Queen's University
40th Annual Anesthesiology Research Day

Scientific Program Director and Residency Research Coordinator:

Ian Gilron, MD, MSc, FRCPC

Research Day Moderator:

Glenio Mizubuti, MD, MSc

Scientific Adjudicators:

Anthony Ho
MD, MSc, FRCPC

Jason Erb
MD, FRCPC

Guest Adjudicator & Lecturer: **Beverley Orser MD, PhD, FRCPC, FCAHS**

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Joel Parlow, MD, MSc, FRCPC

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Research Nurse:
Sheila McQuaide, RN

Postgraduate Medical Secretary:
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Institutional support:

• Queen's University • Kingston Health Sciences Centre (KGH & HDH Sites) • Providence Care

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The A. William, Austin & Amos Friend Memorial Visiting Professorship
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SCIENTIFIC PROGRAM OUTLINE

0800 – 0810 **Opening Remarks**
– Dr. Joel Parlow

0810 – 0850 **Introduction of Research Day Presentations**
– Dr. Ian Gilron

0850 – 0935 **Oral presentations (3)**

0935 – 1010 **Nutrition break**

1010 – 1125 **Oral presentations (5)**

1125 – 1230 *** LUNCH** (provided) *****

1230 – 1345 **Oral presentations (5)**

1345 – 1415 **Nutrition break**

1415 – 1500 **Oral presentations (3)**

EACH 10-MINUTE ORAL PRESENTATION WILL BE FOLLOWED BY A 5-MINUTE QUESTION PERIOD

The Judges will be:

Dr. Anthony Ho, Professor, Queen's Dept of Anesthesiology & Perioperative Medicine

Dr. Jason Erb, Assistant Professor, Queen's Depts of Anesthesiology & Perioperative Medicine and Critical Care

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1500 **Dr. Beverley Orser,** Professor & Chair, Dept of Anesthesia, University of Toronto

*** Guest Lecture ***

Postoperative neurocognitive deficits: What's wrong and what can we do about it?

Wine & Cheese to follow with * Awards Presentation * (Donald Gordon Center)

Oral Presentations (alphabetical order)

Courtney BANNERMAN, BSc, PhD Candidate (Queen's Neuroscience)
Targeting gene networks in spinal cord injury pain (update)

Matthew BILBILY, PGY-4
Use of objective neuromuscular monitors among Canadian anesthesiologists (update)

Matthew BRUDER, PGY-3
A Pilot Study to Investigate Labor Epidural Failure Rates at Kingston Health Science Centre (update)

Daenis CAMIRE, PGY-2
Measurement of Movement-Evoked Pain versus Pain at Rest in Postoperative Pain Treatment Trials (proposal)

Carl CHAUVIN, PGY-3
Use of waveform analysis as a post-placement test for thoracic epidural catheters (update)

Emily COOK, PGY-3
Examination of the Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery at KHSC (update)

Farzad Izaddoust DAR, MSc, MD candidate, Queen's Medicine
Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES-Canada) (update)

Rosy FOURNIER, PGY-2
Is functional activity level as measured by a wearable activity tracker correlated with hospital length of stay following lower limb arthroplasty? (proposal)

Minnie Tingxiao FU, BSc, MD candidate, Queen's Medicine
Post-Retraction Citation in Anesthesia (proposal)

Fraser JOHNSON, PGY-2
Using visual risk display of Myocardial Injury after Noncardiac Surgery to obtain informed consent (proposal)

Sarah MAXWELL, PGY-4
How does maintenance of intra-operative hemodynamic stability with esmolol, labetalol or fentanyl impact recovery during elective outpatient laparoscopic cholecystectomies? (update)

Mohammed MOHIUDDIN, BSc (Hons), MD candidate, Queen's Medicine
Adherence to Consolidated Standards of Reporting Trials (CONSORT) Guidelines for Reporting Safety Outcomes in Trials of Cannabinoids for Chronic Pain (update)

Rex PARK, BHSc, MD candidate, Queen's Medicine
Magnesium for the Management of Chronic Noncancer Pain in Adults. (update)

Jaqueline SILVA, PhD, Postdoctoral Fellow, Queen's DMBS and DAPM
Involvement of the CCL17/CCL22:CCR4 axis in the development of inflammatory pain. (update)

Emma TORBICKI, PGY-3
Does the leadership style employed by anesthesiologists (positive versus negative) affect operating room (OR) team performance? (update)

Danika VAUTOUR, PGY-4
Concordance Between Resident Self-Assessment and Faculty Assessment of Competency and Effect of Resident Seniority, Faculty Leniency and Year of Assessment on Accuracy (update)

Poster Presentations (alphabetical order of first author)

Temporal analysis of spinal cord injury pain
C. BANNERMAN, J. Segal, J. Silva, S. Duggan, N. Ghasemlou

Circadian Rhythm of Chronic Low Back Pain
Jesse JOYNT, Daenis Camiré, Elizabeth Brown, Scott Duggan, Étienne Bisson, Ian Gilron, Nader Ghasemlou

Control of somatosensation by neuro-immunity: a potential role for neutrophils?
Mitra KNEZIC and Nader Ghasemlou

Depletion of sensory neurons in the mouse
Pascale PATENAUDE and Nader Ghasemlou

Cellular and molecular contribution of dendritic cells to inflammatory pain
Madeline ROBINSON, Pascale Patenaude, Nader Ghasemlou

Dissociating sensory from motor: Temporal assessment of pain in experimental autoimmune encephalomyelitis
Julia SEGAL, Courtney Bannerman, Ian Gilron, Nader Ghasemlou

Involvement of the CCL17/CCL22:CCR4 axis in the development of inflammatory pain
Jaqueline Raymondi SILVA, Courtney Bannerman, Abigail Marshall, Jelena Petrovic, Erika Haberfellner, Ian Gilron, Nader Ghasemlou

Targeting gene networks in spinal cord injury pain

C. Bannerman, J. Segal, J. Silva, S. Duggan, N. Ghasemlou

Aim of Investigation

Translating research from laboratory animal studies to human applicability is one of the more challenging steps in biomedical research and often a point where many once promising therapeutic candidates are found to be ineffective. The rodent research model of spinal cord injury (SCI) has undergone many revisions over the years, with the development of the Infinite Horizon's impactor allowing researchers to accurately create injuries in rodent models. The current rodent model involves the impactor's probe descending onto the spinal cord with a predetermined force before quickly retracting upwards. In the case of a human SCI, there is sustained pressure on the spinal cord after the injury until it can be surgically relieved, which can take hours. From this study we aim to characterize a more clinically relevant model of spinal cord injury: the compression injury.

Methods

The contusion surgery is performed on female C57BL/6J mice that are at least 8 weeks of age. A moderate contusion (50 kdyn, 0 seconds of delay) and compression contusion (50 kdyn, 60 seconds of delay) are performed with the Infinite Horizons impactor device (Precision Scientific Instrumentation, Lexington, KY). The procedure for the sham (control) mice is completed in a similar manner minus the impact. Over a period of 6 weeks post-injury, the mice are scored for mechanical, thermal cold, and thermal heat sensitivity using the Von Frey assay, the acetone test, and the Hargreaves radiant heat test, respectively. The behavioural assessments involve the mouse removing their foot off of the stimulus when they experience hypersensitivity. The locomotor recovery is assessed using the Basso Mouse Scale (BMS). We will use flow cytometry to evaluate immune cell differences and histology to study the structural difference between the two models.

Results

The mice who received the compression injury show significantly greater thermal heat and mechanical hypersensitivity in comparison to a moderate injury. The compression injured mice's mechanical threshold was significantly different from the moderately injured mice 7-35 days after injury. The compression mice had significantly increased thermal heat hypersensitivity 7-10 days after injury. The acetone test resulted in no differences between the two groups. The compression injury also resulted in significantly lower BMS scores in comparison to the sham and moderately injured mice. We are currently assessing immune and structural differences in the spinal cord between the three injury groups at 7 and 43 days after injury using histology and flow cytometry.

Conclusions

Creating a rodent model of spinal cord injury that more closely mimics an injury sustained by a human, helps facilitate the translation of potential therapeutics from mouse to human. Conveniently, the compression model uses the same equipment and model organisms that is currently used by spinal cord injury labs. This will allow for the compression model to be quickly adopted and utilized by labs around the world, potentially transforming our approach to spinal cord injury research, and advancing the development of novel therapeutics for those living with a spinal cord injury.

The Use of Objective Neuromuscular Monitors Among Canadian Anesthesiologists

Matthew Bilbily, Richard Henry

Research Question(s)

What proportion of Canadian Anesthesiologists at academic institutions routinely utilize objective neuromuscular monitors to assess neuromuscular recovery after administration of a neuromuscular blocking agent?

Related Area of Clinical Need

It has been well documented that post-operative residual neuromuscular blockade is common and may adversely affect patient outcomes by increasing the risk for post-operative pulmonary complications. Most commonly, when neuromuscular blockade is used, visual or tactile evaluation of twitch amplitude is utilized by anesthesiologists to gauge recovery from neuromuscular blockade. However, we now know that even experienced anesthesiologists cannot detect fade when the Train of Four (TOF) ratio is greater than 0.4. Since a TOF ratio of greater than 0.9 is required to assure adequate recovery of neuromuscular function, perhaps we should be relying on objective monitoring to gauge recovery of neuromuscular function rather than subjective assessment of TOF.

Hypothesis:

The majority of Canadian anesthesiologists at academic institutions do not routinely use objective neuromuscular monitors.

Study design

1. Develop a survey to assess the following areas:
- proportion of Canadian anesthesiologists who utilize objective neuromuscular monitors
- perceptions of accuracy of subjective neuromuscular monitoring
- barriers to use of objective neuromuscular monitors (access, practicality, etc)
2. Distribute survey to staff/resident anesthesiologists at academic institutions across Canada
3. Analyze results of survey respondents

Reference

Butterly A, Bittner EA, George E, Sandberg WS, Eikermann M, Schmidt U. Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. Br Anaesth. 2010;105(3):304–9.

Debaene B, Plaud B, Dilly M-P, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology. 2003;98(5):1042–1048. This landmark paper showed that residual paralysis may still be relevant 2 h after injection of a single dose of intermediate-acting neuromuscular blocking agents.

Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. J Am Coll Surg. 2004;199(4): 531–7.

A Pilot Study to Investigate Labor Epidural Failure Rates at Kingston Health Science Centre

Matthew Bruder, PGY3 Anesthesiology
Supervisor: Dr. Patterson

Background: Despite resident best-practices, busy labor and delivery wards and the demands of on-call residents mean that frequently laboring patients with epidurals are not closely tracked. And while entirely non-functional epidurals or complications certainly prompt anesthesiology response and follow-up, poorly functioning epidurals, or those in patients progressing through labor quickly, may fall through the cracks. Simply put, epidurals are often placed, then removed following delivery, without the physician who placed them ever being aware of exactly how effective they were. This pilot study aims to remedy this situation and collect department-wide data on the failure rates of labor epidurals at Kingston Health Science Centre (KHSC).

Clinical Need / Knowledge Gap: There is currently no local data on rates of labor epidural failures, incomplete sensory blocks, number of replaced epidurals, or common complications or labor epidurals at KHSC. Data on the *overall* failure rates of labor epidurals are widely available. However, without local data, it is difficult to identify possible areas for improvement at KHSC. This pilot study aims to collect this data, facilitating comparison to other similarly sized academic medical centers in North America.

Study Objective: To ascertain the local rate of labor epidural failures and poorly functioning epidurals at KHSC

Methods: A retrospective chart review of 6 months of labor epidurals will be undertaken. Following Research Ethics Board approval, electronic health records for all laboring patients who received lumbar epidurals will be reviewed. Data recorded will include patient age, BMI, number of epidural replacements and placement attempts, level of placement and catheter depths, epidural infusion rates and modes (bolus vs continuous), physician level of training, number of epidural boluses, sensory block level, any co-analgesics required, and any complications. In keeping with similar studies, epidural failures will be defined as those requiring replacement or significant manipulation to provide an adequate sensory block. Following data collection, we will stratify epidural failure rates across several different sub-groups, including high vs low BMI, and according to physician level of training.

Hypothesis: We expect that local rates for labor epidural failures and poorly effective epidurals will fall in line with similarly sized academic centers in North America.

References

1. Arendt K, Segal S. Why epidurals do not always work. Review of Obstetrical Gynecology 2008;1(2):49-55.
2. Eappen S, Blinn A, Segal S. Incidence of epidural catheter replacement in parturients: a retrospective chart review. Int Obstet Anesth. 1998;7: 220-225.
3. J. Hermanides, M. W. Hollmann, M. F. Stevens, P. Lirk; Failed epidural: causes and management, BJA: British Journal of Anaesthesia, Volume 109, Issue 2, 1 August 2012, Pages 144–154.
4. Kinsella SM. A prospective audit of regional anaesthesia failure in 5080 caesarean sections. Anaesthesia 2008;63:822–33.
5. Pan PH, Bogard TD, Owen MD. Incidence and characteristics of failures in obstetric neuraxial analgesia and anesthesia: a retrospective analysis of 19,259 deliveries. Int J Obstet Anesth. 2004; 13:227-233.

Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: A follow-up review

Daenis Camiré, Amanda-Ross White, Tim Brennan, Henrik Kehlet, Jason Erb, and Ian Gilron

Background: Postoperative pain is one of the most prevalent and disabling complications of surgery that is associated with personal suffering, delayed functional recovery, prolonged hospital stay, and chronic postsurgical pain. Previous studies have distinguished between pain at rest (PAR) and movement-evoked pain (MEP) after surgery. In most studies including both measures, MEP has been shown to be substantially more severe in intensity than PAR. Furthermore, since MEP is commonly experienced during normal activities (e.g. breathing, coughing, walking etc.), it has a greater adverse functional impact than does PAR. In 2011, a previous systematic review by Srikandarajah and Gilron, showed that only 39% of reviewed trials included MEP as a trial outcome and 52% failed to identify the pain outcome as either PAR or MEP. Consequently, an editorial in 2011 by Kehlet and Dahl confirmed that there has been no progress in the quality of assessment, despite the need to include movement-associated pain in perioperative analgesic trials was emphasized almost 20 years ago.

