max) for class B,C and D patients.[38]



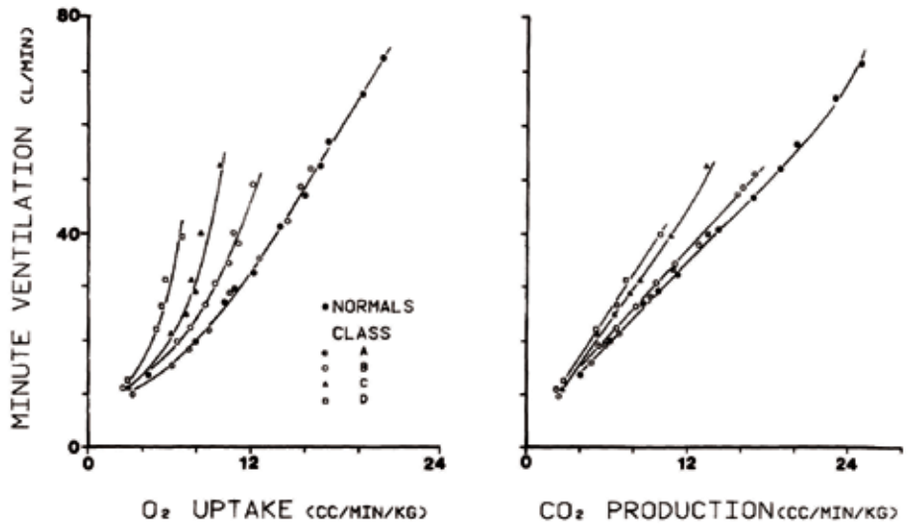
Lactate threshold was reached sooner in class D than either class C or B patients but at the same % VO2 max.

Figure 5. The rise in mixed venous lactate concentration is shown as a function of normalised work (% VO2 max) and treadmill time for the patients shown in figure above.[38]



Minute ventilation increased more steeply relative to O2 consumption and CO2 production with worsening heart failure[38] due to increased dead space (VD/VT) in patients with heart failure.[39]

Figure 6. The relationship between minute ventilation, O2 uptake and CO2 production for the four functional classes of cardiac patients and normal subjects. End stage values are given.[38]



23 patients with NYHA Class I-III were studied using CPET and ejection fraction monitored using a cadmium telluride detector. Resting ejection fraction increased from 41.4% at rest to a peak of 46.5% at anaerobic threshold and declined to 37.2% at peak exercise.[40] VO2 time constant kinetics are prolonged in patients with EF< 35%.[41]

DYNAMIC TESTS

Exercise ECG

Exercise ECG induced ST ischaemia has a sensitivity and specificity of 66% and 84% respectively, depending upon number of vessels involved.[42] Failure to achieve 85% predicted heart rate in the presence of 0.1mV ST depression in a supine cycle ergometery stress ECG may be a more significant predictor of perioperative events than a positive test itself.[43]

Stress ECHO

Transthoracic echo is limited in predicting perioperative morbidity[44] and ejection fraction parameters poorly correlate with exercise capacity.[45-50]

A meta-analysis comparing 68 studies of 10,049 people reviewed exercise stress ECHO (ESE) to thallium imaging (TI). This demonstrated TI-indicated therapeutic intervention in 72.1% compared with ESE at 46.3%. Both ESE and TI demonstrating a moderate to large defect had a 14% post-operative cardiac event rate. The likelihood ratio for a postoperative myocardial event was 4.09 with ESE compared to 1.83 with TI, attributed to a lower false negative rate with ESE.[51]

530 patients with known or suspected ischaemic heart disease underwent dobutamine stress ECHO (DSE) prior to non-cardiac surgery. DSE identified 115 patients with previous infarction, 214 patients had new or worsening wall ischaemia and 130 patients with ischaemia and previous infarction. There was one fatal and 31 non-fatal post-operative myocardial infarctions. High-risk patients for perioperative cardiac events were those with a history of developing ischaemia at less than 60% of their age – predicted maximal heart rate (OR 7.00) and patients with congestive heart failure (OR 4.66).[52]

Kertai et al assessed with meta-analysis studies comparing the prognostic accuracy of ambulatory ECG, exercise ECG, radionuclide ventriculography, dobutamine stress ECHO and dipyridamole stress ECHO for predicting perioperative cardiac risk in patients undergoing major vascular surgery. DSE had high negative prediction value of 90-100%. Receiver operator characteristics (ROC) analysis demonstrated a trend towards better performance for stress ECHO predicting perioperative cardiac death and myocardial infarction than the other tests but was only significant against scintigraphy.[53]

PERIOPERATIVE MORBIDITY, MORTALITY AND CARDIOPULMONARY EXERCISE TESTING

Older et al. prospectively studied the outcomes of 187 elderly patients 60 years and older using CPET undergoing elective major abdominal surgery. 132 patients had an anaerobic threshold (AT) >/= 11ml/kg/min and 55 had an AT < 11ml/kg/min. The cardiovascular mortality rate in the group with an AT >/= 11 ml/kg/min was 0.8% and in the group with AT>/= 11ml/kg/min + cardiac ischaemia was 4%. The cardiovascular mortality rate in the group with an AT < 11 ml/kg min was 18% and in the group AT< 11 ml/kg/min + cardiac ischaemia the mortality rate was 42%.[13]

Table 3. Mortality data: AT above and below 11mls/kg/min. (Adapted from Older et al.[13])

AT/ ml/kg/min	Patients	Ischaemia with CPET	CVS deaths	% mortality
< 11 no ischaemia	55	0	10	18
<11 + ischaemia	55	19	8	42
>/= 11 no ischaemia	132	0	1	0.8
>/= 11 + ischaemia	132	25	1	4

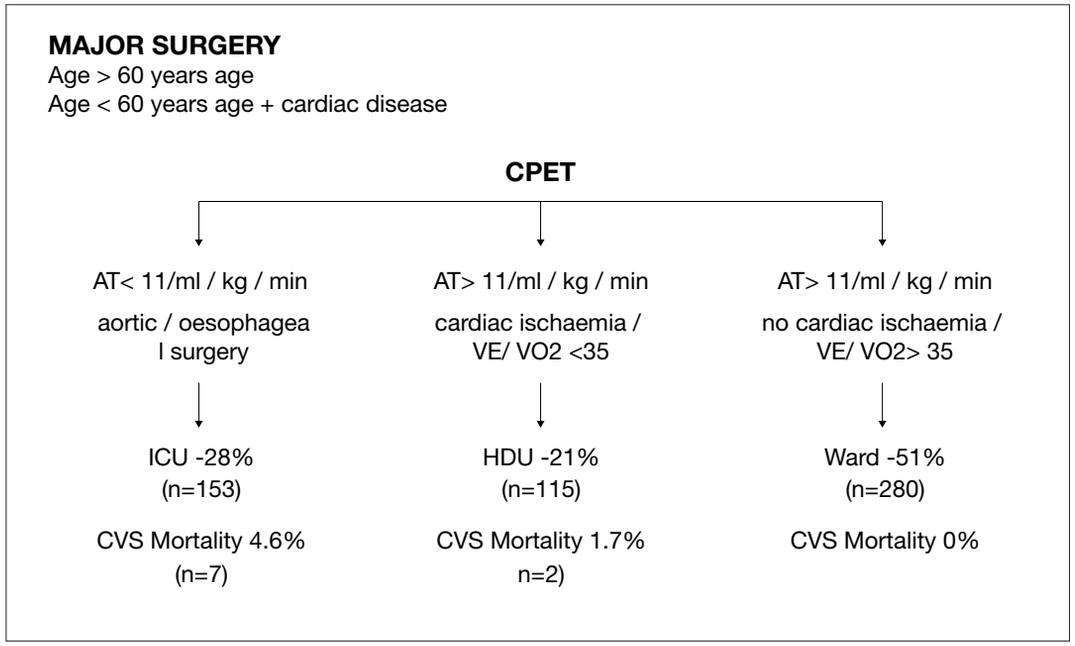
CPET was used to electively triage 548 patients greater than 60 years of age or those with known cardiopulmonary disease scheduled for major abdominal surgery based upon the anaerobic threshold result. 153 patients were triaged to ICU because of an AT < 11ml/kg/min or because of oesophageal or aortic surgery.

115 patients were triaged to HDU with an AT> 11ml/kg/min, myocardial ischaemia or VE/VO2> 35.

280 patients were triaged to the ward with an AT >11mls/kg/min and without myocardial ischaemia and VE/VO2 < 35.

Overall mortality was 3.9%. 11 of these patients had poor CPETs, and two died 30 days post-aneurysmectomy due to haemorrhage. Six of the other 10 patients died of disease progression, two from surgical complications and two from unrelated causes. Five patients died with an AT>= 11ml/kg/min. Two of these patients had early ischaemia, one had severe pulmonary disease, one of surgical complications and one following palliative care. 279 patients were triaged to the ward and two died as a result of their underlying disease.[14]

Figure 7. Flow charts showing post-operative triage site and outcome following major surgery. CVS= cardiovascular system. (Adapted from Older et al.[14])



389 adults underwent CPET testing prior to major hepatobiliary surgery. An AT< 10ml/kg/min was found to be the most significant predictor of post-operative mortality across all age groups but more so in patients 75 years and greater. Age was associated with reduced fitness and increasing mortality compared with survivors. Patients with normal cardiorespiratory fitness irrespective of age spent the same number of days in hospital and critical care services. Cardiorespiratory fitness was predictive of mortality and hospital length of stay after major elective surgery in older people.[15]

171 patients were screened preoperatively using CPET and the Veterans Activity Questionnaire Index for risk assessment of post-operative complications in patients undergoing major surgery. Median complication rate on post-operative day seven was one. The AT was greater (11.9 vs 9.1 ml/kg/min) in the group with <= to one complication compared to those with >1 complication.[23]

Wilson et al. demonstrated in 859 patients over 55 years of age undergoing major abdominal surgery that an AT <10.9ml/kg/min, VE/VCO2 >34 and history of ischaemic heart disease were significant predictors of 90 day mortality. The most significant effect was seen in patients with a reduced AT without a history of cardiac risk factors. [24]

153 patients were assessed with CPET prior to major colorectal surgery and stratified into AT>= 11ml/kg/min and those with an AT<11ml/kg/min in a study comparing ward care with critical care services and post-operative complication rate.

55 patients had an AT >= to 11mls/kg/min and were triaged to ward care post-operatively and 98 patients had an AT <11mls/kg/min where 39 were allocated to ward care and 51 to the critical care unit (CCU). 7 patients allocated to the ward with an AT <11mls/kg/min had a cardiac events, whereas no patients with an AT <11ml/kg/min triage to CCU or with an AT >/= to 11ml/kg/min had a cardiac event post-operatively.[25]

108 of 204 patients were assessed using CPET prior to hepatic resection. An AT <9.9 ml/kg /min was predictive of mortality and a VE/VCO2 = 34.5 at AT was predictive of perioperative complications.[26]

415 patients underwent CPET testing prior to open and endovascular abdominal aortic aneurysm repair. An AT <10.2 ml/kg/min, peak VO2 <15, VE/VCO2 >42 and inducible cardiac ischaemia were associated with 30 and 90 day mortality on univariate analysis. Multivariable analysis demonstrating an AT< 10.2 ml/kg/min was associated with 30 day mortality and peak VO2 <15 ml/kg/min at 90-day mortality. Both AT and peak VO2 with two sub threshold values was associated with both 30 and 90 day mortality on multivariate analysis.[27]

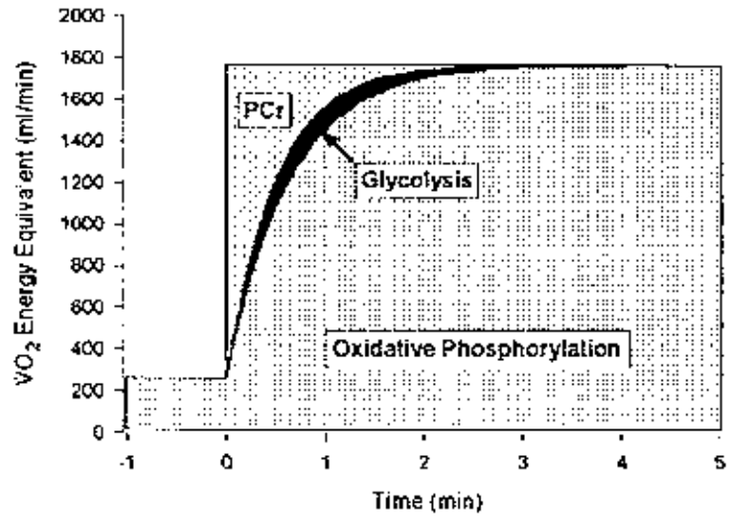
ANAEROBIC THRESHOLD, EXERCISE CAPACITY AND ANAESTHESIA

The surgical population is increasing with age, comorbidities and intervention rate.[7,18] A good practice of post-operative care occurs in 58%[1] of elective patients and 37.5% in patients greater than 80 years of age.[19] A high-risk surgical population account accounts for 80% of mortality and 12.5% of surgical procedures and less then 15% will be admitted to intensive care services.[20] A single post-operative complication is associated with a median reduction in survival of 69% independent of preoperative risk.[21]

Age is associated with higher ASA status, organ systems dysfunction, multiple medications, poor physiological reserve and acute surgical presentation.[1,16,17,19,20,21] Ageing reduces exercise capacity due to changes affecting muscle mass, cardiovascular function[54] and pathophysiology.[55] A higher level of fitness parameters including peak VO2 is associated with a reduction in all cause mortality, particularly relating to cardiovascular risk.[56] Peak VO2 declines more in men than women with age[57] and AT appears to decline less with age than peak VO2.[61]

Exercise capacity is associated with the ability to aerobically generate ATP,[58] which is reduced in individuals with heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, and diabetes.[59]

Figure 8. Potential contribution of metabolic pathways at onset of exercise



Schematic illustrating the potential sources of ATP, expressed in VO2 energy equivalents, at the onset of moderate intensity exercise (steady-state VO2 = 1750mL/min or 50% VO2 peak for individual with VO2peak = 3500mL/min. The major source of energy in the first few seconds of exercise is Pcr hydrolysis. The net contribution from anaerobic glycolysis to ATP supply will be expected to vary as a function of the rate of increase in oxidative phosphorylation during this transition in metabolic demand.[58]

Older has suggested that chronological age differs from physiological age with regards to anaerobic threshold, and the decline in AT depends more upon co morbidities and fitness than age, and suggests that physiological rather than chronological age should be used to risk stratify patients for surgery.[13,14,60]

Snowden has demonstrated that the decrease in cardiorespiratory fitness across all age groups correlates with post-operative mortality, and in decedents, age is associated with reduced cardiorespiratory fitness and increased mortality.[15]

The average oxygen consumption following major surgery is 4.5-5ml/kg/min and may be as high as 6-7 ml/kg/min. Post-operative cardiac output will have to be approximately 65-70% greater than it was for the same oxygen consumption for CPET due to the lower oxygen extraction ratio following surgery when comparing post-surgical metabolic stress with CPET O2 consumption.[11,12]

Surgery on different organ systems appears to demonstrate differing post-operative physiological demands. An AT <10-11ml/kg/min identifies increased perioperative morbidity and mortality in patients undergoing major abdominal surgery.[13,14,23,24,25] Low risk lung resection surgery is associated with a VO2max >20ml/kg min, and correlates with post-operative morbidity <10% and mortality </= 1%. [35] An AT <10.2 ml/kg/min, peak VO2 <15, VE/VCO2 >42 and inducible cardiac ischaemia identifies high-risk patients for 30 and 90 day mortality undergoing abdominal aneurysmectomy.[27]

The AT for abdominal surgery may be a surrogate marker of some other physiological parameter of bowel function. The bowel may not have the same tolerance to hypoxaemia as skeletal muscle as there is post-operative bowel wall oedema, anaemia and depressed cardiorespiratory function due to the effects of anaesthetic drugs and surgery. The AT during exercise reflects the ability of the cardiorespiratory systems to maintain the aerobic regeneration of ATP, and for bowel function, may represent a physiological requirement for patient survival.[61]

CPET is currently limited by the paucity of multi-centred blinded trials in risk assessment. Most trials are single centred and four studies have exceeded 300 patients in the use of CPET for perioperative risk assessment.[14,15,24,29] Prediction of five-year mortality has not been substantiated with univariate analysis of CPET variables.[29]

The METS Study[62] is a multi-centred international trial based in Toronto, Canada, comparing CPET to physician's subjective assessment of functional capacity, DASI and NT proBNP in patients undergoing non-cardiac surgery. The primary objective will be the comparative prognostic assessment of 30-day mortality and non-fatal myocardial infarction, and mortality at one year.

The Substudy of the METS Study[63], based at the Alfred Hospital, Melbourne, Australia has the primary aim to assess whether the preoperative 6MWT is predictive of quality of recovery at 30 days and disability free survival at 12 months following elective major non-cardiac surgery.

Secondary objectives are to study the correlation between the 6MWT and CPET in their ability to risk stratify elective patients having major non-cardiac surgery.

Several centres across Australia and New Zealand will be involved in The METS trial and Substudy of METS Study.

ACKNOWLEDGMENT

I would like to thank Karlman Wasserman, Paul Older and Grant Mawston for their suggestions with this article.

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Orphan outcomes, risk and ethical collaboration

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SCENE: HOSPITAL PRE-ADMISSION CLINIC

The first patient of the day is a 70-year-old female with hypertension, ischaemic heart disease (previous myocardial infarction), chronic airways disease and type 2 respiratory failure, on intermittent supplemental home oxygen, type 2 diabetes, chronic renal failure (creatinine=180 µmol/mL), BMI=35. She presents for elective total knee replacement. Her pain medication is a fentanyl patch. She reports the operation is being undertaken for the relief of pain, and because "the doctor says my X-ray will only get worse". She has been on the waiting list for 10 months, and has a date for surgery in six weeks' time. The patient says the surgeon has told her that his surgery is "very safe", and likely to lead to a good result, but because of her medical condition, she is a bit "risky". She has been advised that she will need to talk to the anaesthetist about the risk of the anaesthetic.

"Anesthesia is an adjunct to the care of the patient; hardly ever is it an end in itself....Anesthesia... is not of itself the therapeutic act which makes possible the correction of deformity, the restoration of health, or the staying of death. It merely makes possible the acts which can accomplish these things. The inseparability of anesthesia from the total care of the surgical patient is to us the compelling reason why surgeon and anesthetist, engaged as they are in a common task, cannot with profit pursue separate goals." (Beecher and Todd, 1954)[1]

ANAESTHESIA – ATTRIBUTABLE RISK

Beecher and Todd summarise the state of play well – the core business of an anaesthetist is to enable a successful operation, with a good patient outcome as a result. At the time of Beecher and Todd's report (1954), the anaesthesia – attributable death rate was estimated at 1:1560 (0.06%, a figure which was considered high enough to constitute a "public health concern". Since the early 1960s, Australian anaesthetists have been at the forefront of international work which has more clearly defined the risks of anaesthesia.[2] The most recent Australian report[3] reveals death as a complication of anaesthesia occurring at a rate of approximately 1:55,000 (0.002%) operative procedures. The precise definition of anaesthesia-related mortality in the Australian context varies between the states, but in the majority of those regions participating, appears to encompass death occurring within 24-48 hours of a surgical procedure.

However, anaesthesia-related deaths (at 0.002%) contribute only a tiny proportion of overall procedural mortality. Thirty-day post-operative mortality is a widely accepted (although interestingly, rarely publically reported) measure of surgical outcome.[4] Much of the data informing all-cause post-operative mortality (usually addressing 30-day all-cause mortality) appears in the anaesthesia literature. Surgical literature addressing outcomes (especially 30-day outcomes) is often confined to specialised surgical journals, and is often relevant to sub-specialty surgical fields (for example, cardiac surgery, vascular surgery, colorectal surgery etc). However, there are several large scale surveys looking at 30-day outcomes relating to pooled non-cardiac surgical procedures from Europe[5] and North America[6], and one survey from Australia.[7] Unique among developed nations, New Zealand has commenced collecting and publicly reporting (via its Post Operative Mortality Review Committee, POMRC) national 30-day post-operative mortality.[8] Many of these surveys and reports combine elective and emergency procedures, and the results are remarkably consistent. The evidence suggests that pooled outcomes from all surgical interventions (elective plus emergency) result, on average, in a 2-5% 30-day all-cause mortality, with mortality rates after surgery rising inexorably with age.

BACK TO THE PRE-ADMISSION CLINIC:

So what do we tell this patient? Do we limit our discussion to anaesthesia-related mortality? As the anaesthetist representative in the clinic, do we discuss only those complications over which we may have some control, and about which we have excellent, local and contemporary data, that is death within 24-48 hours of anaesthesia, possibly due to anaphylaxis, difficult intubation, and potentially, perioperative myocardial infarction? Or do we widen the discussion to include her 30-day mortality risk? Who "owns" this procedural risk? Is it a potential surgical complication? Or a potential anaesthesia-related complication? Who therefore has the responsibility to provide patients with information about this risk? How do we ensure that other specialist colleagues provide us with the best information to inform this patient about her perioperative risk, and optimise her condition, should she elect to proceed with surgery? How do we find the best evidence to inform the risk of all-cause mortality for this patient? And is this information likely to be of much, or any, interest to the patient, or affect decision-making for elective surgery?

30-DAY ALL-CAUSE POST-OPERATIVE MORTALITY: THE EVIDENCE

The prospective European Surgical Outcomes Study[3] of 46,500 patients demonstrated an overall pooled crude in-hospital mortality rate of 4% after all surgery, including a death rate of 3.6% in the UK. North American data for selected non-cardiac procedures demonstrated a pooled 30-day mortality rate of 3% (ranging from 0.55% for laparoscopic cholecystectomy, to 6.5% for colectomy).[4] Of greater significance for our population, Australian data from the REASON trial[5] demonstrates for patients over the age of 70 years, an all-cause 30-day mortality of 5% after all non-cardiac surgery, and a 30-day mortality rate of 3% for patients having elective surgery and requiring more than one night in hospital.

The 2011 report of the NZ POMRC[8] demonstrates an overall 30-day mortality rate for elective knee arthroplasty for patients between 65-79 years of 0.70%.

If we agree the patient presenting for elective knee arthroplasty needs to understand mortality risk, what data do we use? Do we know our own hospital outcomes? Do we have any valid Australia-wide data? Can we use the New Zealand data (above) – is it relevant in our own country, or at our hospital? Are patients in New Zealand comparable to those in Australia presenting for elective joint replacement? The 2011 POMRC report demonstrated that in New Zealand over a four-year period (2005-09) a total of 25,617 elective knee replacement procedures were performed. Of these approximately 20% of cases were performed on patients of ASA3. Fewer than three operations on ASA4 patients were performed. The ASA score was never intended as a preoperative risk prediction tool. What, therefore, do we really know about the preoperative risk factors of patients presenting for joint arthroplasty surgery in New Zealand? And what do we know about the post-operative processes in that country (such as use of high dependency or intensive care wards) which we may rely on for post-operative care?

DEATH – A SURGICAL, ANAESTHETIC OR "ORPHAN" COMPLICATION?

