Queen's University
39th 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:

Louie Wang
MD, MSc, FRCPC

Cara Reimer
MD, MSc, FRCPC

Guest Lecturer: **Daniel McIsaac MD, MPH, FRCPC**

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Joel Parlow, MD, MSc, FRCPC

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Administrative Coordinator, Research:
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Jess Shelley, RN, BNSc, CCRP

Research Nurse:
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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 (Kingston General & Hotel Dieu Sites) • Providence Care

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SCIENTIFIC PROGRAM OUTLINE

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

0810 – 0820 **Introduction of Research Day Presentations**
– Dr. Ian Gilron

0820 – 0920 **Oral presentations (4)**

0920 – 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. Cara Reimer, Assistant Professor, Queen's Department of Anesthesiology & Perioperative Medicine

Dr. Louie Wang, Associate Professor, Queen's Departments of Anesthesiology & Perioperative Medicine and Biomedical & Molecular Sciences

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1500 **Dr. Daniel McIsaac,** Assistant Professor, Department of Anesthesiology & Pain Medicine, University of Ottawa

*** Guest Lecture ***

"Frailty and perioperative medicine: the emerging field of geriatric anesthesiology"

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

Oral Presentations (alphabetical order)

Courtney BANNERMAN, BSc, MSc Candidate (Queen's Neuroscience)
"**Characterization of a novel mouse model of contusion-compression spinal cord injury**" (proposal)

Matthew BILBILY, PGY-3
"**Use of objective neuromuscular monitors among Canadian anesthesiologists**" (update)

Sophie BRETON, PGY-4
"**Can healthcare-associated HCV outbreaks occur through reuse of anesthetic medication vials accessed with clean needles and syringes?**" (update)

Matthew BRUDER, PGY-2
"**A Pilot Study to Investigate Labor Epidural Failure Rates at Kingston Health Science Centre**" (proposal)

Carl CHAUVIN, PGY-2
"**Epidural waveform analysis for confirmation of thoracic epidural placement in the epidural space**" (proposal)

Emily COOK, PGY-2
"**Examination of the Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery at KHSC**" (proposal)

Jamei ENG, PGY-4
"**Effect of Sugammadex versus Neostigmine/Glycopyrrolate on postoperative cognitive dysfunction in elderly patients.**" (proposal)

Yuri KOUMPAN, PGY-4
"**Spinal anesthesia is associated with lower recurrence rates after resection of non-muscle invasive bladder cancer.**" (update)

Jordan LEITCH, PGY-4
"**Randomized Control Trial of Novel Formulation Trigger Point Injections for Relief of Chronic Myofascial Pelvic Pain**" (update)

Jeffrey PARKER, PGY-4
"**A retrospective cohort study to examine the effectiveness of perioperative brachial plexus nerve block to reduce healthcare use after shoulder surgery: Targeting the Quality-Based Procedures program**" (update)

Nicole RELKE, BScH, MD Candidate, Queen's University
"**Impact of an EEG-guided anesthesia protocol on postoperative cognitive disturbances in elderly cardiac surgery patients: An extension of the ENGAGES-Cardiac multicenter trial**" (update)

Alaa SABBAHI, Fellow
"**Benefits and Barriers to use of Active Warming Methods during Cesarean Delivery**" (proposal)

Navroop SANDHU, PGY-4
"**Addressing the shortage of rural and remote physicians: what are Canadian Anesthesiology training programs doing to combat the problem and how do these initiatives impact the future practice location of trainees?**" (proposal)

Oral Presentations (alphabetical order)

Julia SEGAL, BSc, MSc Candidate (Queen's Biomedical & Molecular Science)
"**Neuroimmune mechanisms controlling circadian pain in experimental autoimmune encephalomyelitis**" (proposal/update)

Joanna SEMRAU, BSc, MSc Candidate (Queen's CNS)
"**Quantitative predictors of post-operative neurological impairment in cardiac surgery patients**" (update)

Emma TORBICKI, PGY-2
"**Does the leadership style employed by anesthesiologists (positive versus negative) affect operating room (OR) team performance?**" (proposal)

Danika VAUTOUR, PGY-3
"**Concordance Between Resident Self-Assessment and Faculty Assessment of Competency Over the Span of a Residency Program with the Transition to Competency-Based Medical Education**" (update)

Sam WALSH, PGY-4
"**Postsurgical Pain After Hospital Discharge: A Systematic Review**" (update)

Poster Presentations (alphabetical order)

The impact of medication administration timing on maternal outcomes in postpartum hemorrhage
William Knoll, Marta Cenkowski, Wilma Hopman, Nader Ghasemlou, Gregory Klar

Cancellation of Elective surgery: Prevalence, Reasons, and Impact on Patients' Perception of the Healthcare System.
Wan Xian Koh, BSc, MD candidate, UBC, Dale Engen

Examining the Covariation between the Gastrointestinal Microbiome and the Chronobiology of Thermal Nociception in Murine Models
Justin Lim, Caitlin Lundell-Creagh, Brooke Snetsinger, Henry Wong, Jeffery Stafford, Kaitlyn Tresidder, Nader Ghasemlou, Prameet M. Sheth

The role of circadian rhythms in somatosensation
Caitlin Lundell-Creagh, Kaitlyn Tresidder, Ian Gilron, Nader Ghasemlou

Skin-resident γδ T cell morphology and activation
Abigail Marshall, Jacqueline Silva, and Nader Ghasemlou

Advanced dynamic weight bearing: an observer independent test to model disability
Sarah Phillips, Julia Segal, Qingling Duan, Ian Gilron and Nader Ghasemlou

Characterization of a novel mouse model of contusion-compression spinal cord injury

Courtney Bannerman, BSc; Julia Segal, BSc; Jaqueline Silva, PhD; Scott Duggan, MSc, MD; Nader Ghasemlou, PhD

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 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. 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. 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.