Study Question: In postsurgical pain treatment trials: 1) what is the frequency of use of pain at rest (PAR) versus movement-evoked pain (MEP) as a trial outcome, and 2) what methods are used to assess MEP?

Purpose of Study: Main data to be extracted will be:
1. Designation of movement-evoked pain as the trial primary outcome
2. Designation of pain at rest as the trial primary outcome
3. Distinction between movement-evoked pain and pain at rest in assessing pain
4. Method of evoking pain for the assessment of movement-evoked pain

Study Design: We will search the following electronic bibliographic databases: MEDLINE, EMBASE, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register). As a convenience sample of 2014-2019 postsurgical pain treatment trials, this review will be limited to thoracotomy, knee arthroplasty and hysterectomy surgical procedures involving humans and will focus on randomized controlled clinical trials and meta-analyses that report pain as a trial outcome. Articles will be excluded if they: are not randomized controlled trials, include a mix of surgeries, do not deal with outcomes following surgery, do not report pain scores, or report pain only after 1 week postoperatively. No analysis of subgroups is planned at this time.

Progress: A suggested timeline of this study is 12-24 months. Approximately 1200 articles will be reviewed with around an estimated 30-40% of these results meeting inclusion criteria will be included in the analysis (N=400-500). Currently, the PROSPERO Review Protocol registration is complete (pending review). Next steps are to submit the Review Protocol to JMIR Research Protocols and continue data collection and analysis.

Limitations: Given that the focus of this review is on pain outcome measurement only, reviewed trials will not be evaluated with respect to trial quality or risk of bias. As the expected time in adopting recommendations from the previous 2011 systematic review is indeterminate, there may be potential for misrepresentation of earlier articles in bolstering analgesic trial methodology.

References:

Kehlet, H., and Dahl, J. B. (2011). Assessment of postoperative pain-need for action! Pain, 152(8):1699-700.

Srikandarajah S, Gilron I. (2011). Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: A fundamental distinction requiring standardized measurement. Pain, 152(8): 1743-1739.

Use of waveform analysis as a post-placement test for thoracic epidural catheters

Investigators: Carl Chauvin, John Murdoch, Rachel Phelan, Gregory Klar

Background: Administration of analgesic drugs via epidural catheters is an important analgesic option in the perioperative setting. However, the failure rate of thoracic epidurals is consistently estimated between 15-30% using conventional placement techniques.[1,2] Establishing more reliable means of placing well-functioning thoracic epidurals and assessing their continued functional status with confidence remains an important and elusive goal.

Epidural waveform analysis (EWA) has been shown to be a useful clinical adjunct for confirming proper placement of an epidural catheter.[1,2,3] To date, however, no study has previously demonstrated the continued utility of EWA in assessing epidural catheters in the post-operative period. We seek to show that for suspected failed or equivocally functioning epidurals, EWA is an efficient, non-invasive, reliable adjunct to determining the functional status of the epidural.

Study Design: The study is a prospective control pilot study. Patients will be identified pre-operatively and consented to participate in the clinical study. Thoracic epidural will be conventionally placed pre-operatively using a loss-of-resistance (LOR) technique. After catheter insertion and positioning, a test dose of 3cc of lidocaine 2% will be administered, followed by a 5cc normal saline flush.[4] The catheter will then be transduced via EWA. Presence or absence of a pulsatile waveform will be recorded, as will the presence or absence of a block to ice after 15 minutes.

Post-operatively, epidural catheters will be flushed in PACU with 5cc normal saline, and again transduced for EWA. Patients will be assessed for the continued presence of a block to ice. Epidurals producing a bilateral block of 2+ levels will be categorized as *functional*; those producing no block, a unilateral block, or a block of only 1 level will be categorized as *failed/equivocal*. Participants with the latter result will then have a bolus of 3cc lidocaine 2% administered through the epidural. After 15 minutes, the block will again be assessed with ice.

Post-operative EWA result will be compared with pre-operative EWA result, pre-operative block to ice, and block to ice following epidural lidocaine bolus in the failed/equivocal epidural group.

Hypothesis: For equivocally functional epidurals in the PACU setting, EWA will reliably distinguish between *properly positioned* (i.e. lidocaine bolus produces bilateral 2+ dermatome block) vs. *secondary failure* (i.e. lidocaine bolus has negative result).

Progress: Iterative trialing of study protocol has led to fine-tuning of study design and identification of potential barriers to data collection. Given the unfamiliarity of the EWA technique to many clinicians, we have elected to limit data collection to study investigators as well as a subset of regular APMS practitioners. Accordingly, participant enrolment and data collection is scheduled to occur primarily over a research block in July 2019, continuing thereafter as needed to achieve adequate enrolment.

References:

1) Leurcharusmee P et al. Reliability of waveform analysis as an adjunct to loss of resistance for thoracic epidural blocks. *Reg Anes Pain Med*. 2016;40:693-697.
2) Arnuntasupakul V et al. *A randomized comparison between conventional and waveform-confirmed loss of resistance for thoracic epidural blocks*. *Reg Anes Acute Pain*. 2016;41:368-373.
3) de Médicis E et al. *Technical report: optimal quantity of saline for epidural pressure waveform analysis*. Can J Anaesth. 2007;54:818–821.
4) Lennox PH et al. *A pulsatile pressure waveform is a sensitive marker for confirming the location of the thoracic epidural space*. J Cardiothorac Vasc Anesth. 2006;20:659–663.

Examining the *Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery* at KHSC

Investigators: Dr. E Cook, Dr. J Dion, Dr. K Marosi, R Phelan and Dr. M McMullen

Background: In 2017 the Canadian Cardiovascular Society (CCS) suggested that levels of cardiac biomarkers (BNP or NT-proBNP) should be routinely measured before elective noncardiac surgery to optimize perioperative cardiac risk stratification[1]. The population targeted in this screening initiative includes; patients 65 years or older, patients 45-64 years of age with significant cardiovascular disease and, patients with a Revised Cardiac Risk Index score ≥1. The guidelines also recommend obtaining daily troponin levels in patients with positive BNP or NT-proBNP levels, as an elevated postoperative troponin is known to be the strongest predictor of 30-day mortality[2].

After these guidelines were released, the measurement of BNP/NT-proBNP levels was implemented as part of the presurgical screening process at Kingston Health Sciences Center (KHSC). A protocol for the management and follow-up of patients with positive results was developed but effective implementation requires collaboration with multiple stakeholders (attending surgeons, anesthesiologists, postgraduate trainees, nursing staff and laboratory medicine teams). The adherence to the CCS guidelines at KHSC remains unknown despite their system wide adoption at our institution. The goal of this quality improvement project is to determine the rate of appropriate application of this protocol at KHSC.

Study Design: The proposed stages involve:

1. Chart review of patients with a positive preoperative NT-proBNP to determine if patients received appropriate follow-up and examine 30-day morbidity and mortality
2. If follow-up rate is suboptimal, determine if it is a failure to order tests or follow-up on positive results; implement an intervention aimed to improve compliance with the guidelines
3. Chart review of patients with a positive preoperative NT-proBNP after the intervention is implemented

Update: The initial chart review of patients with a positive preoperative NT-proBNP from July 2018-December 2018 is near completion. The initial data showing KHSC's adherence to the guidelines and the incidence of postoperative events in patients with an elevated preoperative NT-proBNP will be discussed.

[1] Duceppe E, Parlow J, Macdonald P, et al. *Can J Cardiol* 2017; 33: 17-32.
[2] Devereaux PJ, Chan MT, Alonso-Coello P, et al. *JAMA* 2012; 203: 2295-304.

Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES-Canada)

Farzad Izaddoust Dar, Deborah DuMerton, Logan Begbie, Kai Chen, Nicole Relke, Rob Tanzola, Rachel Phelan, Tarit Saha. Funding: CIHR GRANT 159482

Post-operative delirium is a common complication associated with cardiac surgery. The cardinal feature of delirium is an acute onset fluctuating change in mental status characterized by disorganized thinking, confusion, agitation, somnolence, and/or sensory perturbations. Whereas hyperactive delirium seldom goes undetected, hypoactive delirium is more subtle in its presentation and is often missed. Both are associated with increased morbidity, mortality, prolonged hospital stay and increased health care expenditure. Risk factors for developing post-operative delirium include older age, male sex, mild cognitive impairment, dementia, sensory impairment and chronic disease. Specific risk factors related to cardiac surgery have also been identified and include type of surgery, number of transfusions and length of mechanical ventilation.

Current treatment strategies for post-operative delirium are not well established, highlighting the need to devise prophylactic strategies. Randomized controlled trials and observational studies have demonstrated that titration of depth of anesthesia using the bispectral index (BIS) reduces the incidence of post-operative delirium. Burst suppression is a pathological electroencephalographic pattern that is associated with low BIS values, deep anesthesia, and is independently associated with increased risk of post-operative delirium and poor-outcomes. These previous studies support the notion that anesthesia may be a potential modifiable risk factor for developing post-operative delirium, however no validated anesthetic approaches have yet been devised attempting to reduce or modify risk of post-operative delirium. The objective of this study is to determine whether EEG-guided anesthesia modifies the incidence or severity of post-operative delirium and its associated complications in older cardiac surgery patients.

This is a multi-center, double-blind, randomized controlled trial spanning 4 centers across Canada. Patients over 60 undergoing elective cardiac surgery are randomized to receive standard-of-care or EEG guided care which includes EEG waveforms and BIS, with burst-suppression as the main trigger to titrate anesthesia. Patients undergoing off-pump procedures, circulatory arrest, or with a history of pre-operative delirium and/or intra-operative awareness are excluded from the study. A total of 1200 patients will be recruited across all Canadian sites. The primary outcome is the incidence of post-operative delirium detected using the Confusion Assessment Method (CAM), as well as chart review with 3rd party adjudication in the first 5 post-operative days. Secondary outcomes include length of hospital stay as well as pain scores, falls, cognitive function and mortality at 30 days and 1 year postoperatively, assessed using validated questionnaires.

This study is currently in progress. At Kingston Health Sciences Center, 189 patients have been enrolled, with 700/1200 patients enrolled across all sites. An increase in the rate of enrolment is anticipated with the addition of Toronto General Hospital to the trial beginning June 2019 with projected completion of enrollment by Q4 2020. Demonstration of reductions and/or decreased incidence of delirium with EEG-guided anesthesia is anticipated to have a significant impact on the anesthetic approach to older cardiac surgery patients.

Is functional activity level as measured by a wearable activity tracker correlated with hospital length of stay following lower limb arthroplasty?

Rosy Sylvie Fournier
Supervisors: Melanie Jaeger, Rosemary Wilson, Steve Mann

Background: Recovery from lower limb arthroplasty surgery has been improved by fast track protocols, with ongoing efforts towards decreasing their length of stay (LOS).[1] Unfortunately, not all patients recover on this timeline, and there are outliers who spend a significant amount of time in hospital.[2] Preoperative identification of these patients has been attempted via standardized measurement tools, but these scores are labour-intensive and require significant personnel time during pre-operative visits. More efficient means of predicting length of stay and home readiness would decrease resource utilization and help to streamline same-day surgery patient selection.[3]

Clinical Need / Knowledge Gap: Recent studies have demonstrated that using data from wearable activity trackers (WAT) is feasible and reliable in patients following lower limb total joint arthroplasty.[4] There is already available data suggesting that activity trackers can be used preoperatively to predict postoperative activity levels, but little published research correlating this with length of hospital stay.[5] We hypothesize that preoperative activity level measured using wearable technology would be correlated with hospital length of stay following lower limb joint replacement surgery.

Study Objective: To assess whether pre-operative activity levels, as measured by wearable technology activity trackers, predict hospital length of stay and recovery-related outcomes after joint replacement surgery.

Study Design: We will employ a prospective single group design where data are collected in the pre- and post-operative settings. Once booked for lower limb arthroplasties, 80 patients will receive a WAT (FitBit™). Data collection will begin two months prior to surgery, two weeks later, and at the time of surgery. Demographic data will include Blalock and WOMAC scores and will be collected at time of surgical booking and the day prior to surgery, along with age, sex, anesthetic type, ASA class, procedure type (THA vs TKA), and use of minimally-invasive surgical techniques. Statistical analyses will be conducted to assess the predictive value of preoperative activity on hospital length of stay. Exploratory analyses will be conducted using secondary outcomes of postoperative pain and activity interference.

References

1. Michael Raphael, Melanie Jaeger, Janet van Vlymen. *Easily adoptable total joint arthroplasty program allows discharge home in two days*. Can J Anesth/J Can Anesth (2011) 58:902–910
2. Rosemary Wilson, Judy-Watt-Watson, Ellen Hodnett, Joan Tranmer. *A randomized controlled trial of an individualized preoperative education intervention for symptom management after total knee arthroplasty*. Orthop Nurs (2018) 35(1): 20-29
3. Rebecca Moyer, Kathy Ikert, Kristin Long, Jacquelyn Marsh. *The Value of Preoperative Exercise and Education for Patients Undergoing Total Hip and Knee Arthroplasty A Systematic Review and Meta-Analysis*. JB JS (2017) 5(12): e2
4. Kristen K. Rumer, Anirudh Saraswathula, and Marc L. Melcher. *Prehabilitation in our most frail surgical patients: are wearable fitness devices the next frontier?* Curr Opin Organ Transplant (2016) 21(2): 188-193
5. Joshua Twiggs, Lucy Salmon, Elizabeth Kolos, Emily Bogue, Brad Miles, Justin Roe. *Measurement of physical activity in the pre- and early post-operative period after total knee arthroplasty for Osteoarthritis using a Fitbit Flex device*. Med Eng Phys (2018) 51:31-40

Post-Retraction Citations in Anesthesia

Minnie Tingxiao Fu**, BSc**
Alaa Sabbahi**, MD**
Nick-Hugh Wisdom**, BSc, MD**
Anthony M.-H. Ho**, MD, FRCPC, FCCP**

Introduction: Many scientific papers have been retracted for many reasons (1), but yet authors are still citing those retracted papers in a positive way (either to support or refute their findings and argument) or negative way (acknowledging the retraction without incorporating into the argument) (2).