Given that much of the data and hence debate about the subject of 30-day all-cause post-operative mortality appears in the general medical or anaesthesia literature, it is likely that many surgeons (like our hypothetical surgeon referred to in the introduction) may not consider 30-day mortality a "surgical" complication. Many (approximately 30 to 50%) of these deaths appear to be cardiac,[9] and others are likely due to thromboembolic events, generalised sepsis, respiratory failure and other "non-surgical" outcomes. Many anaesthetists may concur with the apparent view of ANZCA and other anaesthetic groups that we "own" adverse outcomes occurring only in the tight 24-48 hour post-operative timeframe. Anaesthetists may therefore consider 30-day all-cause mortality as "not our problem", and hence not an anaesthetist's responsibility for discussion at a preoperative consultation. Intensivists may see and assume care for some of the patients who are at risk for poor post-operative outcomes, but in many Australian hospitals may not be involved in preoperative decision making for surgery. General practitioners, who often initiate the referral for surgical opinion, may also be unaware of the data informing preoperative patient risk and post-operative outcomes. It is possible, therefore, that many patients are not aware of this information when they provide "informed consent" for surgery.

Cardiology referrals are frequently undertaken for preoperative patients. It is likely most anaesthetists would consider a cardiology referral appropriate for our hypothetical patient. Especially for patients with a history of ischaemic heart disease and unassessable functional reserve, specialist consultations may provide essential information for patients and anaesthetists. However these consultations are only of value when the right questions are asked at the time of referral. The most recent guidelines from the American College of Cardiology/American Heart Association Task Force[10] recommends that if a (cardiology) consultation is requested, "then it is important to identify the key questions", and that the consultant "must provide a comprehensive assessment of the patient's risk". Fleisher et al state that "the purpose of the preoperative evaluation is not to give medical clearance but rather to... provide a clinical risk profile that the patient, primary physician and non-physician caregivers, anesthesiologist and surgeon can use in making treatment decisions that may influence short and long-term cardiac outcomes."

The 30-day mortality risk can perhaps be viewed as a "procedural" complication, although where the responsibility lies to discuss this with patients may yet be unclear. What seems beyond dispute is that at least some informed and engaged patients would likely consider all-cause post-operative mortality information somewhat relevant to their decision-making processes. This information is also relevant to clinicians (especially anaesthetists) who are responsible for appropriate targeting of post-operative high dependency or intensive care beds. And departments and hospitals interested in improving post-operative outcomes for their patients are also likely to be interested in their institutional results. Without such results, and in the absence of valid outcome data, hospitals and clinical units may find opportunities and capacity for improvement constrained.

Anaesthetists have long had an interest in risk stratification, risk prediction, risk communication and risk management. The ASA classification was devised after a sub-committee of the American Society of Anaesthetists was charged in 1940-41 with the task of studying and devising a "system for the collection and tabulation of statistical data in anesthesia".[11] However, it was determined that the development of a preoperative "risk" score was too complicated, and that the development of a physical status score ("descriptor") was more realistic, and would likely be more useful. It was revised and announced to members of the American Society of Anesthesiologists in 1963.[12] Notwithstanding the subjectivity inherent in the ASA score, and its relative 'clunkiness', its continuous use by anaesthetists for over 50 years supports the view that anaesthetists are well placed to assess and communicate perioperative patient status and risk.

WHAT INFORMATION SHOULD PERIOPERATIVE CLINICIANS (INCLUDING ANAESTHETISTS) PROVIDE PATIENTS?

Lipworth, Strong and Kerridge[13] argue that it is expected that doctors tell the truth; patients can only make informed decisions if they are in full possession of the relevant facts. "Truth telling in medicine is also seen as a manifestation of respect for patients, both as a way to improve health outcomes by involving people in their own care, and as a way to maintain trust between doctor and patient".

The standard ethical framework provided to medical and nursing students, and to practising clinicians is derived from the work of Beauchamp and Childress dating from the 1970s. These authors described the four principles underpinning biomedical ethics:[14] respect for autonomy, nonmaleficence, beneficence and justice. Arguably, and with specific regard to surgical decision-making, there is always a required "trade-off" between the likelihood of doing good (beneficence) versus the risk of harm (maleficence). Respect for patient autonomy requires that patients are informed about the expected outcomes from surgery, including the risk of adverse outcomes (acknowledging the uncertainty around measurement of this risk). In order to respect patient autonomy, patient's values, including tolerance of risk (of good or bad outcomes) must (according to Beauchamp and Childress) be of the utmost importance in decisions for, or against, any medical intervention.

Another widely respected modern ethicist, Julian Savulescu[15] describes an approach of "rational, non-interventional paternalism". He argues that doctors ought to be more than medical information providers in a shared decision-making platform. Savulescu's approach is to encourage doctors to act as "argument provider", in order to encourage patients to clarify their own values, and thereby improve the quality of their healthcare decisions. Under Savulescu's model, the doctor will have a rational view about what is "best" for the patient, and will attempt (by rational argument) to convince the patient to share this point of view. To successfully negotiate these conversations with patients, Savulescu argues that doctors require "new skills". He summarises thus:

"Medicine is entering a new era. Doctors are now required not only to have medical knowledge, but knowledge of ethics, of what constitutes a value judgement, of the fact/value distinction, of how to make value judgements and how to argue rationally about what ought to be done. This requires new skills. It is relatively easy to be a fact provider (though how to present facts itself presents a problem). It is easy to turn decision-making over to patients and say 'There are the facts – you decide'. It is difficult to find all the relevant facts, to form evaluative judgements and critically examine them. It is even more difficult to engage a patient in a rational argument and convince him you are right. If doctors are to avoid the shortcomings of being mere fact providers, if they are to function properly as moral agents, if they are to promote patient autonomy, they must learn these new skills... gone are the days when they could make uninformed judgements of what was best for their patients and act on these. Gone too are the days when they did not have to provide a justification for the position they were advocating. And that justification goes beyond the fiction of a 'purely medical' justification".

In his introduction to the National Confidential Enquiry into Patient Outcome and Death (2011) "Knowing the Risk",[16] the enquiry chair Mr Bertie Leigh commented that the National Health Service needed to move on from the "standards of benevolent paternalism that society... expected in the 1970s". In Leigh's words, "our society increasingly expects patients to be managed with Decision Aids and other professional techniques for raising the quality of the patient's understanding of what is involved and their participation in decisions about their treatment". This report recommended (for consultant medical officers, and in relation to surgery) that "an assessment of mortality risk should be made explicit for the patient and recorded clearly in the consent form and on the medical record". Unfortunately, the report gives no clear advice as to how such a risk assessment can or should be made. The report acknowledges that accurate quantification of patient risk is a "complex" challenge.

HOW DO WE BEST INDIVIDUALISE PATIENT RISK?

Risk is evaluated within a conceptual framework, which allows consideration of whether treatment should be pursued. Controversially, the concept of "futility" is often used where the burdens of the intervention clearly outweigh the benefits. The concept of futility in itself is worthy of research, "however there is no agreement as to whether assessments of futility should be quantitative or qualitative, and how burdens and benefits should be defined … this recognises that there are many outcomes other than survival that matter to patients".[13] How is risk currently measured, and how adequate are these measures?

The ASA score is well known to Australian anaesthetists. Despite the fact that the ASA score was never intended as a risk predictor, increasing ASA score does correlate with increasing likelihood of post-operative morbidity and mortality.[17] The ASA score is simple to use, but has been criticised for its lack of "granularity",[18] its inherent inter-observer variability,[19] and its failure to incorporate any aspect of the surgical condition or procedure.

Since the 1990s there has been renewed interest in the development of patient-specific risk prediction tools. Subsequent to Goldman's original description'[20] the best known tool is Lee's Revised Cardiac Risk Index.[21] This tool enables a patient-derived risk score for the likelihood of cardiac death or major complications to be calculated on the basis of surgical procedure risk and various patient-related data. However even the highest risk subgroup in the Lee classification has a mortality rate of 11%, and the score does not include adverse outcomes due to, for example, sepsis, respiratory failure or thromboembolic events.

The Charlson comorbidity index was developed in 1987, and subsequently validated as an age-comorbidity index (the Charlson Age Comorbidity Index, CACI) to predict long-term outcome after non-cardiac surgery.[22] However, as with the ASA score, the CACI does not incorporate surgical information, and is subject to subjectivity in reporting patient comorbidity.

Recently a composite index derived from the ASA score, emergency status and surgery risk class has been developed – the nine-point Surgical Mortality Probability Model (S-MPM),[23] which predicts all-cause mortality. These authors suggest that the S-MPM "may play a useful role in facilitating shared decision-making, developing and implementing risk reduction strategies, and guiding quality improvement efforts".

Scoring tools which have received significant attention in the surgical literature include the POSSUM and related P-POSSUM[24] (and others of the POSSUM family) scoring systems for estimating the risk of in-hospital all-cause mortality after a surgical procedure. Although originally described as a means by which hospital outcomes can be risk adjusted, POSSUM scores have been proposed by surgeons as an "estimate of risk" for preoperative patients, in order that patients can be provided with "as much information as possible to make fully informed consent."[25] While well validated, these scores have been criticised as over-estimating death rates at the extremes of age and for low-risk surgery. And while potentially useful preoperatively, the tools require some estimation of intra-operative variables such as blood loss and peritoneal soiling (for gastro-intestinal surgery), in order to validly predict outcome for elective or emergency surgical patients.

Other tools developed by surgeons, and mainly used to risk-adjust patient factors for benchmarking or comparative audit include the Surgical Risk Scale (SRS),[26] the Identification of Risk in Surgical patients (IRIS) score[27] and E-PASS.[28] The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) has similarly allowed for risk adjustment for the purposes of inter-hospital comparison of surgical outcomes.[29]

COLLABORATION AS A PROFESSIONAL AND ETHICAL DUTY

The CanMEDS framework[30] describes the competencies that are required for medical education and practice, in order to provide optimal patient care and outcomes. ANZCA's revised curriculum emphasises the seven roles in practice (based on the CanMEDS roles), one of which is the "collaborator" (see figure). For an accepted definition of collaborator, see below.

Royal College of Physicians and Surgeons of Canada | CanMEDS

The Macquarie dictionary definition of collaborate is: 1. to work, one with another; co-operate, as in literary work, or 2. to co-operate treacherously: *collaborating with the Nazis*.

For ANZCA, under collaborator, the required key competencies are to:

1. Participate effectively and appropriately in an interprofessional healthcare team.
2. Effectively work with other health professionals to prevent, negotiate, and resolve interprofessional conflict.

THE WORKING RELATIONSHIP BETWEEN SURGEON AND ANAESTHETIST – ETHICAL COLLABORATION

The surgeon and the anaesthetist have clear and distinct roles and focus. However, once surgeon and anaesthetist have entered into a relationship with a patient, from both logical and ethical perspectives, they can no longer "silo" their individual contributions. The patient is likely to view everyone and everything involved in perioperative care as a system functioning with them (the patient) at the centre of the enterprise. Our hypothetical surgeon apparently views the role of the anaesthetist as the "gatekeeper" to surgery. In this view, the surgeon's actions are without downside, and any risk "belongs" to the anaesthetic (and hence to the anaesthetist). And in this world, it is thus the responsibility of the anaesthetist to communicate all the bad news, and "close the gate" to all high-risk patients. Fortunately, although this model of surgical behaviour may have been historically widespread, few real- life surgeons behave this way today.

Effective collaboration requires that Beecher and Todd's "common task" of the surgeon-anaesthetist is enacted with a shared aim and outcome (safe, effective and high-quality patient care). In order to produce the best patient outcomes, surgeons, anaesthetists and others involved in perioperative care will ideally come together under the institutional "umbrella" of a hospital, in order to review policies, processes and models of care, and identify opportunities for improvement. Post-operative mortality is already perceived as a valid measure of surgical care – this data is collected and reported in Australia under the ANZASM framework, and co-ordinated via the Royal Australasian College of Surgeons.[31] Feedback is given to individual surgeons. But this outcome measure has relevance to more stakeholders than just surgeons. Ideally, in the future, all-cause post-operative mortality will be reported to hospitals and health districts, so that multi-disciplinary surgical teams (including surgeons, anaesthetists, intensivists and others) can review and improve surgical outcomes.

The anaesthetist's duties are never enacted in isolation; technical and ethical decisions are always enacted within a relational framework (between peers and colleagues, medical staff and patients), and then even more broadly, as a result of community engagement. The way we conceptualise service delivery and doctor-patient relationships is also socially constructed and reflects the times in which we enact them. Despite good intentions on the part of individuals, and even without conscious awareness, there are many factors that influence decision-making. Seedhouse[32] suggests that no problem arises and no decision is made separate from instincts, emotions and values; they will always influence our logical, reasoned decisions, whether we are aware of these influences or not. Further, these influences will inform the evidence we choose to draw on in making decisions. These values are enacted at all levels of relationships. For anaesthetists, the levels of influence will range from community, systemic (local health district, hospital), economic (resources, funding and remuneration), professional and individual relationships, particularly with surgeons and patients.

Savulescu's work[13] highlights the challenges in maintaining effective doctor-patient relationships, while providing "arguments" to patients in an attempt to demonstrate a rational course of action. Particularly within a culture where healthcare is viewed as an "entitlement", these conversations with patients may be difficult. Patients may view the discussion as not about their best interests, but as an attempt to deny them a service to which they feel they are entitled. On occasion, patients may respond emotionally. Anaesthetists will require skills to handle emotionally laden conversations, and for some anaesthetists these will be examples of Savulescu's "new skills".

For anaesthetists, to discuss perioperative risk with surgeons may also be a (sometimes surprisingly) difficult conversation. One reason for this may be that for a surgeon, professional identity is inextricably linked with the decision to operate, and any suggestion that this decision is flawed or inappropriate may be viewed as a threat to "surgeon autonomy". Some anaesthetists may feel that providing outcome data (such as 30-day mortality) to patients constitutes an unacceptable intervention in the surgeon-patient relationship. Other anaesthetists may be uncomfortable in overtly influencing decisions that may impact on a surgeon's (or potentially their own) income. The potential for "capture" (of one professional group by another) may also be relevant. This implies that one role (for example, anaesthetist) is at risk of becoming subservient to the priorities and preferences of the more powerful role (in this example, the surgeon), and fails to keep patients' preferences and outcomes as a priority. Each of these areas is ripe for ethical reflection and review.

PROFESSIONAL REQUIREMENTS AND IMPLICATIONS FOR TRAINING "ETHICAL COLLABORATORS"

Much of professional life as a medical specialist involves exploring and acquiring knowledge within one's own specialty, and yet in the service of patients there is an expectation of mutual understanding, co-creation of knowledge and relational flow in arrangements.[33]

Dominant values in healthcare reflect this required mutuality in the focus on collaboration, and patient-centred decision-making. Both require relational involvement; they are by their very definition, about relationships and cannot be reduced solely to individuals, procedures and processes, although all have a role in conveying the terms of the relationships to all parties. Ethical decision-making is also relationally constructed and enacted, and the quality of the collaborative effort will depend on the quality of information available and provided (to all parties), and the awareness of shared ethical principles and requirements.

It is somewhat of a paradox therefore, that when, in relationship to the patient, outside of the operating room the surgeon and the anaesthetist continue to "collaborate separately" with the patient. Collaboration is enacted in how each represents the other; in what way the tasks of each are distinct, and which are shared. Ideally this would be directly discussed and clarified within surgical teams; in reality the co-operative venture is more likely to be enacted by assumption about the other's role and the habits of one's own profession, neither of which may result in nor reflect the collaboration that is desired. For anaesthetists, one example of this is in the discussion of surgical risk.

In light of the potential for difficult conversations, anaesthetists may consider equipping themselves and their trainees with improved conversation skills, acknowledging the hidden emotional and "identity-related" content of all conversations. The work of the Harvard Negotiation Project[34] may be useful for trainees and consultants. These writers simplify conversations to three "layers". The simplest of these is the "facts" conversation (for example, anaesthetist to surgeon "Your patient has a 10% mortality risk for this procedure."). The second layer to this conversation is the "feelings" conversation (for example, the surgeon may 'hear': "This is a high risk patient, and your decision to operate is poor"). And finally, the "identity" conversation (for example, the surgeon 'hears': "You are the sort of surgeon who always makes poor decisions to operate"). The key to dealing with difficult issues is the acknowledgement of layers of conversation – conversations relating to facts, feelings and identity. By taking a "learning" perspective, anaesthetists will more effectively deal with the challenges of discussing risk information with patients and colleagues.

FUTURE CHALLENGES

With ageing populations and increasing expectations of healthcare systems, anaesthetists are meeting older and sicker patients presenting for elective surgery. Evidence from the field of behavioural economics, and especially the study of road safety show that "risk" tends to have its own homeostasis.[35] That is, the safer a perceived activity (such as driving on a section of highway after a safety upgrade), the more individuals will compensate with increasingly risky behaviour (faster driving), so that the outcome (accident rate, mortality) remains relatively constant. Known as the Peltzman effect, this has also been described as "the natural progress of opulence".[36] For surgery, the corollary may be that increased perceptions of safety (due, for example, to improved anaesthesia outcomes, and increasing use of intensive post-operative resources) have led to higher and higher risk individuals being offered surgery (on the grounds that overall survival has improved markedly), whereas their risk may have previously been considered "prohibitive". As perceived risk impacts behaviour, without valid outcome data it may be difficult to disentangle "perceived" from "actual" risk.

As healthcare systems increasingly look to provide value for interventions and spending, outcome measures become pivotal to decision-making. Anaesthetists are already involved in making decisions for resource allocation for surgical patients, for example, identification of high-risk post-operative patients who require intensive care or high dependency care. There is little hard data to inform these decisions, but in a resource-constrained system, anaesthetists should expect that such decisions and recommendations will be scrutinised by clinicians, administrators and patients. Particularly when these resources need to be prioritised and/or rationed, outcome data will be required in order to justify such decisions.

If anaesthetists are to continue to play a significant role in effective risk communication and risk management of surgical patients, the following should be considered:

1. Need for better data. Thirty-day post-operative all-cause mortality is already an accepted measure of surgical care, and in Australia, is currently included in reporting to surgeons as part of their continuing professional development, through the voluntary ANZASM process. It is timely for Australia to follow the lead of New Zealand in this area, and establish public collection and reporting of surgical outcomes. Attempts also should be made to identify other post-operative outcomes, which are relevant to patients, and which reflect the quality of decision-making for surgery, and of the surgical journey.
2. Better platforms for data sharing and quality review. Given that anaesthetists and others influence the perioperative care and outcomes of surgical patients, a collaborative approach to joint reporting, reflecting and acting on outcome data would likely result in better patient outcomes. It is also likely that this collaboration will best occur under the "umbrella" of a hospital or clinical unit. Only by reporting and examining outcomes, can outcomes be improved. And only by involving all clinicians who influence patient care, can processes and systems be constantly refined.
3. An increased focus on "risk" – risk assessment, risk stratification, risk communication and risk management. Anaesthetists need to continue to move away from the "gatekeeper" role, where a patient is deemed "fit" or "unfit" for surgery. Anaesthetists are trained to understand and use "risk" metrics and language. Anaesthetists should focus on specific and explicit use of risk language when talking with patients and clinical colleagues. A more explicit "risk focused" discussion will help set appropriate expectations for patients, and allow for more appropriate alignment of scarce resources.
4. Better risk scoring tools. Valid risk prediction tools for post-operative mortality and morbidity can only be developed with better data, and with better sharing of outcome data. Anaesthetists are best placed of all craft groups to lead development of these tools.
5. An increasing focus on communication skills training, for anaesthesia trainees and senior doctors. Discussion of risk can be challenging for clinicians and patients alike. Anaesthetists need training in the skills required to have difficult conversations, both with patients and with colleagues. They will also need skills to support patients in clarifying their values (including their tolerance of risk), and to make decisions, which conform to those values.

"The two great goals are facilitation of therapy (the surgical procedure in this case) and the patient's safety. Notwithstanding the frequent attempts to emphasize one of these aspects over the other, it is clear that in reality they merge into the single goal: a successful therapeutic procedure." (Beecher and Todd).

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Royal Dental Hospital Day Surgery Unit – The same as other day surgery units, but different

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Dr Tony Bajurnow has an interest in providing high quality perioperative care for patients, many with disabilities, undergoing dental surgery. He has previously conducted research on informed consent in this challenging area.

INTRODUCTION

The Royal Dental Hospital Melbourne is the only free-standing public dental day surgery unit in Australia. It is a dental facility, not a Medicare facility, and can only treat pensioners and healthcare card holders. Our patient population comes from across Victoria and travelling time to and from the day surgery unit may be up to eight hours on the day of surgery. The age of our patients ranges from one year and the oldest person anaesthetised was 91 years old.

There are several factors that are increasing the challenges to day-stay anaesthesia. The population is growing older and developing more medical problems while keeping their teeth longer, added to this is an increase in the numbers of patients with autism spectrum disorder and other behaviour management problems.

Many of the management principles discussed may be applied to dental anaesthesia in general.

There are three broad categories of dental patients in theatre.

1. **Children:** We average 1716 children per year. We have a high percentage of children with autism spectrum disorder, ADHD and children who cannot be treated successfully with routine chair dentistry.
2. **Oral surgery:** Numbers average 1738 patients per year. These patients are booked for anaesthesia if the surgery is technically difficult or if the patient cannot be treated successfully with routine dentistry.
3. **Special needs:** Numbers average 282 patients per year. These patients are severely disabled by physical, medical, psychiatric or psychological problems and are unable or unwilling to attend for routine dental treatment.

Special needs patients are often unco-operative and it is difficult, and sometimes impossible, to have an adequate assessment of the patient's medical conditions before administering anaesthesia.

We carried out an audit of our special needs patients in 2006 – total of 286 patients. The percentage of these patients with additional medical problems are listed in Table 1.

Table 1. Percentage of special needs patients with additional medical problems. N=286.

Medical problem	%	Medical problem	%
Intellectual deficiency	73	Brain damage	8
Epilepsy	40	Wheelchair/bedridden	7
Cerebral palsy	20	Deaf	7
Dysphagia/reflux	18	Obesity	7
Cardiac problems	16	Hypothyroid	6
Blindness	10	Dementia	5
Down syndrome	10	Asthma	5
Autism	8	Chromosomal/other	5
Psychiatric illness	8	Severe anxiety	4

MANAGEMENT OF PATIENTS AT ROYAL DENTAL HOSPITAL DAY SURGERY UNIT

1. Pre-anaesthetic assessment of the patient

The difference between our institution and a medical institution is that the patients are referred for anaesthesia by dentists. The two main points to consider is that the dental referral often lacks a proper medical assessment and, after discharge the patient is reviewed by a dentist, thus there is no medical continuity of care for the patient.

Gathering medical/anaesthetic information

The patient fills in a medical questionnaire at the time the dentist books them for theatre. If the patient requires further medical investigation then a letter is sent to the patient requesting that they attend their general practitioner to perform the requested pathology test. This is to ensure that there is a medical practitioner who can follow up any abnormal results to ensure continuity of care for the patient. If the patient has had operations previously then we request the anaesthetic and post anaesthesia care unit notes to be faxed to us. The patient may also be referred to our anaesthetic consult clinic and be assessed by an anaesthetist.