Publishing falsified/unsubstantiated data can lead to devastating consequences. A famous example is the study that linked autism to MRR vaccine (3) that led to major anti vaccine campaigns. The paper was retracted in 2010 but still some scientists and the media continue to cite this paper despite retraction.

Our study focused only on anesthesia articles that been retracted between 2010 – 2014 and the number of times they had cited (positively or negatively) after retractions.

Methodology: by using retraction database, we searched for anesthesia articles that had been retracted from 2010 – 2014. Using Google Scholar, we recorded the number of times these articles had been cited after the retraction dates (month/year). Those which cited the retracted article after the retraction date were examined to see if the citations were (positive or negative way).

References:

1- Grieneisen, Michael L., and Minghua Zhang. "A comprehensive survey of retracted articles from the scholarly literature." *PloS one* 7.10 (2012): e44118.
2- Halevi, Gali, and Judit Bar-Ilan. "Post retraction citations in context." *Proceedings of the Joint Workshop on Bibliometric-enhanced Information Retrieval and Natural Language Processing for Digital Libraries (BIRNDL)*. 2016.
3- Wakefield, Andrew J., et al. "RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children." (1998): 637-641.

Using visual risk display of Myocardial Injury after Noncardiac Surgery to obtain informed consent

Fraser Johnson, PGY2 Anesthesia Supervisors: Dr. M. McMullen, Dr. J. Dion, Dr. C. Nickel

Background: Informed consent is an important aspect of the patient-physician relationship. Prior to agreeing to undergo treatment patients must have risks and benefits disclosed to a "reasonable patient" standard.[1] The 2016 Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment strongly recommend the communication of perioperative cardiac risk to patients.[2] Myocardial injury is the most common post-operative complications and have significant impacts on patient outcomes.[2]
Very few studies have examined the communication of risk to patients, particularly when communicating perioperative cardiac risk. One study looked at the variability of physician's subjective definitions of risk (Low, medium, and high) when communicating perioperative cardiac risk and found great variability between clinicians.[3] When communicating with patients about "evidence" there are studies that have looked at various communication methods; event rate, natural frequencies, bar graphs, and have found improvements with respect to patient understanding and recall when aids are utilized.[4] The aim of this prospective cohort study is a 2-stage research project to address current practice in perioperative risk communication and examine opportunity to improve communication and patient education.

Study Design: The study will consist of two phases. Phase One will assess the current practices with respect to cardiac risk discussion and assess the need for quality improvement. Phase One will be a quality assessment by way of a survey. The survey will be offered after the PSS consultation to patients $\geq$ 45 years old, seen in consult prior to elective orthopedic surgery requiring an overnight admission to KHSC. The survey will assess current risk discussion practices, patient satisfaction with cardiac risk discussion, ability to recall cardiac risk, importance of cardiac risk disclosure, and general feedback. Phase Two will look further in the cardiac risk discussion and assess the effectiveness of incorporating the use of structured, scripted risk discussion with and without the use of a visual aid. In Phase Two, patients will be followed up immediately post-consult visit to assess patient satisfaction with cardiac risk discussion, recall of risk, importance of cardiac risk discussion from the patients' perspective, and general feedback will be sought regarding perioperative education. A subset of consenting patients will be followed-up post operatively to assess recall of cardiac risk.

Hypothesis: The use of visual representation of perioperative risk of Myocardial Injury after Non-Cardiac Surgery during the pre-anesthetic assessment will improve the patients' satisfaction with cardiac risk discussion and their understanding and retention of the risk in the post-operative period.

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THE EFFECT OF INTRAOPERATIVE LABETALOL, FENTANYL AND ESMOLOL ON TIME TO DISCHARGE IN LAPAROSCOPIC CHOLECYSTECTOMY

Dr. SK Maxwell, Dr. J Marois, D. DuMerton, Dr. D Engen, Dr. R Tanzola

Introduction: Abdominal insufflation during laparoscopic cholecystectomy produces a profound sympathetic response resulting in elevations in heart rate (HR) and mean arterial pressure (MAP). Intraoperative management often includes opioid boluses but this may lead to opiate related side effects. Studies have shown that an opioid sparing technique with the sympatholytic esmolol can effectively control intraoperative hemodynamics and improve postoperative outcomes. We evaluated whether using labetalol to maintain intraoperative hemodynamics would be as effective as esmolol at improving postoperative outcomes compared to fentanyl.

Methods: ASA class I-II patients undergoing elective ambulatory laparoscopic cholecystectomy were randomized to one of 3 double blinded groups for management of increased intraoperative HR or MAP 20% over baseline: 1) IV fentanyl bolus 50 mcg q5 min., 2) IV labetalol bolus 5 mg q5 min. or 3) IV esmolol bolus 0.25 mg/kg followed by a titrated infusion of 5-15 mcg/kg/min. Time from arrival in post-anesthesia care unit (PACU) to readiness for discharge was recorded as the primary outcome. Secondary outcomes included perioperative hemodynamic values, analgesic requirements and the incidence and management of postoperative nausea and vomiting (PONV).

Results: The unblinded and final results will be presented at research day. The final sample comprised 172 patients randomized to receive fentanyl, esmolol or labetalol. Five patients were excluded from analysis secondary to surgical complications (N=2), aspiration (N=1) and study design not followed (N=2). In each group, a subset of patients did not have hemodynamic changes that required treatment with the study drugs. The groups were homogeneous with respect to age, sex, BMI, co-morbidities and risk factors for PONV. There were no episodes of hypotension or bradycardia following administration of study drugs that required rescue treatment with phenylephrine or ephedrine. There was no difference in time to discharge or analgesia requirements between groups.

Discussion: This prospective randomized double-blind controlled trial is the first trial to use labetalol to control the hemodynamic changes associated with pneumoperitoneum in laparoscopic procedures. Our study demonstrated labetalol and esmolol safely blunt the sympathetic response to pneumoperitoneum without any episodes of significant hypotension or bradycardia in the perioperative period. Time to discharge, opioid requirements and PONV were similar between groups.

Adherence to Consolidated Standards of Reporting Trials (CONSORT) Guidelines for Reporting Safety Outcomes in Trials of Cannabinoids for Chronic Pain: Protocol for a Systematic Review

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Background

Chronic pain affects a significant proportion of the population and presents a major challenge to clinicians and pain specialists. Despite the availability of pharmacologic treatment options such as opioids, many patients continue to experience persistent pain. Cannabinoids present an alternative option with some data on efficacy; however, to date, a systematic review of adverse events (AEs) assessment and reporting in randomized clinical trials (RCTs) involving cannabinoids has not been performed. As a result, it is unclear whether a clear profile of cannabinoid-associated AEs has been accurately detailed in the literature. As cannabinoids are likely to become readily available for patients in the near future, it is important to study how well AEs have been reported in trials so that the safety profile of cannabinoids can be better understood.

Objective

With a potentially enormous shift toward cannabinoid use for managing chronic pain and spasticity, this study aims to reveal the adequacy of AE reporting and cannabinoid-specific AEs in this setting. Spasticity is a major contributor to chronic pain in patients with multiple sclerosis (MS), with a comorbidity of 75%. Many cannabinoid studies have been performed in MS-related painful spasticity with relevant pain outcomes, and these studies will be included in this review for comprehensiveness. The primary outcome will be the quality of AE assessment and reporting by adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Secondary outcomes will include the type of AE, method of AE reporting, severity of AE, frequency of AEs, patient withdrawals, and reasons for withdrawals.

Methods

We will perform a systematic review by searching for primary reports of double-blind, randomized controlled trials of cannabinoids compared with placebo and any active comparator treatments for chronic pain, with a primary outcome directly related to pain (eg, pain intensity, pain relief, and pain-related interference). We will search the following databases: MEDLINE, Embase, Cochrane Library, and PsycINFO. RevMan software will be used for meta-analysis.

Preliminary Results

The protocol has been published (Mohiuddin et al, JMIR Res Protoc 2019;8:e11637). After screening 280 articles, 41 were included for analysis. The average CONSORT score is 6.5 across RCTs. Currently CONSORT scores are being compared across years of publication, study sponsors and type of drug administration to assess for any trends. Data on AEs and withdrawals has also been extracted and is currently under analysis.

Conclusions

At this preliminary stage, there appears to be a gap in methodology surrounding AE data collection and reporting for RCTs on cannabinoids for chronic pain. The goal of publishing these results is to change research practices and publishing standards in order to more accurately describe interventions. Like in any new therapy, it is essential that accurate information surrounding the safety and efficacy of cannabinoids be clearly outlined and identified to balance the benefit and harm described for patients.

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Magnesium for the Management of Chronic Noncancer Pain in Adults: A Systematic Review

Authors: Rex Park, Anthony M-H Ho, Gisèle Pickering, Lars Arendt-Nielsen, Mohammed Mohiuddin, Ian Gilron

Background: Chronic pain is a common and complex health problem that has a marked negative impact on patients' quality of life, physical and mental health, and economic well-being (1, 2). The direct health care and productivity costs of chronic pain are as high as US $635 billion per year in the United States, which exceed the annual costs from cancer and heart disease (3). Many patients with chronic pain still suffer from unrelieved or undertreated pain due to the incomplete efficacy and dose-limiting adverse effects of current therapies (4). In North America, clinicians have increasingly prescribed opioids for chronic pain despite the lack of rigorous research demonstrating its long-term effectiveness (5, 6). The high prescribing rates have been accompanied by significant consequences. Deaths from prescription opioid overdoses quadrupled in the last 15 years in the United States, with >200,000 prescription opioid-related deaths since 1999 (5, 7). Although the opioid crisis has been receiving heavy attention from the government and regulatory bodies, which resulted in a decrease in opioid prescriptions since 2013, the prescribing rates still remain very high (7). Given concerns related to this crisis, alternative nonopioid options for chronic pain management are needed (8). Emerging evidence supports the safe use of magnesium in controlling chronic pain, but its overall efficacy and safety is still unclear (9, 10).

Objective: This paper aims to assess the efficacy and safety of magnesium compared with a placebo for the treatment of chronic noncancer pain.

Methods: We searched CENTRAL, MEDLINE, and EMBASE to September 2018, together with two clinical trial registries, and the reference lists of retrieved papers.

Selection criteria: We included randomized, double-blind, placebo-controlled studies that evaluated the efficacy or safety of magnesium in the treatment of chronic noncancer pain in adults. Primary outcomes included any validated measure of pain intensity or pain relief.

Data collection/analysis: Two review authors independently searched for and selected studies, extracted efficacy and adverse event data, and assessed risk of bias for included studies. We did not carry out any pooled analyses.

Main results: Nine studies involving a total of 425 participants satisfied the inclusion criteria. The chronic pain conditions investigated in the studies included neuropathic pain, postherpetic neuralgia, CRPS-1, CRPS-related dystonia, low back pain with a neuropathic component, and migraines with and without aura. All studies were at a high risk of bias for sample size.

There was no or mixed evidence of benefit for most chronic noncancer pain conditions. There was some evidence that magnesium may provide some benefit to people with chronic low back pain with a neuropathic component.

Authors' conclusions: For the purposes of routine patient care, there is insufficient evidence to support or refute the use of magnesium to treat chronic noncancer pain. Additionally, no judgement can be made about adverse events or withdrawals. However, some positive 'analgesic signals' from some trials suggest that further investigation is warranted. Larger, double-blind, randomized controlled trials for a variety of chronic noncancer pain conditions conducted over longer periods are needed. Ideally, these trials would be stratified by baseline body magnesium levels and magnesium formulations as different magnesium formulations have different bioavailabilities.

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Involvement of the CCL17/CCL22:CCR4 axis in the development of inflammatory pain

Jaqueline Raymondi Silva, Courtney Bannerman, Abigail Marshall, Jelena Petrovic, Ian Gilron, Nader Ghasemlou

Aim of Investigations: Inflammatory pain is a result of complex and dynamic interactions between the immune and nervous systems. Peripheral inflammation includes the orchestrated recruitment and activation of tissue-resident and circulating immune cells to the site of injury. Most studies have focused on the role of circulating immune cells, while the contribution of tissue-resident cells in pain development remains largely unknown. Previously, we have shown that the expression of CCL17 and CCL22 are upregulated significantly in a subset of immune cells that alter pain outcomes during inflammation. We therefore sought to examine the role of these two chemokines, and their cognate receptor CCR4, in the development of inflammatory pain.

Methods: Male C57BL/6J mice were used for all described experiments, unless otherwise noted. Plantar incisional wound was used to model post-operative inflammatory pain, and intraplantar injection of CCL17 and/or CCL22 was used to assess the direct effect of the two chemokines. Behaviour was assessed using the von Frey assay, Hargreaves radiant heat test and acetone test. Two approaches were used to determine the role of CCR4 in this pain response: the specific antagonist C-021 was used to block the receptor pharmacologically or CCR4 knockout mice were used to assess loss of receptor function. γδ T cell-null mice were also used to assess whether these CCR4+ cells contribute to pain outcomes.