Guidelines on the types of patients NOT suitable for general anaesthesia at the day surgery unit
The following guidelines are to be used in conjunction with the Australian and New Zealand College of Anaesthetists (ANZCA) guideline *PS15: Recommendations for the Perioperative Care of Patients Selected for Day Surgery (2010).*

1. Patients over the age of 85.
2. Patients with cardiac problems:
   - Recent myocardial infarction.
   - Taking anginine.
   - Past history of CCF.
   - Unable to walk upstairs.
   - Patients with significant valvular pathology.
   - Needing arterial lines or CVP for monitoring.
3. Patients with significant functional or anatomical airway problems including marked difficulty with intubation.
4. Patients with bleeding disorders, for example, haemophilia, severe Von Willebrand's disease.
5. Renal dialysis.
6. Asthma or COAD with repeated admissions to hospitals.
7. Patients with a weight >140 Kg or BMI>45.
8. Quadriplegia.
9. Patients with no escort home.
10. Patients with no one to stay with them overnight (or if no cottage accommodation)

Please note: Where possible all patients over the age of 70 are to be booked into the anaesthetic consult clinic. Fit, healthy country patients over the age of 70 years may be booked for theatre after consulting the country patient's doctor and having normal full blood tests and ECG.

It would be preferable to see all patients with a BMI > 35 at the anaesthetic clinic.

2. Obtaining consent for elective dental cases
Dental work is elective and may be performed under local anaesthesia, under sedation or under general anaesthesia. The patient is given information about anaesthesia (Appendix 1) well ahead of the procedure date, and again on the day of surgery. This information includes the training requirements to become an anaesthetist, the risks of anaesthesia and the alternatives to general anaesthesia – sedation, or local anaesthesia by itself. The anaesthetist discusses the procedure with the patient on the day of surgery.

The day surgery unit consent form (Appendix 2) refers to the information about anaesthesia printed sheet, and lists the points that should be mentioned during the consenting process.

In Victoria, when the patient is unable to give consent, and there is no responsible person available, a form 42K – can be completed and permission to proceed with the operation can be obtained from the Office of Public Advocate.

To assess the effectiveness of our consenting procedure we conducted an audit of 500 patients.
Our results showed the following:

- 87% stated that they understood all the information; 5% understood about half the information, and 8% stated that they understood only some of the information. This means that about one in every 10 patients did not understand much, but still signed their consent form.
- 60% were reassured by the information; 40% were scared by the information. Despite 40% being scared by the information – 99% said the information should be given to everyone prior to surgery.

3. Our approach to management of unco-operative adult patients
A large number of our patients have been referred for general anaesthesia because they could not co-operate sufficiently to be treated by routine dental care.

Some of these patients are very big, strong and difficult to manage. Our approach to decreasing the risk of harm to the patient and the staff varies with the information that we have about the patient.

Most patients can be admitted routinely and a premed ordered once the anaesthetist has assessed them.

If the routine admission process has to be altered, because of the patient's behaviour, then it is important that all the staff involved are aware of the changes to the admitting process.

General guidelines on managing disruptive patients

1. Book these patients as first case on a morning list.
2. The patients should have their routine prescribed tranquiliser/sedative in the morning of their appointment.
3. If these patients have a sedative prescribed PRN for periods of severe agitation, then this can be ordered prior to them leaving for the day surgery unit.
4. The staff involved in the patients care may request extra sedation for the patient in the morning of the procedure. This is best ordered by the patient's usual doctor. Commonly prescribed medications are:
   - Temazepam 20mg.
   - Diazepam 5 to 10mg.
   - Oxazepam (Serepax) 30 to 60mg.

Without seeing the patient it is not advisable to order a sedative over the phone.

Children are not ordered sedatives prior to leaving for the day surgery unit unless they are taking sedative medication regularly in the morning.

In the most difficult patients, a process of admission has to be agreed on by all people involved in the management of the patient (Appendix 3). The agreed course of action is printed and distributed to the carers and the day surgery unit staff involved with the patient on the day of admission.

4. Premedication
The decision as to whether a patient requires a premed and how it is to be administered is made after the anaesthetist has seen and discussed the anaesthetic with the patient and or parents/carers involved with the patient.

The dose of the premedication drugs in mgm/kg often varies with the anaesthetist. Some anaesthetists only use premeds in exceptional circumstances, while other anaesthetists routinely premed all paediatric patients.

Some commonly used premedications are:

- Midazolam. Dose range (0.25-1mg/kg) Usually maximum dose of 20mg PO.
- Clonidine. Dose range (1-4mg/kg) PO.
- Ketamine. Dose range (3-7mg/kg) PO or IM.

The above medications can be given as individual drugs or in combination but in reduced doses.

5. Restraining the patient to administer a premed or to induce anaesthesia
The sight of a child being forcefully restrained by staff either to administer midazolam intra-nasally, or while the patient is being induced for anaesthesia, has the potential to upset the parents, and there have been instances where the parents have tried to stop the procedure from continuing. Restraining of children should occur only with the prior knowledge and consent of the parent/s and this should be noted on the consent form.

6. Explanation to parents of possible regression of child's behaviour
Parents of children with autism spectrum disorder are concerned about the effect the procedure will have on their child. They are very apprehensive about the effect of the drugs and the effect that the stress of the procedure will have on their child. The parents should be informed that it is not uncommon for the behaviour of these children to regress for a week or two following day surgery.

7. Anaesthetic technique
In the past, most dental procedures were performed with a nasal endotracheal tube. The day surgery unit was the first dental unit in Australia to use laryngeal masks for most dental procedures and the LMA is now used routinely unless there is a medical contraindication, or a special request is made by the operator for a nasal tube. Paediatric dentists still prefer to have a nasal tube because it gives them more room in the mouth. In these cases, if there is a contraindication to using a nasal tube, instead of using an LMA, it may be preferable to use an oral ETT as it is of a smaller diameter.

In theatre, dentists use local anaesthetic infiltration and the patient often wakes up feeling little or no pain. If an area is inadequately blocked during the procedure there is often a sudden rise in pulse rate and blood pressure. If this occurs the dentist should be asked to infiltrate the area with more local anaesthetic. The most common analgesics used for dental work in theatre are paracetamol and NSAIDs, and in post anaesthesia care unit, intravenous titration of fentanyl, or tramadol.

Monitoring the depth of anaesthesia
In the patients requiring heavy sedative premedication we have found that monitoring anaesthetic depth with BIS/Entropy has allowed very low agent concentration use. We have found this helpful in facilitating a rapid recovery in these heavily sedated patients.

8. Clinical Indicator review for five-year period at the day surgery unit
There were 17,557 general anaesthesia procedures performed during the review period, including paediatric, special needs and minor oral and maxillofacial surgery procedures. The incidence of morbidity requiring transfer to a hospital with overnight stay facilities was 0.13%. There were no cases of mortality recorded. The most common complication was low oxygen saturation.[1]

9. Post anaesthesia care
Those patients referred to the day surgery unit by dentists are discharged from the day surgery unit to be reviewed by dentists. The requirement that there is continuity of medical care of the patient following discharge is not met by this arrangement. To enable continuity of medical care after discharge the patients may ask for us to arrange the Melbourne Medical Locum Service to review the patient on the night of operation. This has been very effective in managing post-anaesthetic problems in our day cases.

About 10% of patients seen by the locum service in one year have active treatment by the locum service (Table 2).

The locum service is greatly appreciated by the staff looking after the special needs patients as well as ensuring continuation of medical care post-operatively.

Table 2. Locum assessment and treatment on the night of procedure

Medical problem	Number	Treatment
Pain	12	Prescribed analgesics
Febrile	3	Antibiotics prescribed
Short of breath	1	Admitted to hospital
Red eye	1	Eye drops
Bleeding	2	Cease aspirin, pressure to socket and review in AM
Very pale	1	Antibiotic prescribed
Motor car accident on way home.	1	Review by LMO in the AM
Hypotensive	1	Noted low BP in the past. Review if indicated tonight
Bilateral wheeze	1	Prescribed Ventolin

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APPENDIX 1 – ANAESTHETIC INFORMATION

This information will help you understand:

1. What is involved in having a general anaesthetic.
2. What complications may occur during your anaesthetic.
3. What alternatives there are to general anaesthesia.

Please read the information below, if you have problems understanding this form please discuss it with your anaesthetist.

General Information About Anaesthesia

When you have a general anaesthetic you are given anaesthetic medicine that makes you unconscious and pain free for the duration of surgery. During the operation you are constantly given a variety of anaesthetic medicine to keep you unconscious. When the operation is finished the anaesthetic medicine is stopped and you will wake up.

When a person is unconscious or has a general anaesthetic they cannot look after themselves. It is the duty of the anaesthetist to look after you while you are anaesthetised.

Who is your anaesthetist?

To become an anaesthetist you must become a medical doctor first, and then train in anaesthesia and intensive care for another 5 years.

Why do we ask a lot of questions before you have your anaesthetic?

The anaesthetic drugs we use are very powerful and can affect any structure in your body. To give a controlled anaesthetic with a minimum risk to you, we need information about:

- Age, weight and fitness level.
- Your medical conditions.
- Medicines or drugs you are taking.
- Any problems with general anaesthetics that you, or members of your extended family, may have had.
- Any known allergies.
- Time of last eating or drinking.

Failure to follow the preoperative fasting instructions may cause serious problems during your anaesthetic.

It is not possible to predict who will have an anaesthetic problem.

If you are young and fit there is less risk in having a general anaesthetic than in driving a car. Medical conditions, lack of fitness, smoking and increasing age are associated with anaesthetic problems. Some things happen extremely rarely, but have very serious outcomes, such as:

- Severe allergic reactions.
- Being aware or awake during anaesthesia.
- Nerve and brain damage.
- Death in healthy people.

More common anaesthetic events with less severe outcomes are

Fatigue, nausea, vomiting, sore throat, dental damage, sleep disturbance, altered mental state, bruising from venipuncture.

The Alternatives To General Anaesthesia

To reduce the risks associated with general anaesthesia you may consider having your dental procedure performed under local anaesthetic only, or have some form of sedation.

1. **Local anaesthetic injection**. The area of the operation is numbed by injection of local anaesthetic and you do not feel any pain during the operation.
2. **Gas Sedation**. Nitrous Oxide “Happy Gas” can be used to relax the patient during the operation. The gas is breathed continuously during the procedure through a mask placed on the nose. Local anaesthetic is injected to make the operative site go numb. The patient becomes relaxed and recall of the procedure may be reduced.
3. **Intravenous Sedation**. Sedative drugs are injected through a small cannula which is inserted into a vein. This is a stronger form of sedation than having gas. Local anaesthetic injection is used to numb the area of operation. The patient becomes relaxed and may have little memory of the procedure.

Discussion of Sedation

Sedation is not general anaesthesia. The patient is awake, but very relaxed, and usually does not remember much of the procedure. The risks of sedation are less than those with general anaesthesia but are not eliminated completely. During sedation the patient receives less medicine and usually has fewer side effects.

Use of sedation requires a cooperative patient and needs to be discussed with the anaesthetist and surgeon to determine whether it is suitable for your proposed procedure.

Meeting with your anaesthetist.

You will meet your anaesthetist either at a Preanaesthetic Clinic, or, on the day of surgery. The anaesthetist will discuss your anaesthetic management, postoperative pain control, and any questions or concerns that you may have prior to surgery.

I have read and understood the above information.

Name _____

Signed _____

Date _____

☐ Self ☐ Parent ☐ Guardian

APPENDIX 2 – ANAESTHETIC / SEDATION CONSENT FORM – DAY SURGERY UNIT

An interpreter was used ☐ Yes ☐ No

1. I have read "INFORMATION ABOUT GENERAL ANAESTHESIA" ☐ Yes ☐ No
   I understand what is written in it ☐ Yes ☐ No
2. The anaesthetist has discussed the anaesthetic and postoperative pain management with me. ☐ Yes ☐ No
3. Regarding Children – I understand that I will be responsible for holding/providing protective restraint for my child, as described by the anaesthetist. ☐ Yes ☐ No
4. I understand that
   a. There are very rare serious complications. ☐ Yes ☐ No
   b. There are some frequent less serious complications. ☐ Yes ☐ No

Notes _____

_____

5. I have been given the opportunity to ask questions and to express any concerns I have about the sedation or general anaesthesia ☐ Yes ☐ No
I have no concerns or questions or ☐ My concerns are _____

_____

6. I understand that to provide appropriate medical care in an emergency I / the patient may have to be transferred to another hospital. ☐ Yes ☐ No
7. I am satisfied with the information provided, and give my consent for the anaesthetic. ☐ Yes ☐ No

Notes _____

_____

My signature _____ Date _____

Witnessing Anaesthetist Name_____ Signature _____

APPENDIX 3 – ACTUAL EXAMPLE OF WRITTEN MANAGEMENT PLAN FOR SPECIAL NEEDS PATIENTS AT THE ROYAL DENTAL HOSPITAL DAY SURGERY UNIT

Instruction/Information Re "John Smith". UR 123456

Booked for RDH Day Surgery on _____

Carer name "Abee Ceed" and contact phone _____ and fax numbers _____

1. Patient "John Smith" to take normal medication at 6.00AM with clear Jelly.
2. No extra sedation prior to leaving home.
3. Arrive at 8.30 AM and Park in _____
4. Use Mobile phone to ring _____ just prior to arrival.
5. Patient "John Smith" will be seated in wheelchair with restraints applied.
6. Patient "John Smith" will be accompanied by carer "Abee Ceed" and 2 males.
7. Patient "John Smith "will have loose fitting sleeves which will allow an injection into the upper part of his arm.
8. An anaesthetist will meet you in the parking bay and accompany you straight to theatre.
9. Consent from "Mary Smith" (Phone _____ MOB _____) for the anaesthetic and dental work will be obtained prior to the day of procedure.
10. "Mary Smith" will attend to admission paperwork after patient "John Smith" is anaesthetised.

Anaesthesia in Australia's Top End

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Dr Brian Spain has been working in the Northern Territory since 1997 and has been involved in several projects looking at cross-cultural communication and healthcare, as well as being involved in the NT response to mass-casualty incidents and the daily care of indigenous and trauma patients.

INTRODUCTION

The Royal Darwin Hospital is located in Australia's Northern Territory (NT) on Larrakia land and is the territory's main tertiary referral centre. It lays 12 degrees south longitude with a monsoonal climate. The principal differences about medical practice in the NT are the high proportion of Aboriginal or Torres Strait Islander patients and the remote locations often involved.

In this article, "indigenous" will be used to describe a person who identifies as being of Aboriginal and/or Torres Strait Islander descent.

NORTHERN TERRITORY

Demographics

The Northern Territory population is approximately 229,000, representing only 1% of Australia's total, but 12% of the indigenous population. Up to 30% of the population of the NT identifies as Indigenous, compared to an average of 4% or less for the rest of the country.[1]

The NT is Australia's third largest state/territory but has the lowest population density; five times lower than the next ranked state of Western Australia.[2]

Royal Darwin Hospital

The Royal Darwin Hospital (RDH) is a 350-bed hospital with a catchment population of 150,000, many from very remote communities. Indigenous patients are over represented within NT hospitals, making up nearly 60% of all acute hospital separations.[3]

The RDH performs approximately 12,000 surgical cases a year, a high proportion of which are emergency. In the 2011-12 year 48% of the all theatre activity was emergency/non-elective.[3]

Table 1. Total number of elective and emergency surgical operations[3]

	2009-10		2010-11		2011-12	
	Elective	Emergency	Elective	Emergency	Elective	Emergency
Cases	6,526	5,301	6,173	5,621	6,618	5,908

The hospital treats a high incidence of trauma, twice as much per capita as the rest of Australia. In 2003-04 the NT rate ratio for deaths from motor vehicle accidents and falls were at least twice the national figure, whilst deaths from drowning and other "unintentional" injuries were at least three times the standardised rate. The NT rate ratio for homicide related deaths, compared to the rest of Australia was 5.13.[4]

National Critical Care and Trauma Response Centre (NCCTRC)

In 2005 the Australian Government funded the establishment of the National Critical Care and Trauma Response Centre at the Royal Darwin Hospital in response to the Bali bombings. The function of the centre is to ensure enhanced surge capacity in response to emergency medical and disaster incidents of national and international significance in the region.

The NCCTRC has funded the hospital to enhance its capacity for trauma surgery and disaster response, including additional medical, nursing and allied health positions. It is also focused on providing clinical and academic leadership towards disasters and trauma care as well as providing training and education.[5]

INDIGENOUS HEALTH

Integral to understanding the health of indigenous Australians is appreciating the importance that culture plays.

The history of colonialism, oppression and displacement of indigenous populations from their land and culture continues to have a direct influence on their wellbeing and interaction with health services today. Indigenous cultures are complex and diverse and it is important not to view them as homogenous.

Health of indigenous Australians

Disparity in health status between indigenous and non-indigenous Australians is large and multifactorial in aetiology. The disparity in life expectancy is greater than indigenous populations of other countries such as New Zealand Maori and North American Indians.[6,7]

Progress has been made in terms of life expectancy with figures from 2005-07 showing improvement, but a difference of 11.5 years and 9.7 years (men and women respectively) persists.[8] In terms of health burden, decreases in excess mortality are being offset by increases in the prevalence and severity of non-fatal conditions.[9] There has also been a shift in the burden of disease from primarily infectious conditions to non-communicable chronic diseases.[10]

There is limited detailed research about the health of the indigenous population who live in cities and towns.[11] The "urban" indigenous represent 74% of the total indigenous population and contribute 60% of the overall health gap.[12] The health gap is the number of healthy years of life lost through disability and death in the indigenous population compared to the total Australian population.[12] Illnesses leading to increased mortality include circulatory disease, cancer, injury, endocrine disorders (including diabetes) and respiratory disease.[13]

Substance abuse (smoking and alcohol) is a significant indigenous health risk factor. Figures (from 2007-08) suggest >50% of the indigenous NT population smoke, compared to 18% of female and 21% of male non-indigenous Australians nationally.[14] Although less indigenous than non-indigenous Territorians consume alcohol (49% vs. 89%), those who do are more likely to do so in a harmful manner (30% vs. 17%)[15]

Research at RDH reinforced this by showing indigenous patients presenting for surgery were younger, sicker (ASA status or prevalence of co-morbid disease) and required more emergency surgery than non-indigenous patients.[16] The likelihood of co-morbid disease in indigenous patients was significantly increased with relative risks of: renal failure 16 times, rheumatic heart disease 14 times, and diabetes four times those of non-indigenous patients.[16]

Rheumatic heart disease

Acute rheumatic fever is an illness caused by an immunological reaction to untreated infection (usually upper respiratory tract) with Group A streptococcus. Rheumatic fever and rheumatic heart disease are typically associated with overcrowding, poor sanitary conditions and other aspects of social and economic disadvantage.[17]

Prevalence rates of rheumatic heart disease have steadily increased to 2% of the indigenous population in the NT, 25 times the rate for other Australians. The highest rate is in the 25-44 year olds, where nearly 3% of the population is affected.[18] Indigenous Australians have among the highest documented rates of acute rheumatic fever and rheumatic heart disease in the world.[19]

Rheumatic heart disease is primarily a disease of the mitral valve, regurgitation being the commonest lesion. In indigenous patients, mitral stenosis progresses rapidly with onset of symptoms at a mean age of 33 years.[18] Aortic stenosis is uncommon, almost always occurring in conjunction with mitral valve disease.

Rheumatic heart disease is an important public health issue, as almost all cases are preventable. It is the result of repeated or prolonged episodes of acute rheumatic fever in childhood or adolescence. It can be prevented by strict follow up and monthly intramuscular injections of penicillin for a minimum of 10 years after the last episode of acute rheumatic fever, or until the age of 21 (whichever is longer). Those with moderate or severe rheumatic heart disease should continue prophylaxis up until 35 to 40 years of age.[18]

Understandably compliance with such prolonged regimes is challenging. Australian figures for 2008 showed 31% of patients missed half or more of their prophylactic penicillin injections.[18] Within the indigenous population poor adherence is considered only rarely due to injection refusal or lack of understanding about rheumatic disease. Instead, major factors relate to the availability and accessibility of health services. Adherence improved when patients felt a greater sense of personalised care and a sense of "belonging" to the clinic.[18]

Closing the gap

In 2008 the Australian Government committed to the "Close the Gap" initiative, which aims to improve the lives of indigenous Australians, in particular to provide a better future for indigenous children.

The initiative has six targets relating to indigenous life expectancy, infant mortality, early childhood development, education and employment.[20] The health-based goals include:

- To close the life expectancy gap within a generation.
- To halve the gap in mortality rates for indigenous children under five within a decade.

A recent prime ministerial statement discussed progress towards these targets.[21] The goal of ensuring access to early childhood education has been achieved. Encouraging progress has been made in year 12 completion, employment outcomes and the mortality gap in children under five, though this is still twice the non-indigenous rate. The progress in reading, writing and numeracy achievements has been more mixed.[21]

Closing the life expectancy gap within a generation is possibly the most challenging target. Currently the greatest disparity in survival is in the 25 to 54-year age bracket. Indigenous Australians are four times more likely to die as non-indigenous when they are 35 to 44 years old.[13] If progress on this target is to be made there has to be a strong and continued focus on the management of the chronic diseases responsible for much of this excess mortality.

World view

It is critically important to appreciate that indigenous people have a different view of health than that familiar to western medicine. For indigenous people, health is:

"Not just the physical well being of the individual but the social, emotional and cultural well being of the whole community. This is a whole-of-life view and also includes the cyclical concept of life-death-life.

Health to Aboriginal peoples is a matter of determining all aspects of their life, including control over their physical environment, of dignity, of community self-esteem, and of justice. It is not merely a matter of the provision of doctors, hospitals, medicines or the absence of disease and incapacity." [22]

This definition was composed by the National Aboriginal and Islander Health Organisation in 1979 (now the National Aboriginal Community Controlled Health Organisation) and remains the preferred definition. Awareness of this alternate "world view" helps frame interactions with indigenous patients and give context to common points of friction. Obligations to relatives or communities may supersede a patient's own treatment, resulting in failure to attend appointments or "absconding" from hospital.[23]

Indigenous patients may feel isolated (socially, culturally or geographically) when in hospital, especially if they are from very remote communities or have been transferred long distances from their homes. Such displacement may be considered more detrimental to their "health" than failing to complete treatment, especially if their condition has not been adequately explained.

Indigenous patients may be fearful of hospitals and western medicines, only presenting late with advanced pathology. Poor outcome due to late presentation can perpetuate a source of this fear, which is that hospitals are places where relatives have gone and died.[23] Great importance may be placed on being close to their community and land when death is inevitable, regardless of distance.[24]

Comprehension of physiology, such as the function of blood, and the aetiology and management of diseases is often limited. Health literacy can be poor, but explanations in the patient's first language, using "worldview" based educational methodologies can be used to improve their understanding of treatment.[24]

Indigenous identity

It is helpful to identify patients who are indigenous, as use of culturally appropriate services can improve interactions with health services and improve outcomes.

Although there are different ways in which an individual can be recognised as Indigenous, all are equally valid.[26] Patients should not be described as "half-caste" or "part" indigenous, nor should assumptions be made on the basis of physical appearance. "Urban" indigenous and those of a fair-skinned appearance may also benefit from culturally appropriate services.

A recent guideline recommended the use of a standard national question "Are you of Aboriginal or Torres Strait Islander origin?" [27] It may be useful to explain to patients why this question is being asked and the ways in which it might benefit them to identify their indigenous status.