Results: Our results show that CCL17 and CCL22 are upregulated early after after post-operative wound and that intraplantar injection of these two cytokines causes a dose-dependent response to mechanical and thermal stimuli. Furthermore, blocking their cognate receptor using the specific antagonist C-021 not only abrogates the response to CCL17/CCL22, but also reduces mechanical hypersensitivity in a model post-operative pain. CCR4-null mice also exhibit a significantly altered response early in post-operative pain, while this effect is not altered by loss of CCR4+ γδ T cells. Interestingly, our results suggest that another population of immune cells and not sensory neurons express CCR4 to mediate these acute pain outcomes.

Conclusions: The present study elucidates the essential role of the CCL17/CCL22:CCR4 pathway in the development of inflammatory pain. We show that the expression of CCL17 and CCL22 is upregulated significantly in a subset of skin-resident immune cells that control pain outcomes during inflammation, and that silencing the receptor is an effective strategy to alleviate inflammatory pain. Targeting these cytokines or their receptor could offer a novel opportunity to reduce post-operative pain.

Does leadership style employed by anesthesiologists affect operating room team performance?

Emma Torbicki, Rene Allard, Darren Beiko, Julian Barling

Related area of clinical need: The OR is a high stakes environment requiring cooperation between interdisciplinary teams to ensure a successful patient outcome. Knowledge regarding the effects of leadership style on OR team performance may result in more cohesion and improved responses to crises. Results of this research may help guide development of leadership training programs for medical personnel. Leadership has been well researched in psychology and business for many years. There are many well-defined leadership styles described in the literature which have been applied to the current study.

Current knowledge gaps in this area: While there is increasing literature examining the impact of team performance on clinical outcomes, the impact of leadership styles on team dynamics remains poorly understood.

Hypothesis to be tested: Abusive and over-controlling leadership styles are associated with poor operating room team performance.

Proposed study design: This is a prospective observational study. Teams of two trained assessors gathered information surrounding 150 operations performed at a tertiary care hospital in Canada between June and August 2014. Randomization was done by assigning numbers to each case list and using a random number generator to select cases. If the patient or healthcare personnel in that room declined to participate another number was drawn at random.

The data collected included: case complexity, preoperative patient health status, emergent or elective surgery, type of procedure, length of stay in hospital, adverse events within thirty days of surgery, and styles of leadership (abusive, over-controlling, laissez-faire, or transformational). The OR personnel involved in each case were asked to fill out validated questionnaires assessing boredom, psychological safety and team dynamics.

Possible pitfalls, feasibility and expected project timeline: The data for this project was collected in the summer of 2014 and is therefore already available for analysis. It should be feasible to finish data analysis by June 2018. Due to the limitations of the study design and the nature of the question it will be difficult to make definitive comments regarding causality. It would be very difficult to randomize anesthesiologists to a particular leadership style for the duration of a case. As such, an observational study such as this one is better suited to study such behaviours.

There is also a potential for bias should certain personnel be more frequently assigned to certain lists compared to others. This would occur most commonly with surgery on young infants and cardiac surgery at our centre. The randomization strategy implemented for this study aims to mitigate this effect.

Additionally, emergent operations occurring overnight (after 2300) were not included in the sample, which may introduce a bias towards certain kinds of leadership.

Concordance Between Resident Self-Assessment and Faculty Assessment of Competency and Effect of Resident Seniority, Faculty Leniency and Year of Assessment on Accuracy

Authors: M. Fleming, G. Mizubuti, M. McMullen, N. Dalgarno, N. Cofie, R. Egan, And D. Vautour

Background & Rationale

Improving physician competency requires quality training, the provision of feedback to guide residents in their development, and the valid and reliable assessment of residents' entrustability across a range of competencies. The medical literature shows that medical residents generally do poorly at self-assessing their performance (Gordon 1991; Eva and Regehr 2005). However, iterative and targeted feedback based upon well-defined criteria has also been shown as a means to potentially improve residents' self-assessment accuracy (Boud 1995). In 2017, all PGME programs at Queen's University shifted to Competency Based Medical Education (CBME). The changes put forth by this new curriculum included evaluations with more precise learning anchors tailored to residency specific objectives and the hope is to provide more targeted evaluation and feedback. This is a great step forward for medical education, however as we already know from the available literature, there are other multiple factors that can explain the differences in accuracy of medical resident's self-assessment and have been explored to a limited extent.

We sought to first confirm or refute the current literature on self-assessment in Medical Education within our own department. In addition, our goal was to identify whether resident level of seniority and faculty leniency have an impact on accuracy of self-assessment. Should there be a difference attributable to faculty leniency, perhaps faculty development could lead to residents having a better understanding of 'where they stand' and improve the residents' ability to accurately determine the limits of their competence; a skill that is essential for continuing professional development and has the potential to enhance patient safety and quality of care in the future.

As of April 2019, data collection, entry and analysis for the pilot study within the residents of the Anesthesiology Department has been completed. Abstracts of our project have been sent to Medical Education conferences and the final manuscript is projected to be completed by summer 2019.

Project Status

Phase 1- Instrument Design -**Completed**
Development of a self-assessment tool
Phase 2 – Pilot Study Data Collection-**Completed**
Pilot data collection of daily faculty and resident paper assessments. Qualitative data will subsequently be compiled, analyzed, and triangulated by research assistants from the OHSE (Office of Health Sciences Education)
Phase 3 – Data Collection, Analysis-**Completed**
Completed by health education research associates from the Faculty of Health Sciences at Queen's University
Phase 4 – Results communication-**In Progress**
Abstract sent to the ICRE conference 2019 (poster presentation). Final manuscript anticipated to be completed by August 2019

Outcomes

Through this project we will:

1. Establish an approach to resident self-assessment within the Department of Anesthesiology at Queen's University.
2. Collect data on self-awareness accuracy trajectory across Anesthesia residents at different stages over a 1.5 year period.
3. Provide the literature with one of the first longitudinal self-assessment studies concentrating not only on *if* self-assessment is accurate, but rather *how* accuracy is influenced by resident seniority, faculty leniency and year of assessment.

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Critical Appraisal Essay – Dana Archibald, PGY1, Anesthesiology & Perioperative Medicine

Publication title: "***Continuous epidural infusion vs programmed intermittent epidural bolus for labour analgesia: a prospective, controlled, before-and-after cohort study of labour outcomes.***"

Authors: A. Bullingham, S. Liang, E. Edmonds, S. Mathur and S. Sharma

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Introduction

Continuous epidural infusion (CEI) of local anesthetics was initiated as a common technique for labour analgesia in the 1980s as an alternative to the previously used intermittent boluses administered by practitioners[2]. Patient controlled epidural analgesia was then introduced in 1988 as a method to deliver top-up doses in addition to the baseline infusion[4]. More recently, programmed intermittent epidural bolus (PIEB) or automated mandatory bolus (AMB) have been proposed as the technique with the highest efficacy and patient satisfaction[2,5-12]. Technological advances of pumps, cost and convenience are other factors that have influenced the selection of labour epidural settings both historically and currently. The mode of epidural administration is an important aspect to optimize as an effective epidural dramatically impacts women's labour and delivery experience, may have improved outcomes, and can reduce the resources required from an anesthetic perspective.

Methods

This study was a prospective, controlled, before-and-after cohort study of a labour epidural analgesia protocol change from CEI to PIEB+PCEA. It was carried out at a tertiary referral hospital in Sydney, New South Wales, Australia. Written consent was not obtained from patients, as it was an evidence-based institutional change of practice with ethics approval from the Western Sydney Local Health District Human Research Ethics Committee. Patients were assigned to either PIEB+PCEA or CEI for labour analgesia. Patients in the PIEB+PCEA group received ropivacaine 0.1% with fentanyl 2μg ml^{-1} with a 5ml intermittent bolus programmed hourly (delivered at a rate of 250ml h^{-1}) plus a PCEA 5ml bolus with a 10-minute lock out period. There was an option of increasing the PCEA bolus to 10ml if necessary. Patients in the CEI group received ropivacaine 0.2% with fentanyl 2μg ml^{-1} at 5-15ml h^{-1}.

The epidural insertion was the same for both groups including a bolus of bupivacaine 0.125% 15-20ml and fentanyl 5μg ml^{-1}. The PIEB+PCEA group received the treatment up until delivery; however, the CEI group had the infusion reduced to 2ml h^{-1} upon starting the second stage of labour. An acute pain nurse or anesthetic registrar followed up with patients the following day using a 10-point verbal numeric rating scale to assess satisfaction.

Women receiving labour epidurals for a standard vaginal delivery met inclusion criteria. Only those who did not receive at least 10ml of epidural solution were excluded from the study. Maternal age, parity, and gestational age were the patient characteristics collected.

The primary outcome was lower limb motor block prevalence. The Bromage scale (grade II-IV) was used to assess the patient's leg weakness every two hours. The secondary outcomes were total local anesthetic dose, total fentanyl dose, duration of the second stage of labour, mode of delivery, hypotension requiring resuscitation, and material satisfaction during the first and second stages of labour. The mode of delivery was recorded as normal vaginal delivery, assisted vaginal delivery (which included forceps, ventouse device or both) or an emergency Caesarean section.

The study determined a required sample size of 149 participants per group to have a 90% power (and significance level α=0.01) to detect a difference based on the estimated prevalence of motor block of 16% in the CEI group and 3% in the PIEB group. SAS software was used to carry out statistical analysis using the t-test to compare continuous variables and the χ^2 test or Fischer's exact test for categorical variables. Confounding effects of patient characteristics that were found on univariate testing were further evaluated for by multiple regression analysis. Subgroup analyses was done for primiparous and multiparous groups.

Results

In the CEI group, 233 patients enrolled and 45 were excluded (4 missing data and 41 receiving less than 10 ml of solution). In the PIEB+PCEA group, 236 patients enrolled and 27 were excluded (all due to receiving less than 10 ml of solution). Therefore, 188 in the CEI group and 209 in the PEIB+PCEA group were included in the analysis—a total of 397 participants. There were no differences between groups regarding patient characteristics.

Primary Outcome

The prevalence of lower limb motor block was significantly lower in the PIEB+PCEA group (1%) than the CEI group (21.8%) in both primiparous (1.3% vs 22.8%) and multiparous (19.7% vs 0%) women. PIEB+PCEA was independently associated with a 31-fold reduction in the odds of motor block after adjusting for maternal age, parity and gestational age (OR 0.03, 95% CI: 0.01-0.14, P<0.001). *(Figure 2, Table 3)*.

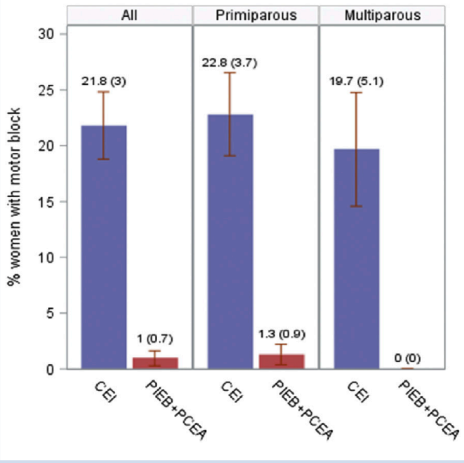

Fig 2. Prevalence of motor block in 397 women who received either a continuous epidural infusion (CEI, *n*=188) or a programmed intermittent epidural bolus with patient-controlled analgesia (PIEB+PCEA, *n*=209) for labour analgesia. Numbers shown indicate proportion (SD). Error bars indicate SD.

Secondary Outcomes

Patients in the PIEB+PCEA group received a significantly lower mean total dose of ropivacaine (40.4mg; SD 23.8) compared to those in the CEI group (72.5mg; SD 43.0). Additionally, the mean hourly dose was lower in the PIEB+PCEA group (7.8mg h^{-1}; SD 0.44) compared to the CEI group (13.8mg h^{-1}; SD 0.89). There was no significant difference in volume determined between the two groups. *(Table 2)*

Table 2 Volume and dose of local anaesthetic and fentanyl received by 397 women during labour via either a continuous epidural infusion (CEI) or a programmed intermittent epidural bolus with patient-controlled analgesia (PIEB+PCEA). Continuous data are summarised as mean (SD). Categorical data are summarised as number (%)

	CEI n=188	PIEB+PCEA n=209	P-value
Total volume (ml)	36.39 (43.0)	40.4 (23.8)	0.069
Total ropivacaine dose (mg)	72.5 (43.0)	40.4 (23.8)	<0.001
Total fentanyl dose (μg)	72.5 (43.0)	80.9 (47.5)	0.069
Hourly ropivacaine dose (mg h^{-1})	13.8 (6.21)	7.8 (3.21)	<0.001

Patients had a significantly shorter duration of the *second stage* of labour in the PIEB+PCEA group (69.4 min; SD 56.3) compared to the CEI group (89.1 min; SD 63.8), however, only in the primiparous subgroup. PIEB+PCEA was independently associated with a 22-minute reduction in the second stage of labour compared to CEI after adjusting for maternal age, parity and gestational age (β=-22.0, 95% CI: -35.7 to -8.3, P=0.002). *(Figure 3, Table 3)*.

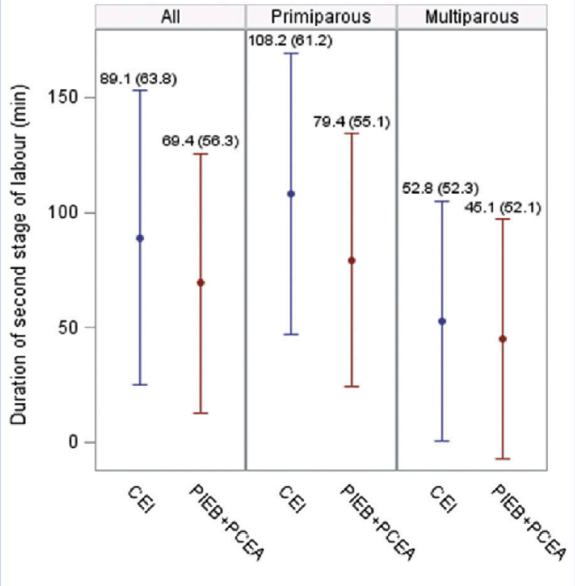

Fig 3. Duration of the second stage of labour in 397 women who received either a continuous epidural infusion (CEI, n=188) or a programmed intermittent epidural bolus with patient-controlled analgesia (PIEB+PCEA, n=209) for labour analgesia. Numbers shown indicate mean (SD). Error bars indicate SD.

There was no significant difference in mode of delivery, fentanyl dose, or in maternal satisfaction during either the first or second stage of labour. *(Table 3)*.

Table 3 Labour outcomes of 397 women who received either a continuous epidural infusion (CEI) or a programmed intermittent epidural bolus with patient-controlled analgesia (PIEB+PCEA) for labour analgesia. Continuous data are summarised as mean (SD). Categorical data are summarised as number (%). LSCS, lower segment Caesarean section

	CEI n=188	PIEB+PCEA n=209	P-value
Lower limb weakness	41 (21.8%)	2 (1.0%)	<0.001
Duration of second stage of labour (min)	89.1 (63.8)	69.4(56.3)	0.010
Satisfaction score in first stage (out of 10)	9.4 (1.6)	9.1 (1.9)	0.104
Satisfaction score in second stage (out of 10)	9.4 (1.8)	9.0 (2.1)	0.051
Normal vaginal delivery	75 (40.0%)	92 (44.0%)	0.406
Instrumental delivery	39 (20.7%)	37 (17.7%)	0.442
Emergency LSCS	74 (39.4%)	80 (38.3%)	0.825

Discussion

The main conclusions of this study were that PIEB+PCEA is preferable compared to CEI for labour epidural analgesia based on the findings of reduction in motor block prevalence, total (and hourly) doses of local anesthetic and duration of labour. These findings are consistent with numerous studies in the literature[4-10], including perhaps the most relevant studies: a meta-analysis of 9 RCTs[2] and a recent Cochrane review[5], which was published only a few weeks prior to this study. This before-and-after study externally validates available studies and demonstrates "real-world" application of existing evidence in the more complex clinical setting. Some studies hypothesize that bolus injections may allow for improved distribution or spread of the solution because of higher pressures with injection[5]. This theory is supported in studies in which participants were imaged with MRI during epidural injection[3]. Total ropivacaine dose was almost half the total dose in the PIEB+PCEA group than the CEI group, which is a larger amount than the reviews[2,5]; however, these incorporate any local anesthetics (either ropivacaine or bupivacaine), which may at least partly account for this difference. We use bupivacaine at our institution, which may be a factor to consider in expectations with applying these findings to local settings. One issue with this study was that the concentration of ropivacaine was changed from 0.2% in "before" period to 0.1% in the "after" period rather than changing only the administration method from CEI to PIEB+PCEA. Regarding PCEAs, there may be more benefit for some patients than others as it could be influenced by cultural and individual level factors (eg. coping skills, previous experiences) and how patients are educated about or interpret PCA use[4].

PIEB+PCEA seemed to be more beneficial for primiparous women with respect to duration of the second stage of labour, which was reduced by 28.8 minutes on average, compared to 7.7 minutes on average in multiparous women and 22 minutes after adjusting for covariates. Therefore, parity may be an important consideration on the individual patient level when making clinical decisions about PIEB+PCEA vs CEI. The reduced duration is consistent with other studies[2,7,11], but the meta-analysis showed only 11.66 minutes on average compared to the 22 minutes in this study. This may be due to differences in adjusting for covariates, particularly parity, as previously mentioned since these were found to be significant in this study.

An interesting finding of this study was that there was no difference in maternal satisfaction between groups. In contrast, maternal satisfaction was found to be higher, and breakthrough pain lower, in PIEB groups compared to CEI in several relevant studies[5-7,10]. However, it is quite possible that recall bias influenced the results as women were interviewed the day after their delivery rather than during or immediately post-delivery. Furthermore, it would have improved the value of this study to collect data on pain scores during labour and delivery of participants, perhaps as a primary outcome, since pain reduction is the main purpose of labour epidurals. Several studies found either reduced pain or equivalent pain, but accomplished with lower doses of local anesthetic[2,5-7].

Instrumental deliveries and Caesarian sections were not significantly different between groups in this study, which is consistent with the previously mentioned meta-analysis and one other study[2,11]. It is conceivable though that there may be fewer of these interventions in the PIEB+CEA group based on a point estimates of rates in this study and one other relevant article[13]. Further investigations would be needed to draw reasonable conclusions.

The most important limitation of this study is that it is a prospective, controlled, before-and-after study; therefore, patients were not randomised or blinded, and neither were healthcare workers or assessors. One cannot be certain that other concurrent events did not occur at or near the time of the protocol change from CEI to PIEB+PCEA. It is important to note though that given the nature of the intervention of patient-controlled analgesia and bolus interventions, it is not easy to blind participants or assessors, even for RCTs. However, randomization is feasible and could have been done to reduce bias. One article[14] outlines some strategies to mitigate bias in before-and-after studies; many of these concepts were implemented in this study, such as using a reporting checklist, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) to reduce reporting and publication bias. Furthermore, the time interval between the "before" and "after" periods of the study was minimal. One important strategy that would have strengthened results would have been to add a control group to both the "before" and "after" phases of the study; however, this would be increase cost, resource use and difficulty of conducting the study. Furthermore, findings could have been compared to national trends, although this is more applicable to some outcomes, such as rates of Caesarian section, than others, such as total local anesthetic dose, that were considered in this study.

Overall this appears to be a well done before-and-after study that reached reasonable conclusions based on the results and is largely consistent with evidence available in the literature. A main point that this study adds to the literature is that the advantages demonstrated by available RCTs and meta-analyses are still evident when applied to an institution and supports adjusting clinical practice and institution protocols. Moreover, it appears to be applicable to our practices at Kingston General Hospital. Although both PIEB and PCA are able to be programmed using the epidural pumps that are currently available at our institution, PCEA is infrequently used and PIEB rarely or never used. CEI of bupivacaine 0.125% with fentanyl 2μg ml^{-1} infusing at 8-12 ml h^{-1} (most commonly at 10 ml h^{-1}) is the routine protocol for the vast majority of our labour epidurals. Although the ideal epidural solution concentration and settings are not yet consistent in the literature, intermittent bolus doses are typically set at 5-10ml every 30-60 minutes beginning 30 minutes after initial placement in addition to a PCEA[15,16]. Some studies[15,16] have been done to compare methods and specific settings of PIEB+PCEA and research is still ongoing in this area.

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Critical Appraisal Essay – Kai Chen, PGY1, Anesthesiology & Perioperative Medicine

Publication title: "***Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the ENGAGES randomized clinical trial.***"

Authors: Wildes TS, Mickle AM, Abdallah AB, Maybrier HR, Oberhaus J, Budelier TP, Kronzer A, McKinnon SL, Park D, Torres BA, Graetz TJ.

JAMA. 2019 Feb 5;321(5):473-83.

General

The problem addressed by this study is an important issue because there is a growing number of surgeries performed on older individuals, delirium disproportionally affects older adults, and delirium is often associated with higher morbidity, mortality, and increased health care costs. Unfortunately, there are few strategies that mitigate or prevent postoperative delirium. The ENGAGES trial studied a wide variety of surgical procedures, making it of particular interest to anesthesiologists participating in a broad range of perioperative care. Most of the authors, including the corresponding author (Dr. Avidan), hail from North American academic institutions and are affiliated with Washington University, through the Departments of Medicine, Mathematics, Psychiatry, and Occupational Therapy. Two authors are affiliated with Harvard Medical School (Dr. Schmitt and Dr. Inouye), and another with the Department of Anesthesiology at the University of Manitoba (Dr. Jacobsohn). Dr. Avidan has published extensively in the area of postoperative delirium, and Dr. Inouye from Harvard Medical School was the inventor of the Confusion Assessment Method (CAM), often considered a highly reliable and validated tool for assessing delirium in research and clinical practice. Dr. Jacobsohn is the current head of the Canadian Perioperative Anesthesia Clinical Trials Network. These researchers are experts in their fields and lend greater credibility to the study.

Introduction

The problem being addressed is whether or not electroencephalography-guided (EEG-guided) anesthetic administration decreases the incidence of postoperative delirium in older patients undergoing major surgery. The current literature, including a recent Cochrane meta-analysis of randomized clinical trials published in 2018,2 suggest that EEG-guided anesthesia reduced postoperative delirium incidence by one-third to one-half. One possible mechanism for this effect could be the avoidance of burst suppression on the EEG. Burst suppression is seen in comatose patients and in those with brain injury, and it is often associated with excessive depth of anesthesia. In fact, burst suppression has previously been associated with increased incidence of delirium, although these prior studies were hypothesis-generating and were not designed to assess causality. The authors of ENGAGES hypothesize that reducing anesthetic administration will lead to less burst suppression patterns on the EEG, and thus decrease the incidence of postoperative delirium. By adjusting the depth of anesthesia based on EEG waveforms with the goal of avoiding burst suppression in one group but not the other, the authors were able to determine whether or not this intervention changed the incidence of postoperative delirium, thus helping to answer their question.

Methodology

The ENGAGES trial is a prospective, double-blind (patients and outcome assessors), randomized control trial and is thus experimental rather than observational. This was a study done in adult humans ages 60 and above who were having general anesthesia for a major surgery. The detailed protocol published on BMJ Open3 states that these surgeries required minimum inpatient stay of 2 days in order to complete delirium assessments and that the general anesthetic must include volatile agents. In the control group, patients would have EEG monitoring; however, clinicians did not have access to the EEG waveforms or derived Bispectral Index (BIS) Values. In the interventional group, clinicians had access to the EEG waveforms and all derived values including BIS, spectral edge frequency, electromyography, and suppression ratio. Both groups had access to the Signal Quality Index, an indicator of whether the EEG electrodes on the patient were providing adequate signal to the monitor, a form of quality control. The population of patients in this study, as described by Table 1, appear reflective of patients encountered in Kingston (e.g. North American, predominantly Caucasian, median BMI 29), and thus applicable to our practice.

Sample size was calculated based on previous reports of the incidence of postoperative delirium in meta-analyses of randomized control trials and the reduction of risk attributed to EEG-guided anesthesia.2 The sample size calculation, including a sensitivity analysis based on varying estimates on the anticipated reduction in the incidence of delirium, are

described in detail in their published protocol.3 The authors proposed enrolling 1232 patients already enrolled in another study (SATISFY-SOS) and justified this sample size based on their calculations. They estimated over 80% power to detect a 7% decrease (95% CI, 3-12%) in the incidence of delirium with a two-sided alpha < 5% (baseline delirium risk 25%). In the original protocol, the authors suggested a minimal clinically significant difference being 3% absolute risk reduction, which would be covered by the lower limit of the 95% confidence interval in the 7% risk reduction estimate model. The authors chose an appropriate alpha and power for their calculations and can be commended for their inclusion of multiple sensitivity analyses, the definition of the minimally clinically significant change, and the publication of their protocol on an open access platform. Nevertheless, they should have factored in an anticipated loss to follow up calculation in their sample size, especially should this impact their ability to detect their stated minimally clinically significant difference.

The study is ethically sound. It required approval from the Washington University School of Medicine ethics committee, as well as written informed consent from participating patients. In fact, patients who were deemed unable to provide informed consent or have higher risk of adverse events potentially related to the intervention (e.g. history of intraoperative awareness) were excluded from the study. Other exclusions included neurosurgery (an obvious confounder), presence of delirium during initial assessment, blindness, illiteracy, lack of fluency in English (many secondary outcomes were measured using English questionnaires), or another surgery scheduled within 5 days of the first. This last exclusion exists because the primary outcome was measured up to post-operative day 5 and may make results from these patients difficult to interpret. All enrolled patients also received a multicomponent safety intervention, including review of medications by a geriatric psychiatrist, education of home environmental safety, and optional home occupational therapy visit for those with a history of recent fall. These measures are all commendable and contribute to patient safety; however, while they are not financial incentives, these measures may have unduly influenced participation.

The experimental protocol was established to test the hypothesis and due to its randomized nature, theoretically accounts for known and unknown confounding variables. Moreover, the study may help establish causality between EEG burst suppression and delirium by meeting several Bradford Hill criteria including experimentation, strength, plausibility, temporality, coherence and consistency (with previous studies). The protocol is detailed enough to be reproducible as the authors have published their protocol on an open access platform. Supplement 2 also includes a manual of operations to further clarify specifics of the methodology. Having adapted this manual to the ENGAGES-CANADA study in Kingston, I can attest to the reproducibility of their protocol.

The primary outcome was assessed by a widely validated and reliable tool (the CAM) with good sensitivity (> 94%) and specificity (> 89%) for diagnosing delirium. Assessors were also trained to administer this tool appropriately beforehand, with uncertain assessments discussed at weekly meetings. These assessments and random assessments were adjudicated periodically by a panel of experts for quality control. Furthermore, a structured chart review was performed to enhance sensitivity in detecting delirium. For patients that could not talk (i.e. intubated, tracheostomy), a validated variant of the CAM called the CAM-ICU was used. The equipment used to assess EEG waveforms was the Bispectral Index Quatro (Medtronic), which is similar to our BIS monitors and fairly simple to operate. While it does not provide a full EEG montage like those utilized by neurologists, it is representative of the tools we have in the OR. Nevertheless, this machine possesses limitations such as altered readings from the presence of muscle relaxants, electromyography interference, poor adhesion to skin, and other electromagnetic interference. Clinicians participating in the study were trained to recognize EEG waveforms and some of these educational resources were made freely available online. Together, these strengths and limitations suggest the researchers chose a balance of practical and valid tools to deliver their intervention and measure their outcome of interest. In addition, they had thorough education, preparation (including an unpublished pilot trial), and checkpoints along the way for quality control.