Language and communication difficulties

Communication difficulties may be due to cultural issues, English comprehension or both. There are over 300 indigenous languages or dialects in the NT alone and an individual may speak many of them.[28] More than 80% of indigenous patients presenting for surgery at RDH did not speak English as their first language.[29]

Indigenous patients may speak in a manner judged to be "poor English" by the non-indigenous. This may be either the recognised dialect of "Aboriginal English" or a creole. A creole is a language that develops from language contact, in this case English, and shows features of contact languages.[30] Although creoles may sound like English it is a discrete language and treating it as English will lead to miscommunications.[31]

Western medical practices often include a question-and-answer routine, a system not common in indigenous discussions. There are also cultural restrictions on who may ask for, or give, specific information related to an individual.[32]

Patients may reply "yes" or give the response they believe is expected of them, even when they do not understand what is being discussed. This may be due to shame stemming from their lack of understanding or a practice known in linguistics as "gratuitous concurrence". This occurs where "yes" is thought to be the desired answer, especially when questions are framed with only yes/no options or in encounters of unequal power.[32]

An issue of particular relevance is the recognised difficulty with numerical concepts such as percentages or other systems of quantification.[28,32] Some indigenous languages have only a limited amount of words for numbers.[33] Saying there is a "2% risk" or "one out of 10,000 chance" may have little meaning to patients.

Research from RDH demonstrated communication difficulties could influence the type of anaesthesia or analgesia patients received.[16] In a quarter of interactions, the anaesthetist felt the patient did not understand an explanation, even when the patient had reported otherwise.[29] Communication difficulties were 31 times more likely with indigenous patients, but could be mitigated in 67% of instances with the use of an interpreter.[29]

In addition to the provision of an interpreter service NT health has developed resources to educate indigenous patients on a wide range of health matters. These include posters, pamphlets, booklets, DVDs and web-based resources, many of which are available in indigenous languages. For example: "Operation Story" is a DVD produced by the RDH Department of Anaesthesia in 2009. It is available in five indigenous languages and discusses patient rights, informed consent, the process of anaesthesia, fasting and smoking cessation. It is available from the hospital and also shown on television in the RDH wards.[29]

Communication hints
For the heterogeneous indigenous population these suggestions may not always be appropriate.

Eye contact
Speak indirectly to a person, limiting eye contact. Strong eye contact might be threatening and make patients feel uncomfortable or vulnerable. Sitting side by side may be the best position.

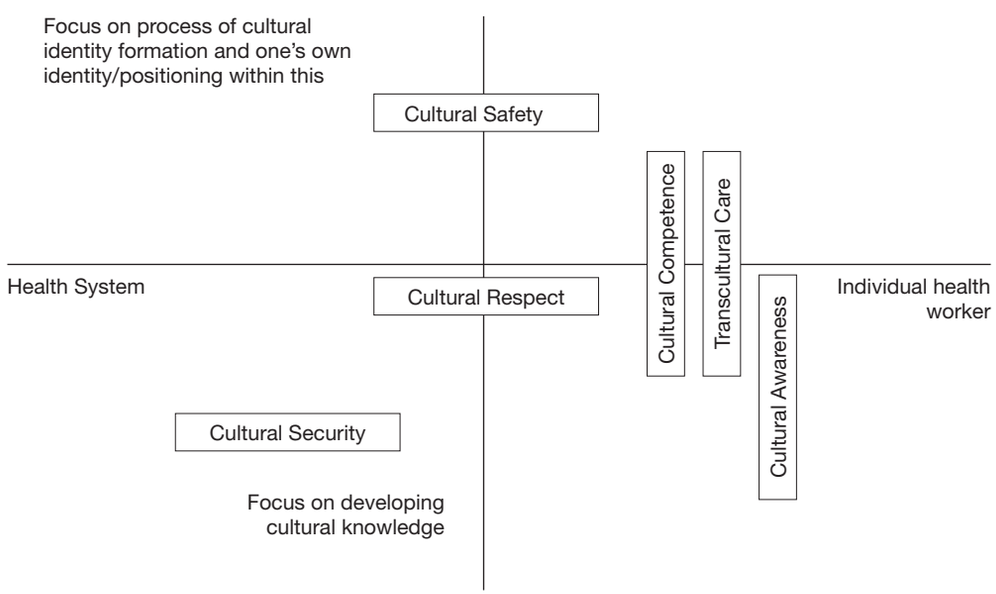
Listening
Indigenous patients often practice active listening, that is they give full attention to what a person is saying. They may not start thinking about a response until the speaker has finished. It may be considered particularly rude to interrupt a person who is speaking.

Speaking
A quiet tone may be used, as a loud voice is understood to convey rudeness or aggression. Active listening, thinking through the response before responding, and needing to translate from English can result in lengthened response times.

Models of indigenous cultural training
Educating healthcare providers about indigenous culture with an expectation they will subsequently adjust their practices has been performed for decades, with questionable efficacy.[34] Much of this is "cultural awareness" training, focused on teaching participants about "other cultures". Criticism of this model has been that it risks the development and perpetuation of the false perception that there is a unified entity called "indigenous culture" that can be described, taught and understood. There is a concern that this type of cultural training can reinforce stereotypical and even negative understanding of what "indigenous culture" is.[35]

Attempting to educate the individual does little to alter the milieu in which health is delivered. Just as a better understanding of the aetiology of medical errors has shifted the focus from the individual to the "system" so this can be seen in models of cultural training.

Figure 1. A comparison of theoretical models underlying indigenous cultural training[35]
(Used with permission)



The "cultural safety" model originates from Aotearoa/New Zealand and was designed to address the way in which colonial processes and structures shape and negatively impact Maori health.[35] The responsibility lies with the health service, but emphasis is placed on assisting the health worker to understand how power imbalances can be culturally "unsafe" and detrimental to patient's health.[34]

NT Health has taken a cultural security approach, which emphasises the responsibility lies within the system as a whole, rather than individual health workers. It is a process, detailed below, which aims to build indigenous culture into services to promote the best possible outcomes:[36]

- Identify those elements of indigenous culture that affects the delivery of health and community services in the NT.
- Review service delivery practices to ensure that they do not unnecessarily offend indigenous people's culture and values.
- Act to modify service delivery practices where necessary.
- Monitor service activity to ensure that services continue to meet culturally safe standards.[36]

Consent
Informed consent in anaesthesia generally relates to a western, biomedical model, where importance is placed on individual patient autonomy and decision-making.

Community relationships are of great importance to indigenous patients, and they may need or wish to include family members in their decisions.[37,38] Patients may defer to the wisdom of an elder or elect to use a family member as a proxy decision maker.[39]

Consent for children can be particularly challenging. The adult accompanying a child may not be the parent, but a different relative. Also, a parent may not make decisions for the child alone and the family or a community member may need to be consulted.[24]

Reviewing indigenous patients early in their operative course is a helpful practice where possible. This facilitates the utilisation of interpreters and allows patients to confer with any necessary individual(s).

Pain
There is a paucity of research into the pain experiences of indigenous patients. What does exist often shows they are less likely to report pain, which may be attributed to stoicism.[40] However, it is incorrect to assume indigenous patients experience less or no pain. ANZCA acknowledges the "provision of quality analgesia requires sensitivity to cultural practices and beliefs, and behavioural expressions of pain."[41]

Cultural factors include the reluctance of patients (especially male) to report pain for fear of appearing "weak".[40] Illness and pain may also be viewed as punishment for some cultural transgression, meaning stigma or shame can impede reporting.[42] Patients may believe clinicians should simply "know" how much pain they are experiencing and treat it appropriately. A traditional healer (ngangkari) in indigenous culture has the ability to "see within" others and identify illness.[42] In a study of the pain experiences of central Australian indigenous women, one of the patients stated:

"Sister you come in here giving me this medicine (points to the intravenous line), you telling me when I can eat, when I can walk. If you thought I had pain you'd give me my paining medicine.[42]"

Behavioural expressions of pain may include "centering" (withdrawing to a sleep like state) or rubbing (of painful areas) with, or without liniment. Some patients may use traditional analgesics ("bush medicine"), but there is little research into their pharmacology or analgesic efficacy.[42]

Indigenous patients may find it significantly easier to use a five-point verbal rating score (VRS) of "none, mild, moderate, severe or unbearable" compared to a numerical rating score (NRS) of 0 to 10. The VRS can be modified to "no pain, a little, more, a lot, or very bad" in patients with poor English.[43]

Indigenous health practitioners
There are many ways in which indigenous Australians are involved in delivering and advancing their own healthcare.

Aboriginal medical officers
The Australian Indigenous Doctors' Association (AIDA) reports there are approximately 175 indigenous medical practitioners and 226 indigenous medical students in Australia.[44]

The vision of the AIDA is for Aboriginal and Torres Strait Islander people to have equitable health and life outcomes. They aim to do this by: providing a unique medical and cultural perspective on indigenous health, maintaining links between traditional and contemporary medicine and growing and supporting current and future indigenous doctors.[45]

Aboriginal and Torres Strait Islander health practitioners (ATSIHP)
These are health workers who: identify as an Aboriginal and/or Torres Strait Islander, are the holder of the relevant qualification in primary healthcare and have a culturally safe and holistic approach to healthcare.[46] Building the capacity of ATSIHP is an important part of managing the disparity in chronic disease outcomes.[47]

There are 288 registered Aboriginal and Torres Strait Island health practitioners with 228 (79%) being in the NT. Qld and NSW have another 10 and 6% respectively.[48]

Aboriginal liaison officers (ALOs)
ALOs contribute to the delivery of a culturally appropriate healthcare service for indigenous patients by liaising between the individuals, communities and the hospitals. They can assist patients and practitioners in many ways but they are not formally trained interpreters or social workers.

Interpreters
It is preferable that formal interpreters are used where possible. It is not appropriate for family members, liaison officers or (in most instances) Aboriginal and Torres Strait Island health practitioners to be used for conducting sensitive consultations or obtaining consent.

An indigenous interpreter service has been available for more than a decade in the NT, but services remain challenging due to issues such as the large number of different languages required and the limited pool of trained interpreters. In some instances (particularly of a dialect spoken by only a small number of people) it may be difficult to avoid a kinship relationship between the interpreter and client.[31]

CONCLUSION
The practice of anaesthesia in Darwin is challenging and at times difficult, but as we go to work each day – be it through monsoonal downpours or a sunny "dry season" morning; we know we can make a small but definite difference to "closing the gap" for indigenous Australians.

For health professionals who stay in the territory, it is the challenges of indigenous health and making incremental improvement that keep most of us here.

ACKNOWLEDGEMENT
We would like to thank Mrs. Frances Abbott, Clinical Nurse Consultant – Culture at RDH, for reading the draft of this article and her helpful suggestions

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Informed choice and consent in anaesthesia: Are we there yet?

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INTRODUCTION

The social and legal environment in which medical services are provided is evolving rapidly in Australia. Thirty years ago when I began anaesthetic practice it would have been inconceivable that I would be sitting at my laptop today writing about the concept of informed choice in anaesthesia as part of the consent process prior to anaesthesia. The prevailing sentiment at that time, 30 years ago, would have been that the attending anaesthetist had a monopoly on medical knowledge and that little patient involvement would be required in a consultation or decision-making process about anaesthesia care. At a preoperative consultation less favoured options of care were seldom discussed and usually there would be scant, if any, discussion of risk. However, one major difference at that time was that the patient was generally always seen the day before surgery and therefore had an opportunity for some discussion about treatment options, although this option was seldom availed upon by patients.

EVOLUTION

Whether we like it or not, there is now a rapidly evolving paradigm shift in the way health services are both delivered and are seen to be delivered in Australia. Health services are now a commodity to be bought and sold in a more open marketplace. Today, medical practitioners are seen as service providers just as are dentists, the legal profession or shopkeepers, who are selling either a service or goods. Our clients, however, as our patients are sometimes called, have always had the right to a fundamental ethical principle enshrined in law, called autonomy. This is the right to self-determination, to make choice without coercion, concerning their own wellbeing. Until relatively recent times, this right of the patient to autonomy when making decisions about anticipated treatment was not usually acknowledged at a conscious level by the medical profession.

THE LAW

The watershed moment in informed consent in Australia came with the outcome of the court case in medical litigation of Rogers vs. Whitaker (High Court of Australia 1992). The determination resulting from this case was that the disclosure of information in the consent process must focus on a ‘reasonable patient’ standard rather than a ‘reasonable physician’ standard. This means that a patient with capacity or their nominated carer must be provided with medical information relevant to the patient’s particular circumstances and concerns. The Rogers vs. Whitaker outcome enshrines the principal in case law of providing patients with a meaningful choice about treatment options. As part of a reasonable informed consent discussion patients should now expect to, and have a right to, a discussion about both recommended treatment and treatment alternatives that allows a decision that reflects their personal situation. Anaesthetists who trained and have practised principally in an era and environment that predates Rogers vs. Whitaker may find the change in emphasis from ‘physician’ to ‘patient’ understandably difficult to integrate into day-to-day practice. Nonetheless this a requirement in law and a change that must be managed, and which, on occasions, may create tension between mentor and trainee in a teaching environment.

Many have discussed informed consent in anaesthesia with great eloquence in recent years but it seems that little has changed in the way we do business other than the pressure, particularly in the private hospital setting, to be ever more efficient in the mechanics of delivering anaesthesia expeditiously. A written and witnessed anaesthetic consent, including both material and general risks, the anaesthetic technique chosen and quite possibly the inclusion of a disclosure of the identity of all relevant persons likely to be involved in the patients care should be part of routine anaesthesia care. Many anaesthetists would say that written informed consent is just another time-consuming burden but I would say that it is empowering as it involves the patient in the decision-making process. Surprisingly, there are many patients that would feel very comfortable with this involvement in their care and would expect, and be happy, to sign such a document. After all, this is often the way our surgical colleagues obtain consent by inviting their patients to make a choice and to confirm this in writing on a request-for-care document.

CONSENT FORMS

It is anomalous that, in contrast to anaesthesia, all other interventional procedures always require a separate written consent form. Why should anaesthesia be seen as the odd one out? To me, this situation seems to belittle the importance of anaesthesia. Most consent forms currently in use are designed for surgical interventions and generally only refer to anaesthesia in a tangential manner or fail to mention it at all. Rarely is there a space on a surgical consent form for consideration of other aspects of care, including anaesthesia. Of note is the increasing requirement in many hospitals for informed consent for the relatively low risk intervention of a blood transfusion. I see written anaesthesia consent as another small step in raising our profile in both the eyes of the public and our colleagues in other specialities.

I also feel that patient choice is an integral part of informed consent. The concept of choice in anaesthesia and the right of a patient to make a choice may seem a relatively indigestible concept to many anaesthetists at this time. We may question, but ultimately accept, the right of a patient who espouses the religious beliefs of the Jehovah's Witness to decline blood or blood products even in the face of potential mortality. Neither should we decline to provide anaesthetic care if it involves treatment with other than our preferred technique. Some anaesthetists may say that we have a right to deny our patients anaesthesia care that we don't personally favour. I remember the Hippocratic Oath I took and agreed to defend. Despite an adequate discussion about options in anaesthetic care, clearly many patients will still leave choices to their anaesthetist either due to an inability to comprehend options or a reluctance to usurp the decision from a medical professional expected to make the right choice.

INFORMED PATIENTS

Our patients requesting our services are increasingly informed thanks to a revolution in the availability of an ever-increasing amount of information in the public domain. The concept that patient ignorance is bliss is no longer applicable in medicine. Every anaesthetist should provide their patients with information about treatment options in anaesthesia where treatment options realistically exist. Such information would include a discussion about risk and benefit based on fact not preference. Ideally, the preoperative discussion of treatment options should be delivered without bias, but I believe it is equally acceptable in a full and open discussion for the anaesthetist to be able to express a preference in an unemotional manner. Some time for refection on treatment options should be allowed for further questions or clarification of information supplied. Naturally there may be reluctance on the part of the attending anaesthetist to give fair discussion to a technique that may not be personally preferred despite reported outcomes to alternatives being of equal risk.

In an ideal world it would be incumbent on the attending anaesthetist prior to the day of surgery to provide appropriate information to a patient anticipating surgery and anaesthesia and to allow sufficient time to consider options and formulate questions. Unfortunately the preoperative assessment often takes place on the day of surgery. In some ways the importance of the preoperative consultation has been trivialised by the many forces that are conspiring against us in the delivery of the best care. This is a situation that must be rectified particularly for more major surgery or the more complex medical patient even if it involves preadmission clinics or an appropriate telephone call. There is no doubt that the provision of anaesthesia can be stressful. Just as developments in anaesthesia have improved safety, our patient population has become older and medical issues more complex. There is an expectation by our patients that we would all be sufficiently well trained and equally competent in the delivery of a wide range of anaesthesia techniques for a particular type of surgery, and like our counterparts in aviation, could manage a wide range of complications no matter how uncommon. It is no longer an adequate response to a patient's request to simply reply, "this is how we or I do it."

CHOICE OF ANAESTHETIC

I acknowledge that choice does not always exist. For many anaesthetists this is the ideal situation.

I also acknowledge that in a particular situation one anaesthetic technique may appear to be clearly superior to another in relation to intraoperative risk and outcome. In the situation where a patient's choice creates a dilemma for the anaesthetist, we truly justify our title of consultant anaesthetist and all this entails. I would anticipate that our training has prepared us for such events. Even in this situation, it is incumbent that we respect our patient's right to autonomy and choice. A common situation where a number of treatment options exist, is that of either hip or knee arthroplasty. Many anaesthetists favour regional anaesthesia in particular for knee arthroplasty but many recent reviews do not show superiority of this technique over general anaesthesia in either rate of deep vein thrombosis or other critical perioperative events. General anaesthesia when employed is usually supplemented with peripheral nerve block or infiltration analgesia to provide early post-operative patient comfort.

Despite the absence of a 'legal' requirement for written informed consent in anaesthesia, many institutions are starting to introduce these documents into mainstream practice. Unlike our surgical colleagues who usually consult their patients at a separate time from the surgical procedure, we as anaesthetists generally have to roll the pre-anaesthetic consultation and consent into one brief consultation. A written consent form is a very helpful tool, without any doubt, of confirming choices requested or techniques agreed by a prospective patient. The consent form could also contain patient wishes regarding prickly subjects such as the extent of resuscitation where such comment may be highly relevant. Clearly, to protect the anaesthetist in such instances, a patient's wishes should be well documented and witnessed. Many patients expect to sign off on consent to anaesthesia and are often a little surprised when advised that as yet this is not a requirement.

The issue of appropriate timing and the adequacy of the time available for an appropriate pre-anaesthetic consultation remains an issue to be addressed.

Patients have the right to choice in anaesthesia where options exist. Anaesthetists have an obligation to offer patients a choice irrespective of their own views about the options available. The final decision ultimately belongs to the patient. Most of us are not there yet. It's time we got off our hands and acted upon the issue of patient choice and written informed consent.

Propofol misuse among anaesthetists

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INTRODUCTION

Throughout the world, propofol is the most widely used agent for sedation and induction of anaesthesia. The unique qualities of propofol, which render it such a popular anaesthetic agent, are also the qualities that make it attractive as a drug of misuse. Unfortunately, propofol more than any other anaesthetic agent commonly abused, is likely to end in death when used for recreational purposes. This is extremely concerning as the incidence of propofol abuse worldwide appears to be increasing.[1]

ABUSE

Pop superstar Michael Jackson's untimely death in 2009, largely thought to be as a result of a propofol overdose, has brought propofol into the limelight as a potential drug of addiction and misuse. It is ironic that just a few days before his death, the American Association of Nurse Anesthetists (AANA) issued an urgent recommendation to treat propofol as a controlled substance in all clinical settings, as they had noted a steady increase in propofol as a preferred drug of addiction among their members.[2] More than 80% of propofol misuse occurs among healthcare providers as opposed to lay people, probably because of ease of access. However, given the recent worldwide publicity afforded propofol after the death of Michael Jackson, experts agree that there could be a dramatic increase in the number of non-medical personnel seeking access to and becoming addicted to this drug. It is freely available for purchase without a prescription on many internet websites.

Addiction will always be an occupational hazard for anaesthetists because of easy access to highly addictive drugs in theatre, and the requisite knowledge and skills to use them. Some experts have suggested that anaesthesia may attract people with pre-existing addiction problems because of the perceived ability to access these drugs. Current literature reports an incidence of general substance abuse of 1 to 2% among anaesthetists, with fentanyl being the most commonly abused drug.[3] The incidence quoted in the American literature is 1.6% among anaesthesia trainees and is one of the highest known incidences of all groups of healthcare providers.[4] Some of the proposed reasons for this include the high workplace stress that accompanies taking care of critically ill patients, exhausting shift work with subsequent chronic fatigue, and ready access to drugs of addiction and abuse. A newer theory is that of occupational exposure to tiny amounts of aerosolised intravenous anaesthetic drugs on a daily basis, resulting in sensitisation of specific receptors and the subsequent potential for addiction in susceptible individuals.[5] This theory remains unproven.

The incidence of propofol misuse is quoted as 0.1% among anaesthesia providers. In an American survey from 2007, one or more incidents of propofol abuse or diversion was reported by 18% of 126 responding academic anaesthesia departments in the previous 10 years.[1] These figures show a fivefold increase in reporting from previous surveys; however, some experts see them as the tip of the iceberg, as propofol misusers often start with opioids or other sedatives and then graduate to propofol. In addition, they often misuse more than one drug concurrently, so propofol abuse may well be underreported. One of the most cited reasons for propofol diversion is the ease of access as compared to other controlled substances. This survey also revealed that about 30% of cases present with death as the first indication of a substance abuse problem, and the vast majority of deaths occur among trainees, particularly those within five years of medical school training.

In an Australasian survey of substance abuse among anaesthetists published in 2005, 44 substance abuse cases were reported in 100 responding programs.[6] The initial presentation was death in 15%. Induction agents were responsible for 20% of cases of substance abuse (compared to only 6% in a similar survey from 1993); unfortunately, the breakdown of agents was not reported. Opioids were responsible for 66%, benzodiazepines 5%, and inhalational agents 5% of substance abuse cases.

Propofol, similar to most drugs of abuse, enhances the levels of dopamine in the mesocorticolimbic reward areas of the brain, which then reinforces behaviour associated with obtaining and injecting the drug.[7] What are the properties of propofol that make it so attractive as a drug of abuse? Firstly, ease of access to a drug that is unrestricted, unsecured and unregulated, and available in a wide variety of clinical settings within most medical facilities. While designated drugs of addiction, such as fentanyl and morphine, have to be accounted for in a register and are kept under lock and key, propofol remains unsecured in most medical facilities.

It is short acting and allows a rapid, clear-headed recovery with no residual hangover, ideal for "on-the-job" use as it is less likely to signal a substance abuse problem. The restful, refreshed quality of sleep afforded by propofol administration, often referred to as "pronapping", is particularly attractive to insomniacs and shift workers. The negative physical effects of sleep deprivation, at least in an animal model, are reversed by propofol anaesthesia with an effect equivalent to natural sleep.[8] Propofol also imparts a strong sense of euphoria at subanaesthetic doses. Some of the terms used to describe the feeling include "pleasant", "relaxing", "elation" and "spaced out".

In addition, there is a lack of routine testing for propofol, and it needs to be specifically requested in drug screening tests. Urine testing for propofol is able to detect repeated usage over a five to seven day period, whereas hair testing can detect usage within two weeks to six months.

Because propofol has such a short duration of action and rapid recovery, it may be self administered up to 100 times a day, often by means of a cannula concealed on the leg or under long sleeves. Unfortunately, the properties that make it so attractive as a drug of abuse are accompanied by a narrow therapeutic index, and accidental or intentional death is a real possibility. It is also highly addictive and sudden withdrawal after chronic misuse gives rise to an intense craving despite lack of compelling evidence of a physical withdrawal syndrome.

MANAGEMENT

The management of propofol abuse is described in detail in the ANZCA resource document 20. A brief overview of management is as follows:

1. Prevention.
2. Initial response to suspected misuse:
   - Investigation.
   - Intervention.
   - Detoxification.
3. Follow up:
   - Rehabilitation.
   - Monitoring and surveillance.

Prevention remains the most important aspect of any management strategy and includes raising awareness through education. A proactive program within departments or group practices is very important, and may involve regular tutorials, compulsory e-learning and mentoring programs, as well as the establishment of a departmental substance abuse policy. Mentoring can be considered as both preventative and therapeutic. A mentor may be able to identify an anaesthetist at risk long before a report of drug diversion, and can guide and support a return to clinical practice as well as assist with ongoing monitoring and rehabilitation.

A substance abuse committee and designated intervention team need to be appointed and details of the members recorded within the substance abuse policy folder, which should be easily accessible within the department. The substance abuse committee is integral in both prevention and management of substance abuse; however, it performs an administrative, not therapeutic function. Among other duties, the substance abuse committee is responsible for education, investigation of reports of drug diversion, appointing an intervention team, monitoring of treatment and follow up support. Of note, in 2005, only 20% of Australasian anaesthesia departments surveyed had a substance abuse policy in place.[6]

A simple, yet effective preventative strategy involves witnessed discarding of unused anaesthetic agents at the end of every case. This will prevent the desperate from trawling through sharps disposal containers for partly used syringes of propofol and other drugs of addiction, a surprisingly common occurrence.

REGULATED DISPENSING

A more controversial prevention strategy is the regulated dispensing of propofol, the subject of much debate within the current literature. Many see this as both inconvenient and potentially dangerous – impeding ready access to propofol in an urgent or emergent situation could be disastrous. As propofol is used universally in such large volumes, regulated dispensing would have a widespread impact in many hospital, outpatient and clinic settings, and would pose a regulatory nightmare. In addition, this measure has been found to be ineffective for the determined diverter. Nevertheless, regulated dispensing does allow earlier detection of drug diversion, which may save lives. Proponents of regulated dispensing say that inconvenience in practice mechanics should not be a good enough reason when talking about preventable deaths. In the US, many hospitals use an automated anaesthesia drug dispensing system (for example, Pyxis MedStation®), which provides drugs to individual anaesthetists, and records usage. The anaesthetist logs in with an electronic identity card, and requests a particular amount of propofol (and other drugs) for use on a specific case or list. Any unused drug is returned to the pharmacy and undergoes qualitative and quantitative assay.[9] The database can be interrogated for abnormal patterns of usage. A system such as this requires excellent co-operation between the departments of pharmacy and anaesthesia, but has led to impressive reductions in the incidence of drug diversion when it is properly instituted.

Interestingly, fospropofol, a water-soluble prodrug of propofol introduced into clinical practice in the US in 2009, was labelled as a schedule IV drug (requires doctor's prescription), whereas propofol itself remains unscheduled. Finally, in the US survey, all programs reporting deaths from propofol abuse were centres in which there was no pharmacy accounting for the drug.[1]

DRUG SCREENING

Another preventative measure used in the US is mandatory random urine testing, which has also been used successfully within the aviation, transportation and military industries there. The Department of Anaesthesia of the Boston Massachusetts General Hospital has adopted this strategy at a considerable cost of $US50,000 per year, which allows one to two urine tests per year plus pre-employment screening for approximately 80 registrars.[4] This is weighed against the cost of diagnosis and management of one substance abusing doctor, in excess of $US100,000. Some of the issues reported include false negatives and positives, and the fact that mandatory testing may well select out substance abusers, who then apply to other programs. Nevertheless, many hospitals in the US require physicians to undergo pre-employment urine testing, and there is a move towards testing after sentinel events as well as randomly.[10]

RETURN TO WORK

Further controversy regards return to work of a successfully rehabilitated anaesthetist, in particular, whether or not the anaesthetist should return to work in anaesthesia. Leading on from this, how soon after detoxification should the anaesthetist return to work, and how long is the subsequent surveillance and monitoring period? For example, in the US, many hospitals require a one-year period of absence from any facility where propofol is used, and the ongoing monitoring period is a minimum of five years. In Australia, the Medical Board of Australia determines limitations on practice, and stipulates conditions regarding ongoing monitoring and testing, level of supervision and restricted working hours. There is no formal policy regarding conditions, as every case is dealt with individually.

RELAPSE

Unfortunately, death is the initial relapse symptom in 15 to 25% of cases, and is most common in the early period of recovery. Death also is the first indication of a propofol abuse problem in up to 30% of cases. Death is even more likely in registrars – 38% in one study.[1] Because relapse is associated with significant mortality, a period away from clinical practice after detoxification may reduce the rate of relapse. This will require placement in a facility where exposure to propofol is unlikely, such as a dialysis centre or primary healthcare facility.

RECOVERY

Although many substance abusing anaesthetists return to work, less than half make a long-term recovery, and only 20% make a long-term recovery within the specialty of anaesthesia.[6] With propofol abuse, these figures are likely to be even lower.[1] Sadly, successful completion of a treatment program is not a guarantee against relapse, and the high incidence of death on relapse is of particular concern. There is tremendous debate concerning return to work in anaesthesia for the rehabilitated anaesthetist. Many experts subscribe to the "one strike and you are out" theory, citing the relapse and death rate as being unacceptably high.[9] Others have concluded that individual consideration, as well as strict re-entry criteria, ongoing monitoring (possibly lifelong) and compulsory enrolment in a physician's healthcare program might facilitate a safe return to work in anaesthesia.[11] Using the analogy of a recovered alcoholic working in a bar, it is clear that returning to work in anaesthesia places the addict in the unenviable position of having to overcome daily temptation to highly addictive and easily accessible drugs.

Anaesthetising the propofol abuser is unlikely to present any issues associated with acute intoxication, as the redistribution half-life of propofol is so short. However, we may be called upon to take care of a patient who has sustained anoxic brain injury, cardiac arrest or aspiration pneumonia secondary to rapid administration of a propofol bolus. Secondary trauma may occur due to the sudden loss of consciousness – it is not unusual for propofol to be injected while driving a vehicle. The chronic propofol abuser presents similar issues to other intravenous drug addicts, such as risk of infection with HIV and hepatitis, poor intravenous access and respiratory issues secondary to chronic aspiration. In addition, propofol abusers are at risk of malignant cardiac arrhythmias and sudden cardiac arrest, a presentation with similar features to propofol infusion syndrome. This is thought to occur secondary to chronically increased production of interleukin-10 and tumour necrosis factor, resulting in diffuse areas of myocardial band necrosis.[7] ST segment elevation in V1 – V3 may be the first indicator of cardiac damage secondary to propofol abuse, and a pre-operative ECG may show this Brugada-like pattern. If these ECG changes are noted, a cardiology opinion is required before proceeding to elective surgery; however, if surgery is urgent, external defibrillation pads should be placed pre-induction and the use of propofol should be avoided.

In conclusion, propofol misuse among anaesthetists appears to be increasing, and an emphatic prevention campaign is the key to reducing the likelihood of a tragic outcome. There needs to be ongoing discussion and debate about regulation of propofol dispensing. Furthermore, there is no consensus about return to work in anaesthesia, despite a significant incidence of relapse and death.

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Where oh where has your Endone script gone? The oxycodone epidemic

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INTRODUCTION

At St Vincent's Hospital in Sydney, discharge prescriptions of oxycodone (Endone) trebled in the seven years to 2012 with little reduction in the prescription of Panadeine Forte [unpublished data]. For the hospital pharmacy this has meant a massive increase in workload, with each Schedule 8 prescription adding 12 minutes to processing times.[1] Can we tell the pharmacists that this increase is a good thing for our patients? Should we instead worry that some of this oxycodone may end up being sold, crushed and injected just up the road in the nightclub district of Kings Cross, or handed out and swallowed at a party? Is that the kind of destination that even causes the problems with these drugs? Maybe the pendulum of opioid liberalisation has swung too far and it is the very patients we prescribe these medications for who experience the most harm.

This article is intended for any anaesthetist who prescribes opioids, which may continue beyond discharge. It details trends in the use and abuse of opioids, particularly oxycodone. It discusses steps being taken in Australian and New Zealand hospitals to reduce perceived over-prescription and abuse of oxycodone, particularly in the acute pain setting.

THE UNINTENDED CONSEQUENCES OF THE LIBERALISATION OF OPIOID PRESCRIBING

Over the past two decades, great changes have occurred in the prescribing of opioids. With the World Health Organization's declaration that "pain is the fifth vital sign" as well as the belief that pain relief is a human right, the management of pain, both acute and chronic, has changed. One consequence has been an increase in the amount of narcotics prescribed across all areas of pain management. The consumption of opioids worldwide increased more than six-fold in the 10 years to 2008.[2] In that same period, supply of oxycodone in Australia increased from 92kg to 1295kg.[2]

An increase in the rate of prescription opioid-related deaths was first noticed in areas of the US with high prescription rates. In the US state of Utah between 2000–09 opioid-related deaths increased nearly five-fold. A retrospective study of non-intentional prescription opioid-related deaths in Utah over one year (2008–09) revealed that those who died were highly likely to have a history of chronic pain (94.2% vs. control group 31.6%). They were also highly likely to have used prescription pain medications in amounts higher than prescribed (52.9% vs. control 3.2%) and four times more likely to obtain additional prescription pain medication from non-prescription sources (65.6% vs. control 8.5%). Oxycodone was the most frequent opioid cause of death among those who died.[3]

Patterns of opioid-related harm also have changed in Australia and New Zealand. Hospital treatment of poisoning by heroin decreased by one third from 1998–99 to 2006–07, with an increase of over 150% in poisoning by other opioids over the same time and a massive 1403.7% increase in poisoning by other synthetic narcotics.[4]

As the availability of synthetic opioids has increased in Australia there also has been a documented increase in deaths where these drugs have been detected. A 2011 study of deaths investigated by the Victorian coroner reported that deaths where oxycodone was present increased from four in 2000 to 97 in 2009.[2] Approximately half of these deaths were attributed to drug toxicity. Polypharmacy was the norm, with only one of these deaths involving the use of oxycodone alone.[2] Roxburgh in 2013 reported 136 fentanyl-related deaths in the 10 years to 2011. Of those who died, 37% had a history of chronic pain while 54% had a history of injecting drug use.[5]

Opioids remain essential in the acute pain setting and in palliative care. However, there is limited evidence that narcotics provide great efficacy in chronic non-malignant pain. Prescription opioids have not been found to improve key outcomes such as pain relief, quality of life or functional capacity in the long term.[6] The risks of opioid-induced hyperalgesia, unintentional fatal and non-fatal overdose, diversion and addiction are all increasingly recognised.[7]

The pain literature is awash with articles related to opioid-related morbidity and mortality, leading to a high level of awareness within chronic pain clinics. Most are taking steps to limit opioid prescribing. With clearer evidence of benefit from opioids in the acute pain setting however, the recognition of harm to individuals and the greater community has been slower. Much of the harm to the community occurs as a result of diversion.

DIVERSION

Diversion can occur in several ways. It can be the supply of a medication prescribed for one person being given or traded to someone else, the use by injection of medication dispensed for use by mouth or the stockpiling of medication dispensed to be taken daily.[8]

Prescription opioids have now become the drug most often associated with first-time illicit drug use in the US.[9] One of the most commonly cited sources by those abusing prescription drugs, especially those aged in their teens, 20s and 30s, is excess medication in the home (dealers being the other most common source). This is often medication left over from a relative's acute condition, since resolved.[10]

In the US, the annual number of fatal drug overdoses attributed to prescription opioids (15,000 nationally in 2008) surpasses that of motor vehicle accidents in some states.[11] Surprisingly, these deaths are not primarily in people diverting and using prescription narcotics in the injected form. Most commonly, deaths occur in people using prescription drugs as an adjunct for their chronic pain management.

In previous prescription drug amnesties it has been shown that drugs finding their way into the home medicine cabinet are rarely disposed of, but are kept for future need, providing a potential source of supply.[10] These drugs are legal, pure and predictable, sterile and now highly available. A person experimenting for the first time is likely to feel much safer using these drugs than others whose contents have not been manufactured to such exact and well-regulated standards. Availability has a direct relationship with abuse and mortality in the non-injecting population.[12] It follows that increased availability of opioids will increase both the number of users and mortality rates.

Diversion of prescription opioids for injection also occurs, but the relationship with availability is a different one. Injecting users have a strong preference for heroin, with 53% of Australian intravenous (IV) opioid users citing it as their first choice of drug versus 2% for oxycodone.[13] If heroin is in short supply they will shift to more available drugs. The proportion of injecting users who injected oxycodone went from 21% in 2005 to 39% in 2012 as availability of this drug increased.[13] The story for methadone is similar. Diversion rates for methadone are inversely proportional to heroin availability and proportional to takeaway, or unsupervised dosing. In other words, injecting users will inject more methadone if heroin is not available and methadone is more available.[8] In rural areas in Australia where heroin is less available, morphine is used more often.[14]

One of the most controversial concepts in drug diversion is the idea that the use of immediate and slow-release oxycodone in illicit intravenous drug use may in fact lead to better outcomes compared to traditional illicit street drugs such as heroin. The dose taken from crushed slow-release oxycodone tablets is more consistent in terms of absorption and the general 'high' reached compared to unreliable, erratic dosages and effects from heroin or even other prescription opioids such as fentanyl retrieved from fentanyl patches.

Dr Marianne Jauncey, the director of the medically supervised injecting room in Kings Cross, feels that with the upsurge of oxycodone used in IV drug abuse, a degree of safety has been reached. There are fewer narcotic drug-related deaths and injected slow-release oxycodone, when crushed and filtered, is an overall 'cleaner' option.

The idea that our prescriptions of Endone may end up being injected may be unpalatable to many, but it is likely that the supply will influence the choice of drug that is injected rather than the choice to inject. It is also important to remember that prescription drug availability for illicit use comes from the entire supply chain, with drugs stolen during manufacturing, delivery, from pharmacies, right through to grandma's medicine cupboard.

UNDERESTIMATION OF ADDICTION

There are numerous definitions of addiction and multiple screening tools in use as a means of identifying addiction in the chronic pain setting. It is extremely difficult to accurately identify the true prevalence of addiction in the grey area between dependence and addiction, however a literature review published in the European Journal of Pain in 2007 found that addiction rates in those using opioid therapy in the chronic non-malignant pain setting are estimated to be up to 50% compared to 7.7% in patients with malignant pain.[15] The estimated prevalence of addiction in the general population is 6.1%.[15] Importantly, addiction can develop over a prolonged period of analgesic use and patients using opioids in the long term must be regularly screened for evidence that analgesic requirements have not fallen into the realm of addiction.

HISTORY OF OXYCONTIN® – 'HILLBILLY HEROIN'

The successful promotion of slow-release oxycodone (Oxycontin®) and the repercussions in diversion were initially seen in the US after its introduction by Purdue Pharma in 1994.

Despite multiple studies that found no significant benefit of 12-hourly Oxycontin over four-hourly immediate-release oxycodone dosing,[16] revenue increased from $48 million in 1996 to reach earnings of over $3 billion between 2002-03.[17] Oxycontin had become the leading drug of abuse in the US by 2004.[18]

After compiling prescriber profiles of primary-care physicians with heavy opioid prescribing records and an assumption of more liberal prescribing practices, Purdue Pharma targeted such physicians in aggressive marketing strategies and heavy bonus schemes for drug representatives. While some of these doctors were involved in the care of chronic pain patients, most were not trained in pain management or addiction issues. With the positive promotion of the use of Oxycontin in non-malignant chronic pain, Purdue Pharma had increased Oxycontin scripts ten-fold by 2002.[17]

Interestingly, opioid prescribing varied geographically in the US. Maine, West Virginia, Kentucky, Virginia and Alabama had oxycodone prescription rates two-and-a-half to five times the national average by 2000.[12] These states also had the highest Oxycontin-prescribing areas, at up to six times the national average by 2000. Oxycontin diversion and Oxycontin-related deaths were first seen in these areas.[12]

One of the consistent messages of Purdue Pharma was that the risk of addiction with Oxycontin was extremely small. In 2009, three company executives were found guilty of misbranding by claiming Oxycontin was less addictive and less subject to diversion than other opioids. This was in similar fashion to the initial marketing of heroin by Bayer in the early 1900s when it claimed heroin had a lower incidence of addiction than morphine. Purdue Pharma was ordered to pay $634 million for misbranding.[19]

ACTIONS

Safe prescribing practices have been identified as a key factor in preventing harm related to opioid use. Limiting unnecessary prescribing and reducing diversion is imperative in reducing damage.

THE NEW ZEALAND EXPERIENCE

A study by New Zealand's Pharmaceutical Management Agency (PHARMAC), in 2012 found approximately 70% of all oxycodone scripts were initiated by hospital clinicians [unpublished data].

As a result of these findings, a recent New Zealand project developed and implemented by the Capital and Coast District Health Board (CCDHB) Pharmacy Integrated Care Collaborative (ICC) group, has led to a significant reduction in oxycodone prescribing across the district.

Alarmed at the significant upward trend in oxycodone prescribing with little reduction in morphine prescribing between 2007–11 (254% increase in oxycodone prescribing), the group aimed to reduce oxycodone as the first line opioid in general practice and hospital care settings. After identifying wards with high opioid prescribing in hospitals (orthopaedics/general surgical) and implementing junior medical officer/nursing education sessions and multidisciplinary pain management, the project led to a 50% reduction in oxycodone hospital scripts.

The team also looked at heavy oxycodone general practitioner (GP) prescribers, implemented prescribing support and continued to raise awareness of the risks of oxycodone via media and special interest medical groups. This led to an overall reduction of 10% within the CCDHB area.

ST VINCENT'S HOSPITAL, SYDNEY

The St Vincent's Hospital Pain Management Department and Pharmacy are developing an action plan with the goal of reducing hospital-based prescribing of oxycodone. Initially it will be aimed at surgical and short-stay wards with a focus on educating patients and junior doctors, weaning off opioids and discharge planning.

A printed information brochure will be provided for all patients planned for elective surgery. Advice included involves expected pain and duration, and methods of alleviating pain by medication and non-medication techniques. It outlines types of analgesic medications, their use and side-effects.

Traditionally the Acute Pain Service has seen patients daily until the patient controlled analgesia (PCA), nerve infusion or neuraxial block has been ceased, with the responsibilty for analgesia then being handed back to the admitting team, unless referral to the chronic pain team was necessary. A pain trainee now oversees those patients remaining on opioids and will create a discharge pain plan that minimises unecesary Endone prescriptions.

As part of the discharge summary, an electronic pain management plan will specifically include an individual's medication regime at discharge with clear instructions on tapering for the patient and their treating GP. The pain trainee will liaise in follow-up with patients discharged under the new scheme. The importance of early referral to a chronic pain clinic, if necessary, will also be highlighted. A patient copy of the individual pain plan will be included in the discharge medication pack. Better instructions for treating general practitioners may avoid ongoing and unnecessary opioid scripts being written after discharge. An audit of prescription numbers, patient pain scores and satisfaction with information provided is being conducted.

GOVERNMENT INITIATIVES

Real-time prescribing practice, involving online 'real-time' monitoring of opioid prescriptions is to be implemented nation-wide by the Australian government by 2015 and is already being used in Tasmania. By being able to track the issuing of opioid prescriptions, the prescribers, the patients being prescribed for and the dispensing of opioids, we may be able to gain far greater control in a similair way to pseudoephedrine prescriptions.

REFERRAL TO PAIN CLINICS

General practitioners are being encouraged to refer any patient taking more than the equivalent of morphine 100mg per day to a chronic pain clinic. Weaning off long-term opioids and a focus on the use of non-drug management of chronic pain is an important aim of pain clinics.

NOVEL MEDICATIONS

There also are new drugs to consider. The role of the newly released Targin® (oxycodone/naloxone combination) in the acute pain setting has greatly reduced Oxycontin prescribing at St Vincent's Hospital and is certainly unfavoured by IV drug users due to its withdrawal-provoking side-effect profile on injection. There is little cost difference between Oxycontin and Oxycontin/Naloxone so we no longer prescribe Oxycontin to patients unless doses exceed 80mg per day, in which case the dose of naloxone can become significant. Yet to be released is 'tamper-resistant Oxycontin'. Reports thus far from the US show drastic reductions in Oxycontin diversion and Oxycontin-related deaths since its introduction in 2012. While this has been a huge change, there has been a sharp return to heroin and other illicit drugs among injecting users.

CONCLUSION

The effort to improve pain management has had major successes, but the large increase in opioid use has had unintended consequences. In chronic pain clinics there has been a rapid response to reduce opioid prescribing, which reflects the lower benefit and higher morbidity of narcotics in this group. Reducing oxycodone and Oxycontin prescriptions, as long as there is not a corresponding increase in other opioids, may be a reasonable end-point for acute pain services to aim for given the known relationship between opioid availability and mortality. Improved education of staff and patients, improved supervision of discharge and follow-up arrangements, and better tracking of opioid prescriptions are good starting points in this process.

Many thanks to Dr Peter Moodie from Pharmac and to Ms Suzanne Welch from St Vincent's Public Hospital Pharmacy, Sydney, for their valuable input to this article.

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Fear and loathing in the operating room

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INTRODUCTION

The complexity of the patients presenting for anaesthesia and surgery is increasing. The therapies and procedures available for treatment are also growing at a rate that appears exponential. The expectation that patients and their carers have may not, however, mirror reality. The aim we all have in clinical medicine is to cure if possible, but certainly to relieve pain and distress.

PAIN

Pain is a universal experience in humans and higher animals. It is the symptom that precipitates more than 70% of patients' presentations to their healthcare provider. The middle-aged man now requiring thrombolysis and stenting probably presented with chest pain. It is unlikely that he reported acute atheromatous plaque rupture following exercise causing critical occlusion of the left anterior descending artery. Similarly, the 24-year-old female student now on the operating table undergoing a laparoscopic appendicectomy probably did not appear in the emergency room listing the five cardinal features of inflammation and point to McBurney's point. The definition of pain however is one that has been debated for centuries.

The Greeks included pain with the emotions and humours. Indeed we have the remnants of this thinking when speaking about the pain of loss or the pain of grief.

James Young Simpson, a Scottish obstetrician credited with reporting the first chloroform anaesthetic, defined pain as "…pain is with few if indeed any exceptions morally and physically a mighty and unqualified evil". He is considered one of the pioneers of early anaesthesia and the infant delivered of the women quoted in the first report of its use was baptised "Anaesthesia".

Modern medicine accepts that pain is the final experience of nociception. That which we refer to as pain is in reality the conscious appreciation of nociceptive input and various influences upon it. Surprisingly, it was not until the 1990s that the International Association for the Study of Pain agreed on the definition offered by the task force on definitions and nomenclature: "…an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."

This definition was, and continues to be, debated and criticised. It is, however, a good start if somewhat more philosophical. It is unlikely that the management of the young lady who suffered acute appendicitis included the management of the emotional experience of this pain. The gentleman suffering the acute coronary syndrome may have however a significant emotional aspect to his pain experience. Being faced with possible mortality, certainly changes in lifestyle, possible financial changes etc can alter this patient's pain.