ENGAGES was designed as a pragmatic trial, which is evidenced by the fact that anesthesiologists could deviate from the study protocol (e.g. deepen anesthetic despite the presence of burst suppression) based on their clinical judgement. Furthermore, the BIS and CAM are practical to use in the OR and postoperatively at the bedside, respectively. Because of the pragmatic elements of the study design, the protocol can be considered highly clinically relevant.

The randomization sequence was computer generated in a 1:1 fashion to EEG-guided versus usual anesthesia care, in blocks of 20 and in 4 strata. The strata were based on cardiac versus non-cardiac surgery, and positive versus negative history of falling in the past 6 months (2x2 combinations to make up the 4 strata) as these were felt to be strong risk factors for postoperative delirium and stratification ensures balance of these particular confounders. The published protocol suggests there was adequate allocation concealment to minimize selection bias. For instance, information about previously randomized patients was hidden from those responsible for enrolling new patients and assigning interventions.

The primary endpoint was incident delirium on postoperative days 1 through 5. The data collectors who were not blind to group assignment included the clinician who provided the anesthetic, recorded vitals and drugs used, and reported adverse events such as undesirable intraoperative movement. Moreover, any research personnel assisting the clinicians with the intraoperative component of the study protocol were also unblinded. This is appropriate as blinding these individuals would negate the point of the study. Delirium (primary outcome) assessors and chart reviewers were blind to group assignment.

The choice of statistical testing was appropriate and was tailored to the distribution and nature (discrete vs. continuous) of the variable tested. The authors even stated they consider $p < 0.005$ as a more stringent threshold for statistical significance, which is appropriate for a study that may be assessing multiple secondary outcomes. To lend further strength to the study, several sensitivity analyses were performed to demonstrate robustness of the data. These sensitivity analyses were aimed to elucidate whether or not outlier values, clinician adherence to protocol, contamination (e.g. the clinician insisted on viewing EEG information from a patient assigned in usual care group), or other patient comorbidities (measured by the Charleston Comorbidity Index) confounded or interacted with their results. Patients were analyzed by intention-to-treat and per-protocol, further improving the robustness of their data.

Results

Table 1 presents the characteristics of the two randomized groups, which are comparable. The authors did not include p values to assess statistically significant differences in the variables presented; however, this is a reasonable approach given that with larger sample sizes, there may be statistically significant difference despite no meaningful clinically significant difference, which may be falsely interpreted by readers as being important. The largest difference was 3.4% higher incidence of tobacco users in the EEG-guided group; such a small difference is unlikely to confound results. After randomization, there were comparable number of patients in both groups (10 vs. 9) whose primary outcome was not collected and the subsequent sensitivity analysis showed this did not impact the results. Given the rate of loss of follow up is less than 2% in each group, this is quite impressive for a clinical trial. Rates of contamination were also recorded and less than 2% in each group, and contamination bias was addressed by including a per-protocol analysis in addition to intention-to-treat analysis. Data was presented in diagrams, charts, tables, and text as appropriate. Supplement 3 provided additional data with regards to the various sensitivity analyses and other secondary outcomes not shown in the main paper. There were certain outcomes such as health-related quality of life and falls at 1 year which were not reported in this paper; however, the authors clearly stated this in their Methods section and it may be their intention to publish this data in the future.

Discussion

The main conclusion is that EEG-guided anesthetic administration, when compared to usual care without EEG monitoring, did not reduce the incidence of postoperative delirium in older adults undergoing major surgery. The results support their conclusion and address the question these researchers set out to investigate. In fact, they demonstrated that their protocol lead to a significant decrease in the duration of burst suppression in the EEG-guided group (by a median of 6 minute), a key element to their hypothesis and demonstrates protocol adherence, yet this difference did not translate to a difference in their clinical outcome. The results are both statistically and clinically relevant as the researchers used appropriate statistical tools with rigor in their analyses and defined the clinical significance of delirium in their published protocol as well as their Background. They also report important differences in adverse events of interest, such as undesirable intraoperative movement, which was higher in the EEG-guided group.

The authors provide an excellent analysis of their results, especially in how it differs from prior studies that have demonstrated large differences in delirium incidence with EEG-guided anesthesia. Specifically, they point out that prior studies were moderate in methodological quality (assessed by Cochrane standards) and suffered from issues such as missing data, contamination, and lack of power since delirium was often a secondary outcome in those other studies. Furthermore, prior studies often included healthier patients and were more explanatory in nature. This point speaks again to the pragmatic elements of the ENGAGES trial, since explanatory trials tend to enroll healthier patients and often reflect ideal situations not always encountered in the real-world. The authors state that the methodological rigor of this trial likely led to different results. This is an important addition to the current body of literature because it is a high-quality trial that presents negative findings that challenges current knowledge in this controversial topic. This is especially important because negative findings are often not published and accounted for in evidence syntheses (publication bias). Finally, this trial is published in a world-renowned journal (JAMA), which is expected to reach a wide audience and stimulate discussion and future research in this field.

The authors stated several limitations to their study. For example, practice patterns at the study's centres may differ from other centres such as ours. For instance, 42% of anesthesia providers in this study were nurse anesthetists or student nurse

anesthetists. This is a significant difference from most Canadian centres. Furthermore, intraoperative fentanyl doses (median 350 to 400 mcg) appear much larger relative to intraoperative hydromorphone (median 0.20 to 0.23 mg) doses compared to the practices I have witnessed in Kingston. MAC values also appear lower (median 0.69 to 0.80) compared to practices at KGH (full disclosure, these are my limited subjective observations). These factors may affect our interpretation of the results but ongoing multi-centre studies such as ENGAGES-CANADA, of which KGH is partaking, and the Balanced Anesthesia Study are likely to provide additional insight. Other limitations include the difficulty in capturing the primary outcome of delirium due to its fluctuating nature, as well as the underestimation of burst suppression duration since it is impossible (and unsafe) for the anesthesia provider to direct their attention to the EEG monitor at all times.

Some unanswered questions include the lower 30-day mortality rate seen in the EEG-guided group (-2.42%, 95%CI -4.3 to -0.8%, p = 0.004), which is hypothesis generating for future trials. Importantly, the study did not report findings in specific subgroups such as cardiac surgery; however, this is the specific population ENGAGES-CANADA is powered to address. Furthermore, the authors did not comment on whether undesirable patient movement affected any clinical outcomes. Not surprisingly, the EEG-guided group required less phenylephrine to maintain MAP, likely due to less volatile utilization, but it is unknown whether this has a clinical impact (e.g. on renal perfusion, peripheral ischemia, acid-base balance etc.).

Applicability

In summary, this study provides important insights into the role of EEG monitoring for the prevention of postoperative delirium in older adults undergoing major surgery. Furthermore, the high methodological quality and pragmatism of this trial increases its utility in applying the findings to clinical practice. Delirium is a common, multifactorial, postoperative complication with few preventative strategies. I look forward to the results of future secondary analyses on long-term outcomes and the results of ENGAGES-CANADA and the Balanced Anesthesia Study, which may address how varying practices at different centres may influence findings.

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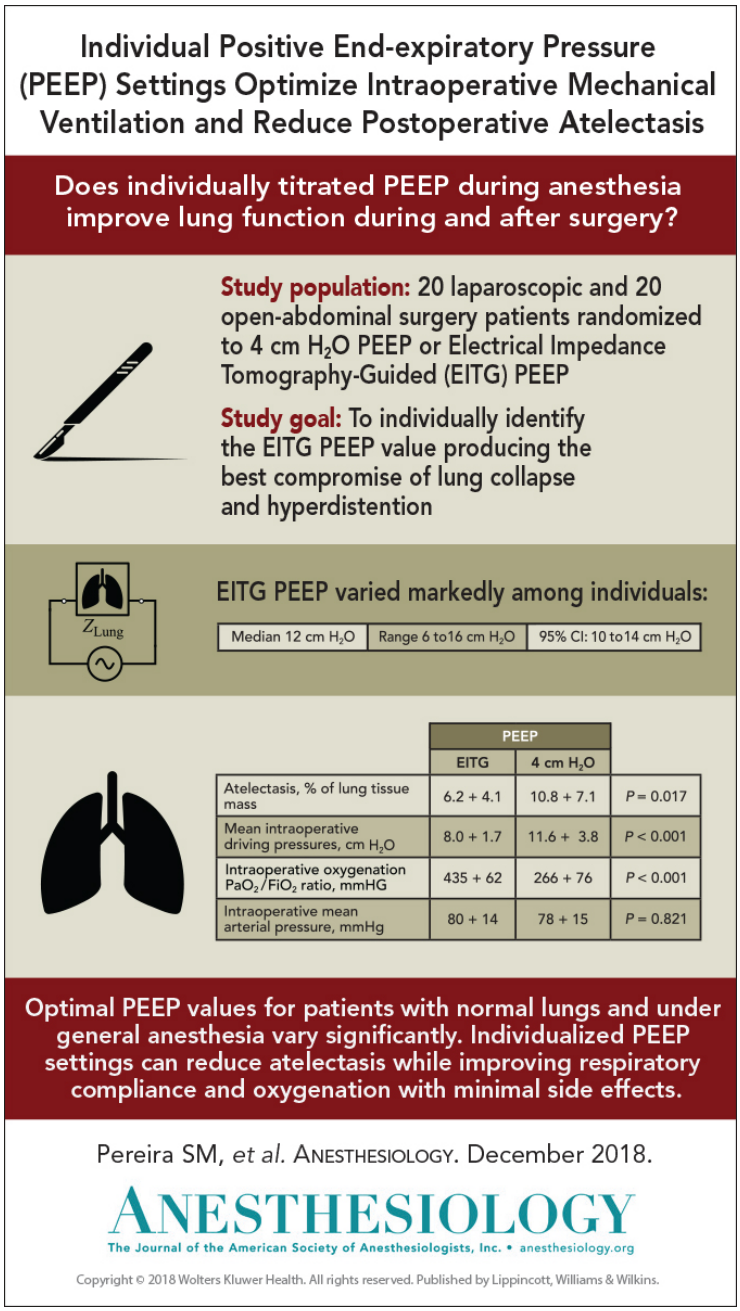
Critical Appraisal Essay – Amy Jiang, PGY1, Anesthesiology & Perioperative Medicine

Publication title: "***Individual Positive End-expiratory Pressure Settings Optimize Intraoperative Mechanical Ventilation and Reduce Postoperative Atelectasis.***"

Authors: Pereira SM, Tucci MR, Morais CCA, Simoes CM, Tonelotto BFF, Pompeo MS, Kay FU, Pelos P, Vieira JE, Amato MBP.

Anesthesiology. 2018 Dec; 129: 1070-1081.



Introduction

Postoperative respiratory complications are a significant cause of perioperative morbidity and mortality. Recent studies have shown that lung protective ventilation with physiologic tidal volumes, 6 to 8 mL/kg of ideal body weight, and fixed low PEEP between 2 to 6 cm H_20 improves clinical outcomes in patients undergoing general anesthesia[1-3]. However, there is currently no consensus on an optimal PEEP level.

Several studies have suggested the use of moderate PEEP from 5 to 8 cm H_2O to prevent postoperative atelectasis[2,4,5]. Another recent trial compared the use of high PEEP at 12 cm H_2O and low PEEP at 2 cm H_2O and found that high PEEP had no benefit in preventing postoperative pulmonary complications, while causing increased hemodynamic instability and fluid requirements[6].

A lack of consensus on PEEP may exist because there is a large variation in required PEEP between individuals, influenced by factors such as chest wall dimensions, abdominal contents, lung weight, and pleural pressures[7-13]. The authors of this study hypothesize that in mechanically ventilated patients with normal lungs undergoing abdominal surgery, optimized PEEP differs between individuals, and can improve lung function during and after surgery compared to a standard low PEEP setting of 4 cm H2O. Testing this hypothesis can potentially reduce the risk of postoperative respiratory complications.

Methodology

This is a prospective, experimental, randomized, pilot study. The population studied included a sample size of 40 patients undergoing elective abdominal surgery, including 20 laparacopic and 20 open. This trial was approved by the institutional review board and patients provided written informed consent before proceeding. Patients over the age of 18 could be included. Patients who were an ASA 3 or greater, or those with moderate to severe obstructive or restrictive lung disease were excluded since the authors were studying patients with normal lungs. This population sample is similar to many of the healthy patients undergoing abdominal surgery at KGH; it does not reflect our large burden of sicker patients and those with lung pathology.

The study compared respiratory outcomes in patients randomized to either a fixed PEEP of 4 cm H2O (PEEP4), or an individually titrated PEEP determined using electrical impedance tomography (PEEP-EIT). The experimental protocol was designed to test the hypothesis. After insertion of an intravenous and arterial line, EIT belt was applied to each patient at the fifth intercostal space. Patients were preoxygenated with 100% oxygen, induced intravenously in the supine position, and intubated. No details were provided about medications used for induction, including the anesthetic agent or use of neuromuscular blockade, both of which can contribute to the amount of atelectasis. No details were provided about which medications used for maintenance of anesthesia either. After intubation, volume-controlled ventilation was started with specified physiologic ventilation parameters: FiO_2 0.5, 4 cm H_2O PEEP, 6-7 mL/kg of predicted body weight tidal volume, inspiratory pause 30%, and respiratory rate titrated to maintain an end-tidal CO_2 of 35-45 mmHg. Baseline EIT signals were recorded in all patients. A standardized recruitment maneuver was performed on pressure-controlled ventilation using 20 cm H_2O PEEP and inspiratory pressures reaching 40 cm H_2O for 2 minutes. PEEP was subsequently titrated by decreasing PEEP by 2 cm H_2O every 40 seconds with continuous EIT monitoring. At each PEEP, the EIT monitor determined the percent of hyperdistended and collapsed lung units. PEEP-EIT was the closest PEEP above the intersection of the collapsed and hyperdistention curves, thereby minimizing both lung collapse and hyperdistension (Figure 1). This method of determining an optimal PEEP by estimating alveolar collapse and hyperdistension was first proposed by Costa et al. in 2009, who found good agreement in collapse estimates between EIT and CT in ICU patients with ARDS.[14] It has subsequently been used in mechanically ventilated post cardiac surgery patients.[15,16] Notably, these study populations are very different from the patient population included in the study of interest.