EDUCATION

Doctors and especially those who specialise in anaesthesia can reasonably be expected to be familiar with the management of acute pain. The cause of the pathology is sought, the diagnosis made and treatment instituted in order to effect a resolution. There may be little attention paid to the pain associated as a separate entity but rather it is managed in a humanitarian way. This is scientific, this is logical and an appropriate way of managing such cases. The cause and effect equation is balanced.

CHRONIC PAIN

Pain can become chronic and is defined as such when persisting for greater than three months or longer than expected following resolution of the pathology, trauma or surgery. Approximately 20% of the Australian population reports moderate to severe pain that fits this time frame. While most doctors are comfortable with acute pain, chronic pain evokes a very different set of reactions.

Patients are rarely described in relation to their symptoms. For example there are no health services that include a 'vomit clinic', a 'cough clinic' or a 'blind clinic'. However, patients with persistent pain are directed to a pain clinic. Their medications are listed as "pain meds", which might include "narcotics, a pain patch or morphine patches" or even "one of those pain pumps". This inaccurate use of terms thinly veils the discomfort and lack of knowledge that many doctors demonstrate when faced with patients with persistent pain. Many of us received little or no education training or acquisition of skills in the management of chronic pain. Allocation of protected time devoted to the management of chronic pain is beginning to be included in medical schools' curricula. Canadian veterinary schools provide eight times more education in the management of pain in animals than Canadian medical schools. Doctors generally do not intend to be cruel, insensitive or to demonstrate lack of care. Chronic pain, however, challenges us in a way that few other aspects of medicine do. Pain is a universal experience but is difficult to describe, difficult to measure and difficult to treat. It must begin with appreciation of the entity. We can accept that the pain associated with cancer is a suffering that should be managed in a compassionate way. This is partly

because the normal progression of cancer is inevitably death. This can no longer be relied upon and increasingly patients are surviving their primary presentation of cancer only to report persistent pain due to the effects of the primary tumour, the surgery, chemotherapy or radiotherapy associated with the treatment. This may alter the caregiver's perception of the patient with empathy fatigue and even resentment of the changed condition.

THE RESPONSE BY HEALTHCARE WORKERS

Not all pain conditions result in the same reaction in healthcare professionals. Headache conditions, such as migraine and trigeminal neuralgia, frequently present with description of symptoms only. Photophobia, phonophobia and nausea accompanying the report of pain are unmeasurable. Despite this, such conditions are more readily accepted and precipitate a more active willingness to help among doctors. By contrast, healthcare professionals without objective medical evidence less readily accept non-specific low back pain or neck pain. This is compounded if medical observers of such patients are informed that sufferers of such pain are influenced by psychosocial factors. These patients' self report of symptoms is less readily accepted and the observers are less sympathetic and less willing to help. These may often be the patients we most need to help. This practice is not confined to doctors. Taylor demonstrated that nurses evaluated patients more negatively if there was no definitive medical evidence for their pain.

This lack of empathy is understandable when taken in the totality of modern medicine, its education and practice. Rollin Gallagher, past president of the American Academy of Pain Medicine, suggested that empathy might be the most powerful tool in the pain medicine tool kit. Perhaps it might be the most powerful in the tool kit used in any branch of medicine. In his editorial on this subject, Dr Gallagher describes how doctors are accustomed to being knowledgeable, effective and right. This was necessary to be successful to get into and through the significant hurdles in medical school. Patients with persistent pain, especially when there is no obvious cause, challenge the confidence that doctors might have in themselves and their ability when their best efforts in relieving suffering may result in little success. This may lead to frustration between doctor and patient (and their families) with possible mutual blame and resentment.

THE ROLE OF ANAESTHETISTS

Things do not have to be this way. The understanding of pain, its pathophysiology, psychological and social influences are increasing and at an increased rate. The neurobiology of pain from intracellular molecular level to the exciting new neuro-imaging techniques is being revealed. This should inform a more mature approach to the patient with persistent pain. Developments in the management of acute pain largely pioneered by the speciality of anaesthesia are exciting and should promise significantly less suffering. This is to be commended and encouraged. Models of acute pain might dominate the thinking of pain, including chronic pain. This erroneously leads many individuals to believe that pain should always be proportional to pathology. The appreciation of acute pain transitioning to chronic pain state and the importance of managing acute pain well to prevent this occurring is growing. Anaesthetists are central to the management of pain at the outset of it evolution. There is a responsibility that future generations of anaesthetists are educated in the management of pain in all its forms. This cannot be achieved in the same time frame as other modules of their training. Many of our teachers and mentors have laid the groundwork of this endeavour. This is especially true in Australia and New Zealand where our College and Faculty have been at the vanguard of pain-related education and training. If we do and teach it well, the fear and loathing that may otherwise occur in the operating room will be transformed into confidence and empathy.

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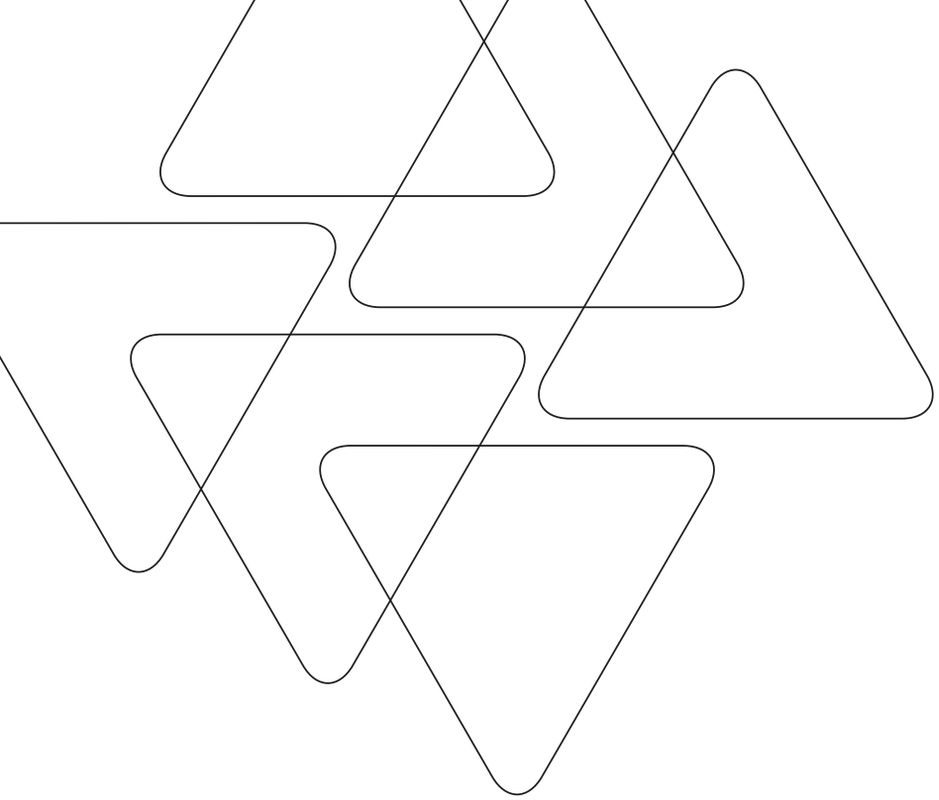

Are urine drug tests useful in management of pain patients?

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INTRODUCTION

Chronic pain, addiction and mental health are co-morbidities that often co-exist.[1,2] The three specialties involved, pain medicine, addiction medicine and psychiatry, often work independently of each other and it is not uncommon to hear patients state that the addiction specialist would not see them because they had a pain problem or a pain specialist refused to see them because of 'aberrant' behaviour, or a psychiatrist required a patient to be 'clean' and off drugs before they would be able to get help. General practice, which provides primary care in all these areas, is often unwilling, or unable, to provide adequate care to patients with one of these problems. With co-morbidity in patients in two or three of these areas, most general practitioners can feel overwhelmed by the complexity of the problem and the patients can feel everyone doesn't want anything to do with them.[3]

A 'universal precautions' approach, which assesses pain management patients in a biopsychosocial model, is recommended.[4] A significant part of that assessment comes after pain mediation has been started and urine drug testing is often used to reassure the prescriber, and other treating doctors, plus the supervising authorities that the patient is taking the medication.

Urine drug tests are relatively inexpensive and are covered by the Medicare Benefits Schedule. For some substances there is a relatively wide period in which the drug can be detected. Supervision of the urine test is ideal, but rarely done, outside a dependence program. Screening may be used to assist patients to stay compliant with treatment and/or to detect addiction or diversion.[5]

In reality, a 'dirty' urine sample will leave often the patient without a prescriber.[6] In part, this may be because too few medical practitioners are methadone prescribers, or are comfortable in treating dependence, or because the patient may not be able to detox or transfer to Suboxone® (Buprenorphine/Naloxone), even if the prescriber was willing, because they are on too high a dose of opioid analgesia.

If there are to be such dire consequences for patients, are urine drug tests useful in management? We have been using urine drug screening for 20 years and in much of that time have relied on gas chromatography mass spectrometry (GCMS) confirmation because routine testing is unreliable. We also use therapeutic blood level monitoring as part of our management strategy. Despite this there are more questions that are *not* answered by testing than questions that are.

MEDICARE BENEFITS SCHEDULE

Urine drug screening in Australia attracts a rebate under Medicare Benefits Schedule items 66623 and 66626.[7] For drugs of abuse, including illegal drugs and legally available drugs taken other than in appropriate dosage, 66623 applies and attracts a benefit of $41.50, but excludes the monitoring of patients participating in a drug abuse treatment program. In this instance detection of a drug, or drugs, of abuse or a therapeutic drug as part of the treatment regime, for example methadone or Suboxone®, is covered by item 66626 and attracts a benefit of $24.10. For any particular patient, this item is applicable not more than 36 times in a 12-month period. When a drug is being used therapeutically by a patient, but not as part of a drug abuse treatment program, a different item applies. For all these items, the detection and quantitation of a drug, or drugs, in blood or a body fluid other than urine, such as oral fluid, is also rebatable.

Urine has traditionally been the matrix of choice for drugs of abuse screening because drug ingestion can be determined over a period of days or even weeks by the detection of drugs or their metabolites, which are more concentrated in urine than in blood. Urine is also a much easier matrix to work with than blood or even plasma. It is typically performed by well-established immunoassay methodologies on clinical chemistry analysers. It remains economically viable for pathology providers despite the deregulation of pathology collection centre licenses in July 2010, which massively increased costs for the sector but failed to have a similar effect on volumes and profit margins.[8] More sophisticated analysis is generally limited to subsidised pathology services, such as may be provided by a public hospital based toxicology laboratory.

Supervised urine collection intrudes on a patient's privacy and adds a tangible expense to the collection procedure: appropriately trained staff, measuring urine temperature shortly after voiding, a dedicated toilet with a colouring agent added to the cistern, clean sources of water turned off and adulterants such as cleaning products removed. The cost of performing such a collection by a pathology provider can easily surpass the meagre benefit of item 66626. Not taking some reasonable precautions allows for adulteration or substitution of the specimen.

Alternatively, collection of oral fluid is inoffensive, non-invasive, the risk of adulteration is lower and it could potentially be conducted during a consultation. With modern analytical techniques such as liquid chromatography tandem mass spectrometry [LCMSMS],[9] it may be possible to analyse a large number of drugs simultaneously in oral fluid within the limits of the appropriate Medicare Benefits Schedule items.

CLINICAL CHEMISTRY

Immunoassay of urine remains the dominant methodology for drug screening within Australia. Microgenics Diagnostics, recently integrated with Thermo Fisher Scientific Australia, supplies the widely used CEDIA® (Cloned Enzyme Donor ImmunoAssay) product line, each consisting of just two or three reagents, for performing very high sensitivity homogenous immunoassays on automated photometric clinical chemistry analysers. Instruments and the skilled staff to operate them can be found in virtually any automated biochemistry laboratory and participation in recognised external quality assurance programs ensures validity of results. Cost effectiveness is further guaranteed with lyophilised reagents, permitting long-term refrigerated storage of up to 36 months, and a linear relationship between kinetic enzyme rate and analyte concentration, allowing simple two-point calibration.

CEDIA® products use E. coli β-galactosidase genetically engineered into two inactive fragments that are able to spontaneously assemble into an intact enzyme that expresses β-galactosidase activity by a process termed complementation. One fragment has a covalently bound analyte (drug or metabolite) that does not affect complementation unless bound by antibody. Free analyte present in a urine sample will compete in a reaction with the enzyme fragment-analyte conjugate for antibody binding. As free analyte concentration in a urine sample increases so too the active enzyme and kinetic rate of chromogenic substrate hydrolysis increases in direct proportion across the calibration range.[10]

Antibodies to the drug targets of immunoassays are most often developed against one or several members of the particular drug class. There are 12 licit benzodiazepines available by prescription in Australia and the CEDIA® benzodiazepine assay has undergone continuous refinement to focus its specificity on this class of compounds. First cross-reactivity to sertraline metabolites was reduced[11] and then the product reformulated to include β-glucuronidase in order to increase sensitivity, particularly towards the higher potency benzodiazepines eliminated primarily as conjugated metabolites.[12] In a comparison of four commercially available immunoassay screening kits, the CEDIA® high sensitivity assay with β-glucuronidase demonstrated the highest positive screening rate for 27 benzodiazepines and metabolites.[13] There is currently no other technology that can produce this sort of result both affordably and potentially within minutes of specimen delivery to the laboratory. Urine drug screening is not the reserve of pain patients; many specimens are the result of overdose and require prompt treatment.

The CEDIA® opiate assay specifically targets morphine and codeine, but will also identify hydromorphone, dihydrocodeine and pholcodine. Seemingly benign, pholcodine can confuse interpretation of results due to its use in Schedule 2 cough linctuses and lozenges and very long elimination half-life.[14] Patients may unwittingly return positive results for opiates two or more weeks after use of pholcodine containing anti-tussives and understandably be unable to provide an explanation for the result. Interpretation of screening results has been improved by the addition of supplementary screens that target specific drugs. The CEDIA® 6-acetylmorphine assay identifies an unambiguous marker of heroin use in opiate positive specimens, but is limited by a detection window of only a few hours following use.[15] Oxycodone is increasingly prescribed and abused but its poor reactivity in commercially available opiate screening assays is widely unknown by clinicians. Addition of the DRI® oxycodone screening assay to the standard urine drug screening panel greatly improves the usefulness of screening for opiates[16], but not without increased cost. Neither 6-acetylmorphine nor oxycodone is routinely included in urine drug screens by all pathology providers.

Like oxycodone, buprenorphine is a semi-synthetic compound derived from the opiate alkaloid thebaine. It is a potent partial opioid agonist sometimes prescribed for pain, but generally dispensed as Suboxone® for the management of opioid dependence in a formulation with naloxone in the ratio of four to one. In 70 patients maintained on 8-24 mg/day of buprenorphine, a cut-off concentration of 5 ng/mL for the CEDIA® buprenorphine assay was found to be appropriate for determining compliance with therapy.[17] However, approaching the limits of sensitivity in an immunoassay may introduce artefacts associated with specificity, and in the case of buprenorphine false positives resulting from therapeutic doses of tramadol[18] and other opiates, such as codeine and morphine[19], can occur. Sacrificing some sensitivity by employing a higher cut-off concentration may improve selectivity sufficiently to eliminate false positive cross reactivity, but this entails hazarding false negative results for patients compliant with therapy.

Reckitt Benckiser Pharmaceuticals included naloxone in Suboxone® preparations with the intent of discouraging parenteral abuse of the sublingual formulation. An unforseen consequence was the potential of naloxone to complicate the interpretation of urine drug screens. Although orally administered with low bioavailability[20], naloxone and its primary metabolite, naloxone glucuronide, both exhibit sufficient cross reactivity with the CEDIA® opiate[21] and DRI® oxycodone[22] assays to produce false positive results when taken in therapeutic doses.

While the CEDIA® buprenorphine assay targets buprenorphine and buprenorphine glucuronide, Lin-Zhi International has developed a similar enzyme immunoassay specific for only free base buprenorphine and norbuprenorphine and not their glucuronide conjugates that appears to be free from opiate crossreactivity.[23] Normetabolites as biomarkers of opioid use have been employed clinically in Australia since the development of methadone metabolite assays. Methadone metabolism is well understood, being rapidly metabolised hepatically by N-demethylation to normethadone. Normethadone is rarely detected because it readily dehydrates to form

2-ethlidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).[24] In validating a CEDIA® EDDP assay by analysing 1381 urine specimens, George et al (2000) found seven were negative for EDDP by immunoassay and GCMS, but positive for methadone. These specimens were presumed to be spiked with methadone by the urine donors in order to simulate compliance.[25] Spiking of specimens by patients in opioid maintenance programs also occurs with Suboxone and currently the only analytical techniques with the requisite selectivity for detection employ mass spectrometry. Of 216 urine specimens analysed in a study by Hull et al (2008), seven were judged to be adulterated from their very low norbuprenorphine: buprenorphine ratios.[17] Very low level quantitation of buprenorphine and norbuprenorphine by LCMSMS, 0.5 ng/mL compared to 5 ng/mL by immunoassay, extends the detection window in urine and use of the metabolite: parent ratio also permits estimation of the time since dosing.[26]

Creatinine concentration is routinely determined on clinical chemistry analysers by the Jaffé reaction to verify the authenticity of urine specimens submitted for urine drug screening. The concentration is determined colourimetrically using alkaline picrate to form a red Janovski complex measured spectrophotometrically.[27] Creatinine is the metabolic waste product of creatine phosphate and is cleared in urine at a fairly constant rate by an individual. Values below 20 mg/dL are considered dilute. Although supplying a dilute specimen is not necessarily considered a deliberate attempt to produce a false negative urine drug screen result, repeat specimens are recommended. Values below 5 mg/dL are not considered to be consistent with human urine. Other urine characteristics that may be measured include urea concentration, specific gravity and pH. A general oxidant test and a sample check assay may also be performed. The sample check determines if a sample contains any compounds that will affect the homogenous enzyme immunoassay by: compromising the ability of the enzyme fragments to reassociate, affecting the ability of the active enzyme to cleave substrate or preventing the colour change of the cleaved substrate. Although these tests are effective at detecting adulteration of urine specimens, since they incur added expense all but creatinine concentration are generally excluded from Medicare rebatable testing.

MASS SPECTROMETRY

Urine drug screening performed by homogenous enzyme immunoassays on clinical chemistry analysers is a useful analytical technique due to its speed and because it produces a very high proportion of true negative results. The rapid return of results, typically within 24 hours of specimen collection, and the cost effectiveness of testing are responsible for putting this test at the disposal of clinicians. But what of positive screening results? If the results are consistent with therapy and patient compliance is believed then no further testing should be necessary. Many pathology providers now have toxicology laboratories that perform confirmatory testing on positive screens for drugs of abuse in urine specimens utilising mass spectrometric detection coupled to either gas or liquid chromatography as part of economically lucrative commercial operations in the workplace drug testing industry. Some laboratories will perform these assays for clinicians as part of medical testing, but since it is outside the scope of what is reasonably rebatable under the Medicare Benefits Schedule it is likely billed privately or subsidised.

Mass spectrometry is the forensic gold standard for the identification of unknown compounds. The quadrupole mass spectrometer is the mass analyser used most often for drugs of abuse testing. An ionised sample is introduced into the quadrupole where the quadrupole filters ions based on their mass to charge ratios. Oscillating electric fields applied to the four parallel rods of the quadrupole stabilise the trajectories of selected ions. In a single quadrupole analyser these ions reach the detector. In tandem mass spectrometers ions selected by the first quadrupole are transmitted to and fragmented in a collision cell and the trajectories of highly specific product ions are subsequently transmitted by a second quadrupole to the detector. Tandem mass spectrometers are not necessarily more sensitive instruments than single quadrupole analysers. It is the improved signal to noise ratio of the tandem mass spectrometer as a product of their greatly increased selectivity that permits a lower level of quantification.

Mass spectrometers are coupled with chromatographic instruments to enhance their ability to identify compounds by separating unknowns with respect to the time they enter the mass spectrometer. This is crucially important for isobaric compounds within the same class of drugs; those that have identical masses, such as morphine and hydromorphone or phentermine and methamphetamine, and very similar physicochemical properties, since they will likely have correspondingly similar mass spectra. A sample in mobile phase moves through an analytical column containing the stationary phase. Each compound's partition coefficient results in differential partitioning between mobile and stationary phases, resulting in differential retention on the stationary phase. Gas chromatography commonly uses helium as the mobile phase and requires relatively sophisticated sample preparation to extract and volatilise the analytes, which are often specific to each class of drugs. Liquid chromatography typically uses a mixture of water and solvents as the mobile phase and sample preparation is sometimes as simple as just diluting the specimen with mobile phase before injection, known colloquially as "dilute and shoot". This may permit simultaneous analysis of multiple classes of drugs.

Because the analytes are already in the gas phase, the electron ionisation commonly employed in GCMS causes drug molecules to fragment in a characteristic way, creating reproducible mass spectra permitting identification and quantification by a relatively simple single quadrupole analyser. Ionisation of analytes in the liquid phase does not cause significant fragmentation and therefore tandem mass spectroscopy is essential to generate sufficient selectivity for drugs of abuse testing. Generally GCMS and GCMSMS are cheaper to purchase than LCMSMS because the sample is already in the gas phase and ionisation and introduction into the vacuum of the mass spectrometer is therefore easily accomplished. It is the relative simplicity of sample preparation and the broad range of analytes that may be simultaneously analysed that makes LCMSMS attractive as the instrument of choice for clinical drugs of abuse confirmatory testing. It is the relative sophistication of the analyser that is frequently underestimated.

It is only in that last few years that LCMSMS has evolved sufficiently within the life sciences to become commercially viable as a clinical testing platform. Most of the major instrument vendors offer applications for the detection of drugs of abuse, but few can be considered "turn key". Microliter Analytical Supplies[28] and Gerstel[29] both offer LCMSMS instrument platforms utilising CTC PAL autosamplers to prepare urine samples online and just-in-time for the analysis of 51 and 49, respectively, pain management drugs and drugs of abuse. They both include a comprehensive panel of opioids, benzodiazepines, amphetamine type substances and cocaine. No cannabis metabolites are included, possibly due to the difficulty in efficiently ionising these compounds in the liquid phase. Microliter Analytical Supplies uses established mixed mode solid phase extraction (SPE) technology to extract and concentrate samples. Gerstel has developed a novel disposable pipette extraction technique as an alternative to traditional SPE that uses a reverse phase sorbent to remove the salts and proteins present in urine to concentrate the analytes. Although it is possible to simultaneously determine some drugs and their much more polar urinary metabolic conjugates, such as morphine, morphine-3-β-D-glucuronide and morphine-6-β-D-glucuronide, both vendors use off-line hydrolysis with β-glucuronidase to simplify the analysis by limiting it to unconjugated and more chemically homogenous compounds. Hydrolysis adds hours or even a day to sample turnaround time.

One of the major biotransformation pathways for opioids is *N*-dealkylation, particularly demethylation. Normetabolites generally exhibit longer half-lives than the parent drug and accumulate with prolonged use, therefore extending the detection window.[30] While adulteration of urine specimens by donors may occur, the ability to detect normetabolites also permits the detection of samples deliberately spiked with drug, although not necessarily the detection of substituted samples. Because oral fluid collection is simple and non-invasive, nonmedical personnel can perform it under close supervision. Opioids, amphetamine type substances and cocaine are readily detectable in oral fluid and the sensitive detection methods required for benzodiazepines due their low concentrations in this matrix have been described.[31] Oral fluid drug screening by LCMSMS may soon be a technically and economically viable option for the management of patients, eliminating adulteration or substitution of samples and permitting rapid analysis for determining compliance or abuse.

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Pain assessment in animals

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INTRODUCTION

Pain in animals has recently been recognised as a significant contributor to animal wellbeing. In the not so distant past these non-verbal beings were not considered capable of experiencing pain and, as a result, did not receive analgesia or pain management therapies. Attitudes have changed and perhaps a significant indicator of this change is the recent modification of both the European and American Colleges of Veterinary Anaesthesia to the European and American Colleges of Veterinary Anaesthesia and Analgesia (http://www.ecva.eu.com and http://www.acva.org respectively).

Historically animals were considered similar to neonates in their inability to experience the sensory and emotional aspects of pain: neonates either did not feel pain or had an altered perception of pain and, while it may be have been accepted that they perceive pain, concern regarding the potential side effects of analgesic drugs may have prevented the administration of pharmacological pain management strategies.[1] There is overwhelming evidence to demonstrate that the neurophysiologic wiring exists in animals to support the belief that they are capable of experiencing pain and for this experience to have adverse effects on their quality of life and welfare in both the short and long term. This pain experience may not be the same as a human but given that pain is acknowledged to be an individual experience it remains that there will be differences in the pain experience within and between species.[2] Animals cannot directly self-report or verbalise their pain experience and are unlikely to interpret efforts to comfort them as “it’ll feel better tomorrow” or “this tablet/injection/epidural will help”. In fact, it has been suggested that their inability to anticipate relief from pain may contribute to additional suffering.[2] Furthermore, as animals do not understand why pain occurs they cannot rationalise it and consequently may experience even more pain.[3] For these reasons it is probably not worth dwelling on the complexities of the emotional component of pain in animals, but to accept they exist and will have a negative effect on an animal, and move straight to assessing and managing pain. Reliable and accurate pain assessment can then facilitate effective pain management and the emotional experience of pain can be minimised, or even prevented. This is an important goal for all veterinarians, but especially those involved in this discipline.

DISCUSSION

Scottish physicist William Thomson, aka Lord Kelvin, is renowned for his statement: “I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science, whatever the matter may be”.

Efforts to quantify pain in animals mirror those in human patients: visual analogue scales, simple descriptive scales and numerical rating scales are all uni-dimensional pain scales, which attribute a number to the pain. There are a number of limitations to these methods of pain assessment in animals as they are based upon interpretation by an observer, the score is purely subjective in nature and is a global score, rather than a combination of specific observations relating to behaviour, response to interactions, physiological status and so on. Furthermore the judgement of the observer is invariably influenced by factors such as familiarity with the species, age, gender and previous personal pain experiences.[4]

Methods of quantifying pain in animals have been developed to minimise subjectivity and include, but are certainly not limited to, nociceptive threshold testing for the assessment of hyperalgesia and the development of composite pain scales based on psychometric principles.

NOCICEPTIVE THRESHOLD TESTING

Nociceptive threshold testing (NTT) has been used for some time[5] but is becoming common place for the assessment of pain and analgesic drug efficacy in a number of species.[6-12] While it is primarily used for research purposes, it is occasionally used in a clinical setting, especially for monitoring animals in chronic pain. Nociceptive threshold testing involves the application of a potentially painful stimulus to an animal to elicit a specific response. This approach enables an objective assessment of hyperalgesia, hypoalgesia and analgesia as the threshold at which a response occurs can be measured and expressed as a number. To perform NTT within an ethical framework consistent with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes[13] there are a number of requirements: the stimulus should provide quantitative information and be applied to a body part where there are minimal variations in neurohistology; the stimulus delivered should be the minimum necessary to elicit a

response; the response should be a natural behaviour of the animal (for example, a leg lift or turn of the head); termination of the stimulus the moment the response is observed must be possible; and tissue damage should be avoided.[5,14] Stimuli may be mechanical, thermal, electrical or chemical but contemporary literature refers most commonly to the use of mechanical and thermal stimuli. While nociceptive neurons respond to more than one type of stimulus their sub-types may be more specific. Small myelinated A fibres and unmyelinated C fibres, however, can respond to both mechanical and thermal noxious stimuli.[15] Electrical stimuli are relatively indiscriminate, which makes interpretation of the response more difficult. Furthermore, while it is desirable to avoid tissue damage it may be impossible, as all forms of stimuli have been observed commonly to produce evidence of local tissue change.

Development of NTT techniques for a given species requires an understanding of normal behaviour, as the response must be repeatable, unambiguous and related to the site of the stimulus. Sheep, for example, as a prey species, have evolved to be relatively stoical and may not display overt signs of pain and suffering. This behavioural trait makes it difficult to identify a repeatable response. Invariably extensive pilot testing is performed prior to a study proper to determine the most appropriate site for stimuli application, the response to that stimuli and the potential impact of the environment and other beings in the vicinity. Ideally the environmental conditions should be controlled and standardised, and the response observed from a distance to decrease the influence of extraneous factors. It is sometimes tempting to distract the animal with food or companions while the test is being performed but this may alter the type of response, the timing of the response, and hence the threshold for a given stimulus.

The site of application of the stimulus may dictate interpretation of the results. If the stimulus is delivered proximal to the surgical site or painful lesion, then primary hyperalgesia (exaggerated responses to painful stimuli at the site of trauma) can be assessed. If, however, the position of the stimulus is distal to the area of interest then it may be that only secondary hyperalgesia (exaggerated responses to painful stimuli in the surrounding uninjured tissue) is assessed. The ideal site for delivery of the stimulus may not be an option if a repeatable response cannot be elicited so a trade off is often made.

Nociceptive threshold testing is not performed in isolation. The results can only be interpreted longitudinally with reference to a pre-treatment baseline. If hyperalgesia has developed the threshold to a given stimulus will decrease from baseline. Conversely, hypoalgesia is associated with an increase in the threshold. Analgesic drug efficacy is often inferred if the threshold increases from the baseline but the majority of studies are performed in animals that have not undergone a painful (for example, surgical) procedure. Interpretation of results is more complicated if surgery or trauma has occurred prior to testing as the response to analgesia may be different following a period of pain or tissue damage.

The advantages of NTT include: a number is generated (temperature in °C for thermal stimuli and force in Newtons for mechanical stimuli); collection of data is relatively objective and inter-observer differences are minimised. There are a number of disadvantages: the response to stimuli may be difficult to interpret in some species and the stimuli may cause tissue damage which may alter subsequent test results and compromise the welfare of the study animals.

COMPOSITE PAIN SCALES

Give that pain is a complex and multi-dimensional experience composite pain scales have been developed for the assessment of pain in animals. A composite score based simply upon the sum of a number of uni-dimensional scores is, however, insufficient to reliably and repeatedly assess pain in animals. The adoption of the psychometric approach has enhanced the value of composite pain scales and a group of researchers from the University of Glasgow have developed the Glasgow Composite Measure Pain Scale (GCMPS)[16] for dogs. This is the only validated pain scale for the assessment of acute pain in dogs and is based upon the psychometric principles of validity, reliability and responsiveness to change. This multi-dimensional scale takes into account not only the intensity of pain but also the consequences of pain. The phases of development were in three parts: 1) specifying measurement goals, identification of the patient population and development of a pool of potential items for inclusion; 2) selection of suitable items from the item pool, expert validation of the selection of items, formal scoring mechanism applied; 3) field testing.[16] The psychometric properties underlying this pain measurement tool were validity (that is, the instrument can measure what it is designed to measure); reliability (the instrument can measure accurately and repeatedly what it is intended to measure with minimal inter and intra-observer variability); and responsiveness (the instrument is sensitive enough to detect statistically and clinical significant differences). Furthermore, the tool was developed to be practical and easy to use and interpret.[4]

The GCMPS categorises and weights spontaneous and evoked behaviours, and interactive and clinical observations (comfort, vocalisation, mobility, demeanour, posture, attention to the surgical wound and response to touch) resulting in a composite score. The short form of the GCMPS for dogs suffering acute post-operative pain was developed for use in a clinical setting where the emphasis is on efficiency, ease of use and guidance for the provision of analgesia. The short form comprises six behavioural categories (vocalisation, mobility, demeanour, posture, attention to the surgical wound and response to touch). The maximum score is 24 (or 20 if mobility is impossible to assess) and it is reported that a clinical decision point for administration of analgesia gave an interventional level of 6/24 (or 5/20 if mobility could not be assessed). This tool forces the assessor to evaluate behaviours that may be associated with pain and draw conclusions about whether or not the animal requires additional analgesia. It therefore contributes to improved pain management, especially in a clinical setting.

The major limitation of the GCMPS is that it is only applicable to dogs and was designed to assess acute post-operative pain. A similar tool for other species has yet to be fully developed and given the undeniable differences in the behaviour of dogs compared to the myriad other species that vets work with it should not be extrapolated across species. Despite this limitation, the GCMPS has had a major influence on the assessment and management of pain in dogs in the acute post-operative period.[17,18]

ACUTE VS. CHRONIC PAIN

The assessment of acute pain in animals is complex, albeit relatively easy, when compared to the assessment of chronic pain in animals. While veterinarians are usually responsible for the assessment and management of acute pain, especially post-operative or traumatic pain, it is the owner or carer of an animal that is well positioned to assess chronic pain, insofar as its impact upon wellbeing.

From a clinical perspective, assessment of chronic pain is difficult as although it is well established that sensory alterations occur following painful stimuli, and hyperalgesia and allodynia may develop, it is difficult to measure these changes accurately. Nociceptive threshold testing has a role to play in the identification of changes in the function of the sensory system and has been used in a number of species for the identification of central sensitisation.[19] Osteoarthritis is a common cause of chronic pain in dogs and given the level of physical activity enjoyed by this species this disease can have significant animal welfare implications.[20] In fact, rupture of the cranial cruciate ligament is not just a footballer's injury, it is one of the most common causes of musculoskeletal disease and lameness in dogs.[21] A recent study further investigated quantitative measurements of sensory changes consistent with chronic pain in dogs with naturally occurring osteoarthritis by evaluating four quantitative sensory tests for clinical assessments in this group of animals.[22] The authors compared well-established threshold level mechanical (von Frey filaments) and thermal tests (cold plate at 6.9-7.9 °C), static weight-bearing, movement induced weight-bearing and gait parameters (pressure plate system). Tools such as these can be used in a clinical setting to objectively and quantitatively assess sensory alterations in animals with chronic conditions. This in turn may be useful in guiding the management of these individuals.

The question has been posed as to whether, if in fact animals can feel pain, do they care about it? If we assume we cannot assess behavioural changes associated with acute or chronic pain then the answer will remain unanswered, or, in the worst case scenario, the answer will be 'no, they don't care'. Enough is known about the behaviour of some species to preclude this worst case scenario but answering it emphatically is difficult. Assessment of health-related quality of life is perhaps a more appropriate approach to assess the impact of pain on well being, as opposed to the pain per se. This approach has been explored by the Glasgow Pain and Welfare Group to measure chronic pain in dogs through its effect on health-related quality of life4. Now validated in the field, their questionnaire does not replace a visit to the vet but helps the owner and veterinarian tailor pain management strategies for an individual in the longer term.[23] The behavioural domains incorporated therein are: activity, comfort, appetite, extroversion-introversion, aggression, anxiety, alertness, dependence, contentment, consistency, agitation, posture and mobility, and compulsion. This is a British questionnaire and in 2012 preliminary work was undertaken to 'translate' the questionnaire into an Australian version suitable for Australian dog owners and vets.

PAIN MANAGEMENT IN ANIMALS

There is considerable overlap between human and veterinary therapeutics and analgesia is no exception. In a surgical setting premedication of animals is routine for sedation, anxiolysis and pre-emptive analgesia. Many veterinary patients are less than co-operative so this pre-anaesthetic medication is especially important. Acepromazine is a phenothiazine tranquiliser and is the most common drug used for premedication. It is usually combined with an opioid and in Australia this is usually morphine, methadone or buprenorphine. Aggressive or unco-operative animals may prompt the use of an α_2 adrenoreceptor agonist drug like xylazine, medetomidine, dexmedetomidine, romifidine or detomidine (depending on the species) as these drugs are excellent sedatives and have some analgesic effects as well. These drugs also are commonly used in combination with an opioid. Intraoperative analgesia involves the use of regional nerve blocks and epidural analgesia but these most often need to be performed once the animal is anaesthetised. Regional nerve blocks performed with the use of a peripheral nerve locator or ultrasound are becoming more commonplace and replacing the not-quite-as-accurate peri-neural infiltration of local anaesthetic drugs based upon anatomical location. For hind limb, perineal, abdominal and thoracic surgery, an epidural injection or catheter delivers local anaesthetics like bupivacaine or lidocaine with or without an opioid to the surgical area. The infusion of analgesic drugs is also employed as part of a total intravenous anaesthetic technique or in combination with gaseous anaesthesia (usually isoflurane) and it is common, certainly in referral hospitals, for animals to receive fentanyl, remifentanil, ketamine, lidocaine and/or medetomidine by intravenous infusion as part of their balanced anaesthetic regime.

In the immediate post-operative period, infusions may be continued or intermittent dosing of drugs such as morphine or methadone may be sufficient. Non-steroidal anti-inflammatories are often administered at this juncture. Carprofen and meloxicam are perhaps the most common NSAIDs for dogs and cats while phenylbutazone or flunixin often are administered to production animals and horses.

Transdermal delivery of drugs also is common in some veterinary hospital environments. Transdermal fentanyl was the first such drug to be adopted into veterinary medicine but placement on the clipped skin of an animal must be considered carefully to prevent removal and subsequent ingestion. Veterinarians counsel owners about the importance of regular observation of these patches if the animal is discharged with the patch in place. Buprenorphine also is delivered by the transdermal route and is especially useful in cats as it appears to be particularly efficacious in this species. Once again, care must be taken to strategically place the patch to prevent removal by the patient. And lastly, lidocaine patches are often used for surgical wound pain and placed around the surgical site at the end of surgery.

Chronic pain management for animals is invariably based upon the administration of NSAIDs as osteoarthritis is the most common indication for long-term pain relief. Tramadol, gabapentin, amantadine and non-pharmacological strategies also are commonly used but there is limited data to provide a sufficient evidence base for the use of some of these drugs. The response to tramadol is variable in dogs but the frequency of side effects is low and rarely serious so this drug is popular for long-term therapy as it is much cheaper (though not necessarily better value) than most NSAIDs.

In conclusion, if pain is measured in terms of its relief, then veterinarians will be hindered in their ability to accurately assess the efficacy of analgesic drugs in specific species and to confidently administer these drugs until pain assessment in animals is more reliable and repeatable. The range of species that most veterinarians care for is wide so this challenge is particularly difficult. In the meantime, decisions about the provision, safety and efficacy of analgesia will be made primarily on empirical grounds and as the pool of data increases pain in animals will be better managed.

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The impact of culture on simulation based medical education

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INTRODUCTION

It is often said "the world is a global village". We are likely to be interacting with people from different cultural backgrounds in our daily lives and work. In the Medical Labour Force 2009 Report of the Australian Institute of Health and Welfare, 45% of medically qualified residents were overseas born, including an estimated 25% who were overseas qualified. This figure increases to 46% overseas trained in rural and remote practices.[1]

This also is true in the field of education. International education activity contributed $15 billion in export income to the Australian economy in 2012.[2] China, India and other Asian countries account for the majority of this international education population. Increasing numbers of international students are enrolled in medical courses.[3] There are many overseas trainees in anaesthesia and pain medicine attracted to the high quality of training offered by the Australian and New Zealand College of Anaesthetists (ANZCA). Simulation-based medical education (SBME) forms part of this training and courses attract overseas participants. In addition, Australia and other western countries export their branded simulation-based medical education courses to other countries and cultures.

The Effective Management of Anaesthetic Crises (EMAC) course was developed and copyright to ANZCA in 2002, and has been in its second revision since 2010. It is required training course for the fellowships of both ANZCA, and the Hong Kong College of Anaesthesiologists (HKCA). It is offered in various centres in Australia and New Zealand and in Hong Kong. The course is standardised with a common curriculum, participant and instructor manual, and timetable. The centres delivering EMAC are accredited and the instructors have to go through specified training.

My interest in the cultural impact on simulation-based medical education came from delivering EMAC in Hong Kong and comparing this with experiences at EMAC course that I have taught in New Zealand as an external instructor. I encountered difficulties in teaching assertiveness and leadership in Hong Kong, which were not problems in the New Zealand course. However I realised we were having other problems in New Zealand, such as interpersonal conflicts, which were rarely seen in the Hong Kong courses. This article is a review of the literature to try and explore the reasons behind these cultural differences in simulation-based medical education.

NATIONAL CULTURE

Hofstede defined culture as "The collective programming of the mind that distinguishes one group or category of people from another."[4] This stresses that culture is a collective rather than individual attribute; that it is not directly visible but manifested in behaviours; and common to some of the group but not all people.

Culture was defined by Merritt as, "the values and practices that we share with others that help define us a as a group especially in relation to other groups."[6] Values are items that can be measured.

Cultural relativism means there are no absolute criteria for considering one cultural group intrinsically superior or inferior to another.

HOFSTEDE MODEL

One of the most influential efforts to describe cultural values was by Hoefstede[4,5] who surveyed work-related value dimensions in over 116,000 employees in more than 70 countries of a multinational corporation (IBM) in 1980 and repeated the study with other collaborators in 2001. He described four dimensions of national culture:

Power distance (PD) is the relationship between subordinates and superiors, and is also the extent to which the less powerful expect and accept that power is distributed unequally. This represents inequality but is defined from below not from above. High power distance cultures accept their position and follow authority, which tends to be centralised and hierarchical. Low power distance cultures are more decentralised and have fewer layers of management with flatter levels of management structures. Comparing the power distance index (PDI), Hong Kong has one of the highest PDI of 68 compared to the PDI of Australia of 36 and one of the lowest PDIs of New Zealand of 22.[5]

Uncertainty avoidance (UA) describes the ways different cultures deal with uncertainty. It indicates to what extent members feel comfortable in unstructured or ambiguous situations. Uncertainty avoiding cultures try to minimise such situations by laws and rules, by safety and security measures. The opposite; uncertainty – accepting cultures are more tolerant of different opinions; they try to have as few rules as possible and embrace the unpredictable. Australia has a midrange uncertainty avoidance index (UAI) of 51, New Zealand similar 49 and Hong Kong a very low UAI of 29.5 Most Asian countries have high uncertainty avoidance, such as Japan 92 and South Korea 85, but Singapore scored lowest at eight. This may reflect the east meets west culture of Hong Kong and Singapore and their aggressive business mindset.

Individualism – collectivism (IND) is the extent to which individual's behaviours are influenced and defined by others. In individualist cultures, ties between individuals are loose; everyone looks after themselves and their immediate family. In collectivist cultures people are integrated into cohesive in-groups, often extended families, protecting them in exchange for loyalty. Australia is a highly individualistic culture with an individualism – collectivism index of 90, New Zealand 79 and Hong Kong 25, which is more collectivist.[5]

Masculinity – femininity refers to the distribution of emotional roles between the sexes. In masculine societies the social gender roles are clearly distinct, that is, men are supposed to be assertive, tough, and focused on material success whereas women are supposed to be more modest, tender, and concerned with the quality of life. In feminine societies the social gender roles overlap, that is, both men and women are supposed to be modest, tender and concerned with quality of life. Hofstede found that women's values differ less among societies then men's values, and that men's values vary along a dimension from very assertive and competitive and maximally different from women's values on one side to modest and caring and similar to women's values on the other. Australia has a masculinity index of 61, New Zealand 58, Hong Kong 57, which are all midrange.[5] With the increasing numbers of women joining the anaesthetic workforce from currently 34% in New Zealand to an expected 40% in 10 years[13] this dimension may become more significant.

An additional dimension was later added of long – short-term orientation. Values associated with long-term orientation are thrift and perseverance. Values associated with short-term orientation are respect for tradition, fulfilling social obligations and protecting one's "face". Hong Kong has a long-term orientation with an index of 96, compared to more short-term orientation of Australia 31 and New Zealand 30.[5]

RELATIONSHIP OF CULTURAL DIMENSIONS

There is an inverse relationship between power distance and individualism – collectivism. Those cultures with high individualism score low on power distance, while those with high collectivism have greater power distance. Merritt6 described a direct relationship between uncertainty avoidance and power distance. Those cultures with low uncertainty avoidance (greater tolerance for ambiguity and desire for flexibility), tend to have low power distance and high individualism. Those cultures with high uncertainty avoidance (preference for rules and set procedures) score high on power distance and low on individualism.

This relationship can be expressed in the formula:

$$\text{Power Distance} = \frac{\text{Uncertainty Avoidance}}{\text{Individualism}}$$

Uncertainty avoidance also relates to masculinity according to motivations. Achievement motivated societies have low uncertainty avoidance and high masculine values, security motivated have high uncertainty avoidance and high masculinity, and socially motivated societies have more feminine values and high uncertainty avoidance.

HIGH CONTEXT AND LOW CONTEXT CULTURES

These concepts may be further understood under the concept of high context and low context cultures. The context in this case, particularly relates to how people communicate in those cultures and where the information that is communicated lays: in the person in high context and in the message in low context cultures. In high-context cultures the interpretation of messages rests on contextual cues. High context cultures are homogenous societies where people are of similar backgrounds and belief systems. Everyone understands the others beliefs and principles and so assumptions are made of how the other thinks. So less information is passed in verbal of written context. The focus of communication is more on the people "who you are". There are often set rules of communication protocol, and often there is more time spent in communicating in formal structures. Examples would be China, Korea, Taiwan, Malaysia, Brazil, Mexico and the Philippines. These cultures tend to have high power distance, high uncertainty avoidance and low individualism.

In contrast, low-context cultures put the most emphasis on information in written or spoken words, they communicate more specifically and tend to be more direct and to the point and focus on the goal or task. These are generally the heterogeneous cultures that are the great melting pots of the world such as USA, and include Australia and New Zealand. People that you may be communicating with may be of very different cultural, religious and belief backgrounds. There is no single set of rules of conduct. So you cannot make assumptions of understanding in communication. These cultures tend to have low power distance, low uncertainty avoidance and high individualism.[5]

CULTURE AND BUSINESS

Hoefstede studied IBM employees around the world and applied these models to business management. These cultural differences may have an impact in decision-making. In lower context cultures, people try to reach decisions quickly and efficiently. They're concerned with reaching an agreement on main points, leaving details to be worked out later by others. In higher context cultures, details are important and they take their time. In problem solving, low context cultures encourage open disagreement, whereas high context cultures avoid confrontation and debate. In negotiating, low context cultures view negotiations impersonally and focus on outcome goals, whereas high context cultures emphasise relationships and a sociable atmosphere when negotiating.[5]

CULTURE AND AVIATION

Merritt studied 9400 male commercial airline pilots in 19 countries, incorporating items from Hofstede's Work Values Survey into the Flight Management Attitudes Questionnaire.[6] They recognised a number of cultural clusters: Japan is distinguished by its high uncertainty avoidance score, the Philippines by its high power distance score; Korea, Taiwan and Morocco as a group are distinguished by low individualism and masculinity; Brazil, Mexico and Malaysia have the second highest power distance scores; and the Anglo (including Australia and New Zealand) and western European countries are notable for having the highest individualism scores and lowest power distance and uncertainty avoidance scores. These clusters can be used to describe various pilot profiles.