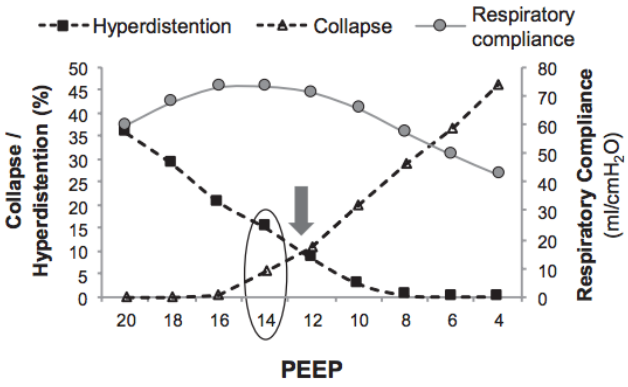


Figure 1: PEEP-EIT was considered the nearest PEEP above the intersection of the collapse and hyperdistension curves.

After determination of PEEP-EIT, all patients underwent a recruitment maneuver of PEEP-EIT for 2 minutes. Patients were then randomized to either PEEP4 or PEEP-EIT; the randomization was stratified based on whether the surgery was open or laparoscopic. No details were provided about how the randomization was performed. The authors collected data on mechanical ventilation, hemodynamics, blood gases, and EIT at baseline after intubation, during PEEP, after randomization, within an hour of surgery, and before extubation. In the laparoscopic cases, data was also collected at the start and end of pneumoperitoneum. Respiratory rate and FiO_2 could be adjusted according to arterial blood gas results or SpO_2. Fluids, blood products, analgesia, and vasoactive drugs, were

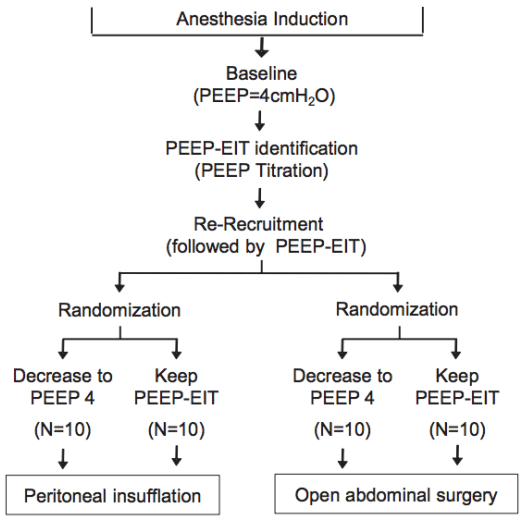


Figure 2: Protocol flow chart.

administered "according to routine protocols" that were otherwise unspecified.

Patients were extubated off pressure-support ventilation with an FiO_2 of 0.5 and PEEP was maintained as per randomization. A chest CT was performed 30 to 60 minutes after extubation, where patients were instructed to hold expiration at functional residual capacity. Ten slices from each CT was chosen to calculate the percentage of collapsed lung; this technique has been validated in normal lungs.[17]

The authors do not explicitly discuss blinding; presumably while the patients and outcome assessors may potentially have been blinded, the anesthesia providers could not be. A lack of blinding puts this study at risk of bias.

The primary endpoint of this study was to identify an individually titrated PEEP value that produced the best compromise between hyperdistension and lung collapse, as determined using EIT. The secondary endpoint was to assess the degree of atelectasis after extubation, as determined on postoperative chest CT. Further outcomes included the impact of PEEP on intraoperative pulmonary function and hemodynamics; no further details about these outcomes are provided at this point.

After confirmation of normal distribution of continuous variables using the Shapiro-Wilk test, unpaired t tests or Mann-Whitney tests were used for univariate analyses and the Pearson correlation test was used for correlation between two variables. This was appropriately done.

Table 1. Baseline Characteristics of the Patients

Demographic and Clinical Variables	All (n = 40)	PEEP4 (n = 20)	PEEP-EIT (n = 20)
Age, median (IQR), yr	52.5 (26–74)	54.2 (33–68)	50.7 (26–74)
Male sex, n (%)	18 (45.0)	8 (40.0)	10 (50.0)
Weight, mean ± SD, kg	77.9±15.6	79±15.9	76.8±15.6
Predicted body weight, mean ± SD, kg	56.4±9.5	54.3±9.9	58.6±8.8
Body mass index, mean ± SD, kg/m^2	29.5±4.3	30.6±4.2	28.3±4.2
Thoracic perimeter, mean ± SD, cm	100.4±8.6	102±9.0	99±8.0
Type of Surgery			
Urology, n (%)	13 (32.5)	5 (25)	8 (40)
Gastric, n (%)	19 (47.5)	10 (50)	9 (45)
Gynecology, n (%)	8 (20)	5 (25)	3 (15)
ASA Physical Status I, n (%)	12 (30)	6 (30)	6 (30)
ASA Physical Status II, n (%)	28 (70)	14 (70)	14 (70)
Hypertension, n (%)	18 (45)	8 (40)	10 (50)
Hypothyreoidism, n (%)	3 (7.5)	1 (5)	2 (10)
Diabetes, n (%)	7 (17.5)	2 (10)	5 (25)
Chronic kidney disease, n (%)	1 (2.5)	0 (0)	1 (5)
Smoking status			
Never, n (%)	27 (67.5)	16 (80)	11 (55)
Former, n (%)	5 (12.5)	2 (10)	3 (15)
Current, n (%)	8 (10)	2 (10)	6 (30)
Active cancer, n (%)	14 (35)	5 (25)	9 (45)
Chemotherapy, n (%)	0 (0)	0 (0)	0 (0)

Chronic kidney disease as defined according to Kidney Disease: Improving Global Outcomes. ASA, American Society of Anesthesiologists; IQR, interquartile range; PEEP4, PEEP of 4 cm H_2O; PEEP-EIT, PEEP guided by electrical impedance tomography.

Results

Of the 40 patients enrolled in the study, no subjects were eliminated. No data collected was excluded from analysis, even outlier data; data missing was less than 5%. The two treatment groups in the study were fairly comparable at baseline, as seen in Table 1. Median age was slightly higher in the standard PEEP group compared to the individualized PEEP group (54.2 vs 50.7), and BMI was slightly higher in the standard PEEP group (30.6 ± 4.2 vs 28.3 ± 4.2). These baseline characteristics were not stratified based on laparascopic or open surgery; this comparison would have been useful based on the primary outcome results. Ventilation parameters were also compared between the PEEP groups, stratified based on laparoscopic or open surgery, as seen in Table 2. There were no significant differences between the two PEEP treatments at baseline or during PEEP titration, prior to randomization.

Table 2. Ventilation Parameters

Time of Acquisition	Parameters	Laparoscopic (n = 20) Randomized Group			Open Surgery (n = 20) Randomized Group		
		PEEP4 (n = 10)	PEEP-EIT (n = 10)	*P* Value	PEEP4 (n = 10)	PEEP-EIT (n = 10)	*P* Value
Baseline	V_T/Kg (ml/kg)	7 ± 0.7	6.4 ± 0.5	0.073	6.6 ± 0.5	6.2 ± 0.7	0.144
	PEEP (cmH_2O)	4.2 ± 0.3	4.1 ± 0.4		4.1 ± 0.1	4.4 ± 0.4	
	Plateau pressure (cmH_2O)	15.7 ± 2.4	13.9 ± 3.3	0.195	13.3 ± 2.5	13.4 ± 1.9	0.883
	Compliance (ml/cmH_2O)	33.5 ± 8.1	37.7 ± 9.7	0.317	42.1 ± 15.7	43.5 ± 7.9	0.807
	Driving pressure (cmH_2O)	11.6 ± 2.5	9.8 ± 3.1	0.188	9.3 ± 2.5	9.1 ± 1.7	0.869
	Collapse on EIT (%)	44.6 ± 15.4	41.7 ± 18.0	0.711	35 ± 16.1	31.3 ± 9.2	0.530
During titration (at PEEP-EIT)	V_T/Kg (ml/kg)	7.1 ± 0.5	6.7 ± 0.5	0.086	6.8 ± 0.5	6.5 ± 0.6	0.125
	PEEP (cmH_2O)	14.3 ± 1.5	12.9 ± 1.6		10.2 ± 2.3	10.3 ± 2.3	
	Plateau pressure (cmH_2O)	19.5 ± 2.0	18.1 ± 1.9	0.130	16.1 ± 3.1	16.8 ± 3.3	0.660
	Compliance (ml/cmH_2O)	77.1 ± 14.0	75.3 ± 8.6	0.742	75.9 ± 18.0	71.9 ± 15.7	0.601
	Driving pressure (cmH_2O)	5.3 ± 0.7	5.2 ± 0.7	0.796	6.0 ± 1.3	6.5 ± 1.1	0.336
	Collapse on EIT (%)	6.5 ± 5.6	4.5 ± 3.9	0.375	3.6 ± 1.8	5.4 ± 2.8	0.097
After randomization (selected PEEP)	V_T/Kg (ml/kg)	7.1 ± 0.7	6.5 ± 0.8	0.071	6.6 ± 0.4	6.3 ± 0.6	0.206
	PEEP (cmH_2O)	3.8 ± 0.3	13.2 ± 1.4	**<0.001**	3.9 ± 0.3	10.1 ± 2.0	**<0.001**
	Plateau pressure (cmH_2O)	13.7 ± 1.4	18.7 ± 2.0	**<0.001**	11.7 ± 1.4	16.6 ± 3.1	**<0.001**
	Compliance (ml/cmH_2O)	39.6 ± 7.2	67.6 ± 6.7	**<0.001**	48.8 ± 13.2	66.2 ± 14.2	**0.011**
	Driving pressure (cmH_2O)	9.8 ± 1.4	5.5 ± 0.8	**<0.001**	7.7 ± 1.5	6.5 ± 1.3	0.070
	Collapse on EIT (%)	42.5 ± 12.6	10.3 ± 10.2	**<0.001**	29.8 ± 14.2	8.5 ± 5.1	**<0.001**

Data are expressed as mean ± SD; V_T/Kg is expressed in ml/kg; PEEP, plateau pressure, and driving pressure are expressed in cmH_2O; Respiratory compliance is expressed in ml/cmH_2O; "Collapse on EIT": collapse on electrical impedance tomography is expressed as percentage of total lung mass; PEEP4, group randomized to PEEP of 4 cm H_2O; PEEP-EIT, group randomized to PEEP titrated by EIT. *P* (*t* test) for the difference between PEEP4 and PEEP-EIT in the same type of surgery (laparoscopic or open surgery). *P* values less than 0.05 are shown in bold.

EIT, electrical impedance tomography; PEEP, positive end-expiratory pressure; PEEP4, PEEP of 4 cm H_2O; PEEP-EIT, PEEP guided by electrical impedance tomography; V_T, tidal volume.

With regards to their primary outcomes, the authors found a median PEEP-EIT of 12 cm H_2O, with a range from 6 to 16 cm H_2O. Interestingly, laparoscopic patients had a significantly higher PEEP-EIT than open surgery patients (13.5 ± 1.6 vs 10.2 ± 2.3 cm H_2O, P<0.001), even though PEEP-EIT was determined before insufflation. The authors found some correlation between BMI and PEEP-EIT (R^2 = 0.371, p,0.001); they proposed that the higher BMI in the laparoscopic patient group may partially explain the difference in PEEP-EIT.

The authors provided adequate details of their secondary outcome: postoperative lung collapse. PEEP-EIT patients had a significantly lower percentage of nonaerated lung tissue than PEEP4 patients (6.2 ± 4.1% vs 10.8 ± 7.1%, p = 0.017). The authors chose "representative images" from two patients to demonstrate collapse as determined by EIT before randomization and by CT postoperatively (Figure 3). Here, the PEEP4 patient had higher pre-randomization collapse and a very high postoperative collapse (26.3% vs PEEP4 mean of 10.8%). The PEEP-EIT patient had lower pre-randomization collapse and very low postoperative collapse (0.7% vs PEEP-EIT mean of 6.2%). While their image selection visually portrays the significance of their results, it does exaggerate the difference in postoperative collapse between the two treatment arms.

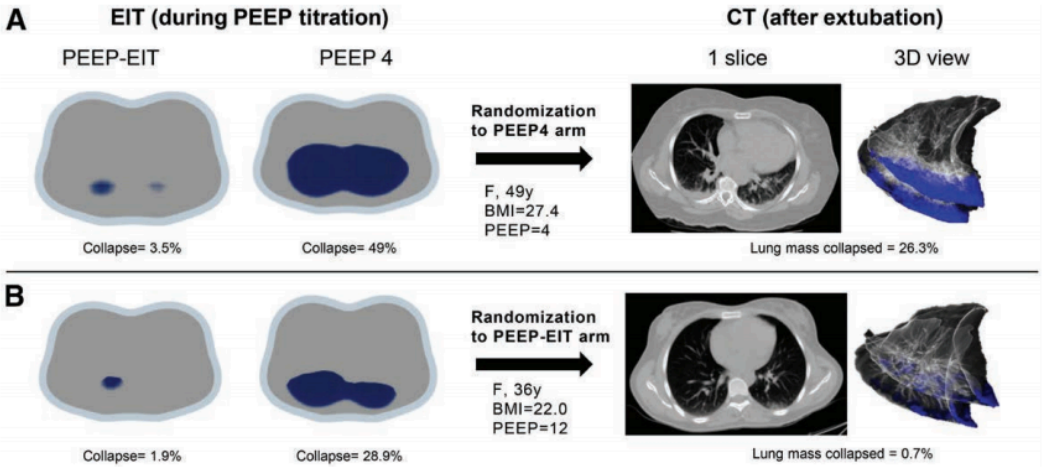


Figure 3: EIT images at PEEP-EIT and PEEP 4 cm H_2O. Chest CT images after extubation. Patient A is randomized for PEEP4 arm, patient B is randomized for PEEP-EIT arm.

The authors also provide results on further exploratory outcomes including pre-randomization driving pressure, post-randomization ventilation parameters, hemodynamics, length of anesthetic time, and length of hospital stay. They found a statistically significant reduction in driving pressure at PEEP-EIT compared to a fixed PEEP of 4 cm H_2O in patients prior to randomization (5.7 ± 1.1 vs 9.9 ± 2.6 cm H_2O). This driving pressure reduction was correlated to BMI: the greater the BMI, the larger the reduction in driving pressure ($R = 0.454$, $p>0.001$). After randomization, driving pressure was higher in the PEEP4 arm than the PEEP-EIT arm (11.6 ± 3.8 vs 8.0 ± 1.7 cm H_2O, $p < 0.001$). Compliance was lower in the PEEP4 arm (35.4 ± 13.4 vs 54.3 ± 13.9 mL/cm H_2O, $p<0.001$). Oxygenation, as measured by a PaO_2/FiO_2 ratio, was higher in the PEEP-EIT arm than the PEEP4 arm in laparoscopic patients (435 ± 62 vs 266 ± 76 mmHg, $p<0.001$) but not for open surgery patients ($p=0.232$).

Additionally, the authors found that while a high percentage of patients required vasoactive drugs during the recruitment maneuvers, none required continuous infusions during surgery. There was no difference in mean arterial pressure between PEEP-EIT and PEEP4 (80 ± 14 vs 78 ± 15 mmHg, $p=0.821$). Length of anesthesia was greater in PEEP4 patients compared to PEEP-EIT patients (235 vs 205, $p=0.013$). The length of hospital stay was not different between the two arms ($p=0.138$).

Discussion

One main conclusion from this study is that PEEP-EIT has a wide range among patients with healthy lungs undergoing general anesthetic, from 6 to 16 cm H_2O. Study results support this conclusion, and are in keeping with previous literature showing wide individualized PEEP.[12,13,18] The authors explain that even in healthy lungs, there is enough variation in patient characteristics to cause variation in PEEP. While BMI and optimized PEEP were positively correlated, BMI alone did not account for individual PEEP variation in this study population.

Another important conclusion from this study is that patients ventilated with PEEP-EIT had less atelectasis on chest CT after extubation compared to those on a standard low PEEP. This is true for both laparascopic and open surgeries. Notably, PEEP-EIT was always higher than 4 cm H_2O; thus an alternative explanation could be that higher PEEP, rather than individually titrated PEEP, reduces postoperative atelectasis. Another treatment arm allowing the comparison of high standard PEEP, low standard PEEP, and individually titrated PEEP would provide useful information about the role of individually titrated PEEP.

The authors also conclude that PEEP-EIT reduces driving pressure. Their data showing a driving pressure reduction in all patients before randomization, and subsequently between the two groups after randomization, is very robust in supporting this conclusion. This reduction in driving pressure is greater in patients with a higher BMI. Previous research has shown that when driving pressures are consistently less than 12.5 cm H_2O, the frequency of postoperative pulmonary complications is lower.[4] In laparoscopic cases, patients ventilated at PEEP 4cm H_2O were consistently exposed to driving

pressures over 12.5 cm H_2O during insufflation; those at PEEP-EIT stayed consistently below 12.5 cm H2O. These results suggest that PEEP-EIT may result in fewer postoperative complications, particularly in obese patients and laparoscopic cases.

The authors also conclude that oxygenation is improved in PEEP-EIT compared to PEEP4. Oxygenation improvement, measured as a PaO_2/FiO_2 ratio, was actually only significantly different in the laparoscopic patients and not in open cases. They report that the two groups do not differ in intraoperative hemodynamic instability, which can be more likely to occur with ventilation causing hyperdistension. Only ASA 1 and 2 patients were included in this study; patients who are less stable may be more likely to have hemodynamic fluctuation with both recruitment maneuvers and higher PEEP.

One major limitation of this study was that the authors did not directly evaluate the incidence and severity of postoperative respiratory complications, which is clinically a more important endpoint than the degree of atelectasis alone. Postoperative atelectasis has been shown to increase pulmonary complications, impair respiratory function, and delay patient discharge.[19,20] However, whether or not the 4.6% increase in atelectasis in the standard PEEP patients actually leads to any difference in patient morbidity and mortality is yet to be determined. This represents an important next step in this field of research.

Another limitation of this study is the patient sample that was chosen to be included. It excludes patients who are an ASA 3 or greater, and those with any moderate to severe lung pathology. Thus, the results from this study cannot be generalized to quite a large percentage of patients undergoing abdominal surgery. The role of a PEEP-EIT in these less stable patients is a salient area of exploration, since these patients are at greater risk of intraoperative hemodynamic instability as well as postoperative respiratory complications. The study sample size is small; thus, it may have been underpowered to detect statistically significant differences in outcomes such as length of hospital stay. Furthermore, there was limited information on surgical factors such as patient position and postoperative pain, which can affect postoperative respiratory outcomes. The length of surgery and anesthesia was longer in the PEEP4 arm, which may have contributed to increased atelectasis.

Despite the limitations of this study, it does present a convincing argument that different patients require different PEEP settings. Since the anesthesia machines at KGH are preset to deliver a PEEP of 5 cm H_2O, I suspect that the vast majority of patients undergoing a general anesthetic in Kingston receive a PEEP of 5 cm H_2O. Critically appraising this study has encouraged me to consider using a higher PEEP setting in selected patients, particularly in those with a higher BMI or undergoing laparoscopic surgery.

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Critical Appraisal Essay – Nick-Hugh Wisdom, PGY1, Anesthesiology & Perioperative Medicine

Publication title: "***Comparison of Dopamine and Norepinephrine in the treatment of Shock SOAP II Trial.***"

Authors: De Backer D1, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL

N Engl J Med 2010; 362:779-789

Clinical Question

"In critically ill patients with shock, does the use of Norepinephrine compared to Dopamine as first line vasopressor therapy reduced 28-day mortality?"

Background

Critical illness complicated by circulatory shock continues to have significant morbidity and mortality. A significant proportion of these patients suffer from septic shock which is a clinical syndrome of impaired oxygen delivery to tissues secondary to an infective insult. This is to be differentiated from SIRS which can be present in the absence of infection. The management of shock is highly dependent on the etiology. In clinical states where there is a reduction in mean systemic venous pressure and consequent impairment in venous return; fluid therapy is a rational first choice. Important to remember though is that early antibiotics continue to be the gold standard in management of septic shock. Administration of fluids alone is often insufficient to attain hemodynamic stability in a shocked patient and adrenergic agents are frequently required to maintain a sufficient mean atrial pressure (MAP). Prior to the findings of this trial Norepinephrine and Dopamine where used as the most common first choice vasoactive agents. The impetus for this study was from mounting observational studies that implicated dopamine with increased mortality in comparison to norepinephrine in the setting of shock. *The Sepsis occurrence in Acutely ill Patients* (SOAP) illustrated, quite convincingly, that dopamine administration was an independent risk factor for death in the intensive care unit.

Design

This was a pragmatic trial aimed to answer an objective clinical question. It was a double-blinded, randomized and multicentred. The randomization was computer generated block sequence with stratification according to the participating ICU. The five-digit reference numbers generated from the randomization was placed in sealed opaque envelopes which were open only by the person responsible for preparation of the study medications.

The power calculation was based largely on mortality data reported by the SOAP trial which indicated a baseline 28-day mortality of 43% among patients treated with dopamine and 36 % among those treated with norepinephrine. They needed to recruit 765 patients to each treatment arm in order to attain an eighty percent power in order to detect a fifteen percent relative difference at a two-sided alpha level of 0.05.

The study was carried out between December 19, 2003 and October 6, 2007 across eight centres located in Spain, Austria and Belgium. The inclusion criteria were patients, who were over the age of eighteen, requiring vasopressor for fluid unresponsive shock. The specific hemodynamic criterion was as follows: MAP < 70 mmHg or a systolic pressure < 100 mmHg despite adequate fluid therapy. In

addition there had to be clinical signs of tissue hypoperfusion such as urine output less than 0.5 mL/kg/hr, altered mental status or serum lactate greater than 2 mmol/L. Patients were excluded from the study if they had received vasopressor therapy for greater than 4hrs prior to enrollment, if they presented with serious arrhythmias or if they had been declared brain dead. At the conclusion of the study 1679 patients were enrolled, 858 in the dopamine arm and 821 in the norepinephrine arm.

The primary outcome was all cause mortality at twenty-eight days, secondary outcomes include hospital length of stay, need for renal replacement therapy, vasopressor free days and the occurrence of serious adverse effects. These were generally thought to be the clinically relevant outcomes that would lead one to select one vasopressor over another in the context of treating shock.

Patients in the study received norepinephrine or dopamine based on their allocation post randomization. Doses adjusted to a map that was left to the discretion of the treating clinician. Doses of dopamine was increased /or decreased in increments of 2 mcg /kg /min (max 20 mcg/kg/min. Doses of norepinephrine was increased/or decreased by 0.02 mcg/kg/min (max 0.19 mcg/kg/min). Open labelled norepinephrine was added if patients failed to meet target MAP after reaching the maximum dose of the study drug Tapering of open label drug was conducted first before study drug tapered. Tapering of study drug only when target BP maintained for 12 hrs without open label drugs Study drug was interrupted if any serious adverse events occurred (defined)If Patient recovered from shock and had a subsequent episode of shock requiring vasopressors within 28 days, the initial study drug was reinstituted.

Results

The data analysed based on the intention to treat model. This allows for a more reliable estimate of the effectiveness of the treatment as this approach reflects what would happen in actually clinical practice. In terms of the primary out-come: there was no significant difference in the 28-day mortality 52.5 percent in the Dopamine arm versus 48.5 percent in the norepinephrine arm (OR 1.17; 95% CI 0.97-1.42; P= 0.10). in terms of secondary outcomes there were no significant difference in: Length of stay, need for renal replacement therapy, days free of vasopressor during 28 days after randomization however there were more serious adverse events in dopamine group 1. Arrhythmias: Dopamine group 24.1% vs noradrenaline group 12.4% (P <0.001) 2. Myocardial infarction: Dopamine group 19% vs noradrenaline group 25% (P 0.29). The baseline characteristics were similar between groups: Septic shock {Dopamine (542 (63.2 %)): Norepinephrine (502 (61.1)} , Cardiogenic shock {Dopamine (135 (15.7 %)): Norepinephrine (145 (17.6)} , Hypovolemic shock {Dopamine (138 (16.1 %)): Norepinephrine (125 (15.2)}, Age {Dopamine (Median 68 (55-76) Norepinephrine (Median 67 (56-76)} , APACHE II {Dopamine (Median 20 (15-28) Norepinephrine (Median 20 (14-27)} , QSOFA {Dopamine (Median 9 (7-12) Norepinephrine (Median 9 (6-12)}. The authors conducted a subgroup analysis which resulted in the pivotal finding that in terms of cardiogenic shock the 28- day mortality was significantly increased in Dopamine group versus Norepinephrine group.

Discussion

The implication of the study was at the time potentially practice changing as there was clinical equipoise with regards to vasopressor therapy in the treatment of cardiogenic shock. This is was evident as the American College of Cardiology -American heart association guidelines had recommended dopamine as the first agent to increase arterial pressure among patients who have hypotension as a result of an acute myocardial infarction. In order to incorporate findings from this trial into everyday clinical practice we have to bear in mind the generalizability and validity of the

data. This was a multicentre trial with inclusion and exclusion criteria similar to other trials looking at the clinical question therefore there was excellent external validity. The block randomization process utilized minimized the possible confounders inherent in the comparison groups with potential for significant heterogeneity. The concealment of sequence and blinding of the treating physicians and those analysing the data affords for excellent internal validity of the study. The trial was however not without limitations. It is important to consider these limitations when bringing the science to the bedside. The major limitations brought forward by the authors. The infusion rates of dopamine selected were equipotent to norepinephrine with respect to systemic arterial pressure and the fact that there were only minor differences in the use of open-labelled norepinephrine, which was mostly related to early termination of the study drug due to the occurrence of arrhythmias that were difficult to control. I am not entirely sure how this assertion affects the validity of the results other than the increased mortality in cardiogenic shock may have been an issue of dosing rather the drug themselves as dopamine is a less potent vasopressor than Norepinephrine. Since the publishing of the study other authors have brought forward several problems that they found with the study methodology such as the fact that the study authors did have a clear definition of what would constitute the resolution of shock. Some critics also mention the fact that the amount of fluid administered, 1L of crystalloid or 500 ml of colloids may not have been adequate for certain subsets of patients. I tend to disagree with this assertion as the authors did state that the patients included would have clearly been deemed to be failing fluid therapy and the onus was on the treating clinician to assess volume status and fluid responsiveness of the individual patients prior to initiating vasopressor therapy. My take home from this trial is that Norepinephrine should be the initial vasopressor of choice in patients with fluid unresponsive shock.

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(in alphabetical order of 1st author)

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