Pilots from individualist, low context cultures were more independent, self-reliant, with individual responsibility and open and direct communication. Those from collectivist, high context cultures showed more interdependence and group orientated activities, more indirect and greater volume of communication.

Pilots from every cultural group agreed that co-ordination and communication are vitally important, such as briefing, verbalising plans and co-ordination between cockpit and crew. However, questioning authority and speaking up are not universally accepted. Low context cultures strongly agreed that junior crewmembers should question their captains, whereas high context cultures strongly disagree. These represent the area of command (power distance) and flexibility with rules (uncertainty avoidance). Pilots from low context cultures such as the US, Australia and New Zealand had very similar views, while high context cultures the more hierarchical command styles were differentiated by the relative importance allocated to rank (Brazil), rules (Taiwan) and relationships (the Philippines).

This study shows that even in a highly specialised, highly regulated profession such as aviation, national culture still exerts a meaningful influence on attitudes and behaviours over and above the occupational context.

CULTURE AND THE OPERATING ROOM

Helmreich compared the Flight Management Attitudes Questionnaire among pilots and the Operating Room Management Attitudes Questionnaire (ORMAQ) in the medical setting.[7] This measured operating theatre staff attitudes towards stress, hierarchy, teamwork and error. Anaesthetists were more accepting than surgeons of the idea that a preoperative briefing important for team effectiveness. Helmreich had previously reported that pilots underestimated the effect of stress and fatigue on their performance: "To our surprise the attitudes of medical professionals were equally unrealistic."[7]

Sexton[8] reported comparison between aviation and medicine in errors, stress and teamwork. Pilots have been trained in CRM for many years to recognise the effect of stress and fatigue. Pilots were least likely to deny the effects of fatigue on performance (26% vs. 70% of consultant surgeons and 47% of consultant anaesthetists). Most pilots (97%) and intensive care staff (94%) rejected steep hierarchies (in which senior team members are not open to input from junior members), but only 55% of consultant surgeons rejected such hierarchies. High levels of teamwork with consultant surgeons were reported by 73% of surgical residents, 64% of consultant surgeons, 39% of anaesthesia consultants, 28% of surgical nurses, 25% of anaesthetic nurses, and 10% of anaesthetic residents, showing that cross discipline teamwork is still an issue and that peoples perspective are different within the same team.

CHALLENGING AUTHORITY

One aspect of human factors that has been recognised as difficult in Asian cultures is challenging authority. Asian cultures may be described as more hierarchical in structure. This may make it more difficult to speak up in a crisis, which is an important step in improving communication in a crisis. A speak up culture and making a second challenge are key learning points in simulation-based medical education training.

Kobayashi[9] used a modified Operating Room Management Attitudes Questionnaire to compare US and Japanese residents' perceived barriers to questioning or challenging their seniors. There were significant differences in items that related to challenging authority where the Japanese residents were less likely to challenge their seniors. However there was more compliance from the Japanese for the pre-session briefing (this study was prior to the WHO Safe Surgery Checklist) but less agreement with verbalisation of plans or procedures.

Kobayashi also used an operating theatre scenario based questionnaire to compare responses in challenging authority between Japanese and US residents.[9] Residents' decisions to make a challenge were related to the relationships and perceived response of the superiors. There was no statistical difference between the US and Japanese residents in terms of the threshold for challenging their seniors. Kobayashi concludes that organisational and professional cultures could override the national culture in this specific area of speaking up to seniors.

PROFESSIONAL CULTURE

When a pilot enters the cockpit he leaves his national culture behind and takes on the professional culture as a pilot. Anaesthesia also has a professional culture. Flin[10] received 222 responses of this version of the ORMAQ from distributing to 374 Scottish anaesthetists. On items relating to leadership structure, anaesthetists' attitudes are positive and non-hierarchical. Anaesthetists tend to favour flatter team structures with shared responsibilities for leadership. Helmreich[7] reported that anaesthetists preferred consultative leadership whereas many surgeons endorsed the mild autocratic style. In relation to confidence assertion the majority of anaesthetists said they would speak up when they perceived a problem, although they were less comfortable when this involved a team member from another discipline. 90% of anaesthetists agreed that they enjoyed working in teams and 92% agreed on the importance of verbalising plans and procedures. Helmreich found that surgeons were even less likely than anesthetists to use team-briefing techniques.

CULTURE AND SIMULATION

I have surveyed pre and post-EMAC course ORMAQ responses in the Hong Kong centre.[11] A total of 48 participants were included with the largest group being 38 Hong Kong trainees. This study has shown that attitudes represented in ORMAQ are subject to the intervention of EMAC. A total of 13 items out of 60 in ORMAQ showed a significant difference between pre and post course questionnaire towards the ideals that are included in the learning objectives of EMAC. There were significant differences in items relating to leadership structure, confidence assertion, information sharing, stress and fatigue, teamwork, work values and organisational climate. The greatest number of items influenced was in the confidence-assertion theme. There was only one item influenced in the theme of leadership structure, which has been observed to be a difficult learning point in this participant group. There were no significant differences pre and post course in the theme of error/procedural compliance, despite this being a learning objective of EMAC. There was a high concordance of agreement in the pre-course items in the theme of teamwork indicating good pre-knowledge in this area.

These results may help to adjust how the EMAC course is delivered to focus more on the themes that are subject to intervention, rather than those which show high pre-course agreement which may be due to pre-knowledge.

So there can be no universal simulation-based medical education curriculum as not all cultures agree on all elements. There are two main categories: low or high context cultures. There is no ideal national culture. Those with low individualism have a greater tendency to be group orientated and to emphasise interpersonal communications. Those with low power distance have less of a gap between superiors and subordinates. A high uncertainty avoidance would mean a preference for keeping to rules and protocols. However as previously explained there is an inverse relationship between individualism and power distance. The best that could be achieved is a midrange for all variables – which is closest to the Germans' culture[12] variables. So it is important to tailor simulation-based medical education courses to the culture of the participants. In high context cultures the emphasis on questioning authority. For low context cultures the emphasis should be on interpersonal communications and group relationships. There is a simulation-based medical education cultural bias towards western cultures as most courses are developed and copyright in western cultures. Many of these courses have been exported to other cultures. Participants in these courses may have travelled from other cultures. When teaching other cultures we may need to tailor the courses according to high/low context cultures.

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Research integrity: what is it and why does it matter?

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INTEGRITY BY NAME…

In October 1966, the *Journal of Experimental Biology* published a paper by R.A. Hammond entitled "The proboscis mechanism of Acanthocephalus ranae".[1] In this brief paper, Hammond describes for the first time the hydraulic and physiologic mechanisms that Acanthocephalus, an internal parasite of fish and amphibians, uses to control its proboscis. The primary purpose of the proboscis is to allow the worm to closely attach to its host. The paper is simple and elegant. Until recently, it had been cited 22 times.

In April 2013, the journal *Nature Communications* published a paper by Yung et al. entitled "A bio-inspired swellable microneedle adhesive for mechanical interlocking with tissue".[2] Yung et al. considered that traditional methods of achieving strong adhesion to soft tissue were potentially damaging (staples for example) or required reactive chemistry, which carries increased risk of inflammatory response. In looking for an alternative mechanism, Yung et al. found the 1966 paper by Hammond. The proboscis described by Hammond swells like a balloon once it is inside soft tissue, helping to maintain contact between the worm and its host. The paper from 1966 with 22 cites has inspired a Nature publication, but more importantly it triggered the idea for development of a new material and mechanism for securing soft tissues. It is hard to imagine that Hammond ever envisaged his work could lead to such a creation.

This story outlines why research integrity matters. The potential influence of some research findings cannot be fully appreciated at the time of publication. We can never know who will draw inspiration from our research findings. We have a responsibility to do what we can now to make certain that anyone using the outputs of our research at some point in the future can do so confidently and with an appreciation that the research findings are honesty reported and reflect research that was conducted well. Research integrity then can be considered a list of traits that define trustworthy and honest research.

THE SINGAPORE STATEMENT

The Singapore Statement was an outcome of the 2nd World Conference on Research Integrity, held in Singapore in 2010.[3] The principles and responsibilities described in the statement are intended to provide high-level advice to researchers, organisations, funding agencies and governments. They outline the common set of principles and responsibilities that apply to all research.

The statement lists four principles: (i) honesty in all aspects of research; (ii) accountability in the conduct of research; (iii) professional courtesy and fairness in working with others; and (iv) good stewardship of research on behalf of others. Fourteen responsibilities stem from these principles. Fortunately, many of these responsibilities are reflected in national guidance documents like the Australian Code for the Responsible Conduct of Research[4] and in most institutional codes of conduct for research.

THE AUSTRALIAN CODE FOR THE RESPONSIBLE CONDUCT OF RESEARCH

The Australian Code was published in 2007 and was produced by the National Health and Medical Research Council (NHMRC), the Australian Research Council (ARC) and Universities Australia. It provides practical advice for institutions and researchers about their responsibilities for ensuring that research is conducted with integrity. Funding agreements between the NHMRC and ARC and institutions makes compliance with the Australian code a condition of continued funding. The Australian code also provides a framework for handling and investigating allegations of research misconduct.

In addition to describing general principles of responsible conduct of research, the Australian code sets responsibilities in seven key areas: management of research data and primary materials, supervision of research trainees, publication and dissemination of research findings, authorship, peer review, conflicts of interest and collaborative research. All of these areas can impact on the integrity of the research record. We consider that there are four that have the potential to cause the greatest impact on the integrity of research.

(i) Management of research data and records

While not the most interesting topic for discussion, the importance of proper management of research data and records is difficult to understate. The data generated through responsible research is the 'gold' in the research lifecycle. It is the data that supports and validates research findings, and enables research to build on itself to provide a clearer picture of the topic under investigation. Proper management of research data provides greater opportunity for comparative research, greater opportunity for collaboration and provides an increased level of protection against allegations of research misconduct.

In principle the idea is simple. Research data and records should be managed well, retrievable, stored safely and kept confidential where required. The practice is sometimes more complicated, and this is especially so where the data may contain personal or sensitive information. Fortunately there are lots of sources of advice, information and assistance from most research organisations.

(ii) Authorship

In research, authorship rewards contribution and assigns accountability. An author of a research output, such as a journal article or a book chapter, is someone who made a significant intellectual or scholarly contribution to the research output and is willing to take responsibility for his or her contribution: simple!

However, the practice of determining authorship is complex. What contribution did the person make and was the contribution significant enough to warrant authorship? For example, was the contribution important for the production of the research findings described in the research output? Did the contribution provide insight into the interpretation of the work? Was the contribution an intellectual or scholarly one? Was the contribution solely technical? Did the author write anything? Who provided the funding? Furthermore, are there certain roles that are automatically included or excluded as authors such as students, statisticians, heads of department? To add another layer of detail, who is first author?

In order to assign authorship correctly, researchers should talk with potential co-authors (including students, colleagues and collaborators) about authorship early in a study and as required, for example, if the research takes an unexpected direction or if new contributors join the collaboration. The discussions about authorship should work towards a plan and cover who's doing what, what's expected in order to warrant authorship, who is probably not an author, who probably is an author and what is the likely order of authors. Discussions and plans should be recorded in writing, mindful that plans with regard to authorship may change dramatically during the course of investigation. Discussing and planning authorship in the early parts of a study may be difficult and delicate. However, given the complexities they will be helpful. They should also reduce the likelihood of complaints when it comes time to publish or even after publication.

There are many guidelines, protocols, and policies for authorship that are provided by various sources including journals, committees, institutions and funding bodies (Table 1). Unsurprisingly, guidance documents are of limited use if they do not reflect current practice, ignore discipline conventions, are too prescriptive or attempt to provide highly specific advice. However, most advice aligns well in terms of general principles and as such will probably help when it comes to discussing and planning authorship.

Table 1. Guidance for authorship provided by selected journals in anesthesia

Journal	Authorship policy or advice
Anaesthesia and Intensive Care	All authors have contributed substantially to the manuscript and attest to the validity of the data and the originality of the text (unless otherwise specified). The manuscript includes or is accompanied by a statement signed by all authors that they have read and accept the "Terms and Conditions for *Anaesthesia and Intensive Care* Submissions" as outlined in this submission process. The role of each author in the study is also described briefly.
Anaesthesia	All authors must meet the requirements of authorship as set out in the guidelines of the International Committee of Medical Journal Editors, that is, all have made a substantial contribution to the acquisition of data and its interpretation AND been involved in drafting the manuscript or revising it. All proposed changes in authorship after submission must be explained, and any changes can only occur with the explicit permission of the Editor-in-Chief.
Journal of Clinical Anesthesia	Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. Where there are others who have participated in certain substantive aspects of the research project, they should be acknowledged or listed as contributors. The corresponding author should ensure that all appropriate co-authors and no inappropriate co-authors are included on the paper, and that all co-authors have seen and approved the final version of the paper and have agreed to its submission for publication.
Pain	The editors review manuscripts submitted under multiple authorship on the assumption that (1) all listed authors concur with the submitted version of the manuscript and the listing of the authors; (2) authors made important contributions in one or more of the following areas: conception and design, analysis and interpretation of data, drafting of the manuscript, or making intellectual contributions to its content; (3) responsible authorities in the laboratory or at the institution where the work took place have tacitly or explicitly approved the final manuscript.
Anesthesiology	Each manuscript must have a "Corresponding Author." However, all authors must have participated in the design, execution, and/or analysis of the work presented, and attest to the accuracy and validity of the contents. All persons or organisations involved in the work must be listed as authors or acknowledged. Manuscripts are received with the understanding that they have been written by the authors; ghostwritten papers are unacceptable. See Cullen D. Ghostwriting in scientific anesthesia journals. Anesthesiology 1997;87:195-6.
British Journal of Anaesthesia	The author must take responsibility for at least one component of the work, should be able to identify who is responsible for each other component, and should ideally be confident in their co-authors' ability and integrity. The British Journal of Anaesthesia follows recommendations of International Committee of Medical Journal Editors; the authorship credit should be based on: 1. Substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data; 2. Drafting the article or revising it critically for important intellectual content; and 3. Final approval of the version to be published. The authors should meet all three conditions. For large, multicentre studies, the group of investigators should identify individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship. All manuscripts submitted to *BJA* must inform the readers of individual contribution which each author made to the research and/or manuscript. Please give initials of the names of each of the authors (such as RD, IKM), and against their initials list the contributions, which they individually made to the work (such as RD: Study design and data analysis; IKM: Patient recruitment, data collection and writing up of the first draft of the paper).

The new authorship policy framework at the University of Melbourne aims to provide the best possible advice to its researchers. The policy is underpinned by the following principles that are hard to argue against and provides a starting point when thinking about authorship and delicate discussions:

"Authorship must only recognise a significant intellectual or scholarly contribution to a research output. An author is responsible for the integrity and accurate reporting of at least their significant intellectual or scholarly contribution to a research output.

In determining this policy, the University considers that authorship:

(i) must be an honest reflection of contribution to research, and

(ii) should be assigned fairly and consistently, and

(iii) should be communicated clearly and transparently between contributors to the research, and

(iv) should be approached with a generosity of spirit whilst remaining true to the policy requirements."

(iii) Conflicts of interest

Conflicts of interest abound in research. The peer-review process is a clear example. We would hope that experts in the field review our grant applications or manuscripts. This will usually mean, especially if we are thinking of national reviews, that someone with whom we have a personal relationship will be reviewing our work. We would all hope the quality or outcome of the review is not affected by this personal relationship – this is one reason why reviewers are often anonymous – but the ideal that a decision will be unaffected by bias cannot be guaranteed. Ethics committees and institutions also must consider conflicts of interest.

Undisclosed conflicts of interest can prevent readers from making an accurate assessment of the integrity of a piece of research. The ubiquity of real or perceived conflicts of interest means that they cannot be eradicated. The principle in effect here is that conflicts of interest must be disclosed and managed so that accurate assessments can be made, or the impact – real or potential – of a conflict of interest can be reduced.

(iv) Research misconduct

All professions must have processes in place for dealing with malpractice or misconduct. Research is no different. These deviations from accepted practice might be deliberate and intentional or reckless and negligent. Many researchers would accept that fabrication, falsification and plagiarism represent the gravest deviations from accepted practice. Products of research that have been falsified, fabricated or plagiarised are in fact not research and deserve no place on the public record.

Research misconduct is not limited to fabrication, falsification and plagiarism. The Australian Code provides the following definition:

"Research misconduct includes fabrication, falsification, plagiarism or deception in proposing, carrying out or reporting the results of research, and failure to declare or manage a serious conflict of interest. It includes avoidable failure to follow research proposals as approved by a research ethics committee, particularly where this failure may result in unreasonable risk or harm to humans, animals, or the environment. It also includes the willful concealment or facilitation of research misconduct by others."

Most institutions will have their own definitions of research misconduct that cover broadly the same types of deviations. It is important to recognise that whatever the definition, research misconduct is something that individuals must report when they think they have seen it and that institutions must investigate when they receive an allegation.

INVESTIGATING ALLEGATIONS OF RESEARCH MISCONDUCT

The Australian Code for the Responsible Conduct of Research[4] provides a framework for investigating allegations of research misconduct. Each institution will likely have its own process for dealing with allegations of research misconduct that take into account employment relationships and industrial relations requirements. There are though three common steps to these processes.

(i) Is it a 'responsible' allegation?

Before taking any formal steps, consideration of an allegation of research misconduct is required in order to determine if it is 'responsible'. Here, we consider responsible to mean that the allegation actually relates to the conduct of research, that the allegation is coherent and sensible, and that the allegation does not appear to be malicious or vexatious. At this point, there may be a need for immediate action to be taken in order to protect the health and safety of human or animals involved in the research. If the allegation relates to falsification or fabrication of data it may also be necessary to sequester documents or computer files so that they can be used in subsequent steps.

(ii) If the allegation were proven to be true, would it amount to research misconduct?

This second step is sometimes called a prima facie assessment, preliminary assessment or inquiry. The purpose of the preliminary assessment is to decide whether a formal investigation is needed, and in essence asks the question above. For some allegations, the preliminary assessment can be completed in a short time. If the allegation is about plagiarism and the documentation clearly shows that slabs of text have been reproduced without proper attribution, there is probably not much to assess. Allegations that relate to analysis of data or authorship will probably require the provision of some discipline-specific advice and this may take more time. Similarly, for some allegations the person conducting the preliminary assessment may need to speak with potential witnesses or even the respondent to the allegation in order to make a decision. Outcomes of the preliminary assessment include a decision to investigate further, referral to other processes, referral to other institutions or dismissal of the allegation.

(iii) Is it research misconduct?

This is the formal investigation part of the process. Normally, a panel of experts will be commissioned to review the material collected, and to hear from both the complainant and respondent to the allegation. Others may also be asked or wish to provide statements to an investigatory panel. The panel needs to identify findings of fact that support their final recommendation, that is, that research misconduct was or was not found. These are not legal proceedings. The standard of proof for these investigations is 'on the balance of probabilities', as opposed to the higher standard of 'beyond reasonable doubt'. This is true for even the most serious allegations. In these situations, one would hope that the quality of material considered by the panel was higher, but the standard of proof remains.

Once a decision has been made, there will likely be opportunity for the respondent to the allegation to appeal the decision, but the specifics of this process will depend on institutional requirements. Once complete, institutions should make relevant parties, such as funding agencies, aware of the outcomes and determine if any action to correct the research record is required.

At all stages throughout this process, the principles of procedural fairness must be considered. There are generally three 'rules' of procedural fairness: (i) the bias rule, which suggests that at all points throughout the process, those making decisions should be as free from bias or conflict of interest as is possible, (ii) the evidence rule which asks that any decision or finding be supported by the material considered by those conducting the investigation (that is, that the decision can be understood by others and appears to be a rational one), and (iii) the hearing rule which requires that a decision-maker (or makers) should ensure that the respondent has had the opportunity to be heard. Failure to demonstrate that procedural fairness has been afforded may render the investigation invalid.

DOES RESEARCH MISCONDUCT REALLY HAPPEN?

The simple answer is yes. Research misconduct can, and probably does, happen wherever research is conducted. There have been surveys conducted to try and determine the rate at which research misconduct occurs. Daniele Fanelli[5] describes the results from a meta-analysis of these surveys. When asked to self-report, the meta-analysis suggests that 2% of researchers commit research misconduct (defined here as fabrication, falsification and plagiarism). When asked to report on the conduct of fellow researchers, this rate becomes 14%. There is some evidence that this is being addressed, with journals retracting more research papers than ever before[6], but even with these retractions, the research record will still contain some reports that have more in common with creative writing than research.

The current and previous world record holders for retraction of publications due to proven research misconduct were anaesthetists. Joachim Boldt was an internationally respected anaesthesiologist with more than 200 publications to his name. Initially, one paper was retracted because ethics approval for the research was not granted. Further investigation into the research indicated that in fact the clinical trail being reported on was not ever conducted. About 90 papers by Boldt have been retracted. The current world record holder is Yoshitaka Fujii with 172 retractions (either pending or complete). Evidence of fabrication of data, fabrication of co-authors signatures, fabrication of employment details and failure to obtain ethics approvals all form part of the story. It is unlikely that there is an underpinning connection between these extreme examples of research misconduct and the discipline. It might even suggest that as a discipline, anaesthesia has demonstrated that it is prepared to tackle these forms of misconduct directly and thoroughly.

QUESTIONABLE RESEARCH PRACTICES

The focus on extreme examples of researchers behaving badly is equal parts interesting and troublesome. Perhaps of more concern is the idea of 'questionable research practices'. Questionable research practices are the behaviours that bridge the gap between research misconduct and the ideal of excellent research conduct. It is thought that questionable research practices have a potentially greater effect on the integrity of the research record than research misconduct.[7] Questionable research practices might include removing outliers from a data set to make the results seem more significant, publishing only results that support previous findings, or even the concealment of conflicts of interest. These examples probably don't carry the same level of 'deviation' from accepted practice as the fabrication of a complete data set for example, but can still adversely affect the integrity of the research record (or at the least our ability to make an informed assessment of it). In the same paper, Fanelli reports that 33.7% of researchers admit to questionable research practices in their own research, and report that 72% of their research colleagues have demonstrated questionable research practices at least one point. There seems to be enough evidence about the prevalence of research misconduct and the less exciting, but probably more important, questionable research practices that something needs to be done.

CULTURES OF RESEARCH ETHICS AND INTEGRITY

Fortunately, there are things that all involved in the research endeavour can do to help ensure that research is conducted ethically and with integrity. The culture of a research group or institution can play an important part. What is it that encourages a strong culture of research ethics and integrity? Clear expectations for research conduct are at the foundation of a strong research culture. This foundation is then reinforced by education and training in the responsible conduct of research. This should extend beyond a 'checklist' approach, and include room for discussion of the principles of research integrity and why they each matter. Finally, a clear message is required from the top of the institution that signals the importance of research integrity.

The story of the worm proboscis outlines why research integrity matters. All of those in the research integrity ecosystem – universities and research hospitals and institutes, researchers, administrators, publishers, funding agencies, governments and the general public – have responsibilities to ensure the integrity of the research record because we can never know when or how our research will have an important influence.

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