Mice who received the compression injury show significantly greater thermal heat and mechanical hypersensitivity in comparison to a moderate injury. Mechanical threshold in compression-injured mice was significantly different from the moderately injured mice 7- 35 days after injury. These mice also had significantly increased thermal heat hypersensitivity 7-10 days after injury. The acetone test for cold pain 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. Creating a rodent model of spinal cord injury that more closely mimics an injury sustained by a human may help facilitate the translation of potential therapeutics from mouse to human.

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 postoperative 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.

Current Knowledge Gaps: As described above, quantitative evaluation of neuromuscular blockade is superior to subjective evaluation and leads to improved patient outcomes. Yet, the practice of many anesthesiologists does not incorporate regular use of quantitative monitors. Why is this the case? Do barriers to access of the technology exist? Are there varying perceptions of the incidence and effect of residual paralysis? Or is it a matter of practicality in the operating room environment?

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

Proposed study design:
1. Develop a survey to assess the following areas:
- primary outcome: proportion of Canadian anesthesiologists who routinely use objective neuromuscular monitors
- perceptions of incidence of residual paralysis
- perceptions of accuracy of subjective neuromuscular monitoring
- barriers to use of objective neuromuscular monitors (access, practicality, etc)
2. Distribute survey to staff anesthesiologists and residents at academic institutions across Canada
3. Analyze results of survey respondents

References:
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.

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Murphy GS, Szokol JW, Avram MJ, et al. Postoperative Residual Neuromuscular Blockade Is Associated with Impaired Clinical Recovery. Anesth Analg. 2013;117(1):133–141.

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Can Sharing Medication Vials with Clean Needles and Syringes Lead to Healthcare-Associated HCV Outbreaks?

Sophie Breton, Melanie Jaeger, Janet van Vlymen, Selena Sagan

Background: In the 1990's, increasing healthcare-associated hepatitis C virus (HCV) outbreaks attributed to poor injection practices served as the impetus for the Center for Disease Control (CDC) to develop the "One & Only" campaign which advocated '1 syringe + 1 needle + 1 time' (CDC Guidelines – Safe Injection Practices to Prevent Transmission of Infections to Patients, 2011). Despite the widespread dissemination of this infection control guideline, healthcare-associated HCV outbreaks continue to be frequently reported. In the province of Ontario, Canada, there have been four independent HCV outbreaks documented in outpatient endoscopy clinics in the past 5 years, resulting in 14 new HCV infections. Thorough investigation of each outbreak concluded that contaminated medications, administered by the anesthesiologist, were the likely source of patient-to-patient transmission. Most of the anesthesiologists involved however, adamantly denied reusing needles or syringes when accessing vials for multiple patients. The American Society of Anesthesiologists (ASA) and the CDC both caution against the reuse of needles or syringes and state that medication vials should only be used for a single patient (ASA Recommendations for Infection Control; CDC – Injection Safety, 2010). Nevertheless, it has remained common practice to share multidose medication vials between patients provided new needles and syringes are used with aseptic technique (Gounder et al., 2013; Kossover-Smith et al., 2017). This medication sharing practice, combined with the inadvertent contamination of an anesthesiologist's workspace may be facilitating these outbreaks.

Purpose: We hypothesized that when caring for HCV-infected patients, anesthesiologists may inadvertently contaminate the medication vial diaphragm, and that subsequent access with sterile needles and syringes can transfer HCV into the medication where it remains stable in sufficient quantities to infect subsequent patients.

Methods: We simulated contamination of multidose medication vials in healthcare settings using cell culture-derived HCV (HCVcc) to determine: 1) whether HCV can be transferred, via a sterile needle and syringe, into a medication vial if the rubber access diaphragm is contaminated; 2) whether HCV remains viable in commonly used medications in sufficient quantities over time to initiate an infection; and 3) whether cleaning the diaphragm with 70% isopropyl alcohol is sufficient to eliminate infectivity.

Results: Contamination of medication vials with 33μL (mean volume of inadvertent contamination) of HCVcc (800,000 IU/mL – the concentration considered the border between low and high viral loads) and subsequent access with sterile needles and syringes resulted in contamination of the vial contents in sufficient quantities of HCV to initiate an infection in cell culture. Second, HCV remains viable for ≥72h in propofol, dexamethasone, rocuronium, lidocaine, neostigmine and phenylephrine. Third, a single wipe of the vial diaphragm with 70% isopropyl alcohol was not sufficient to eliminate HCV infectivity.

Conclusions: HCV can be transferred, via sterile needle and syringe, into medication vials if the diaphragm is contaminated with medically relevant quantities of HCV and the virus remains stable in several commonly used medications. Furthermore, a single wipe of the vial diaphragm with 70% isopropyl alcohol is not sufficient to eliminate HCV infectivity. These results from our laboratory experiments, in light of known survey data suggesting that sharing medication vials with more than one patient is a common practice, highlight the importance of changing our daily practices concerning medication administration. We recommend investment in education and knowledge translation across medical specialties, division (or elimination) of multidose vials, and use of single-dose vials to minimize nosocomial HCV infections.

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

Matthew Bruder, PGY2 Anesthesia
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.
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Use of waveform analysis as a post-placement test for non-functional thoracic epidural catheters

Carl Chauvin, Gregory Klar, John Murdoch

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 trial. 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% with epinephrine 1:200 000 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).

References:

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Examination of 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. M. McMullen, Dr. J. Dion

Background: In 2017 the Canadian Cardiovascular Society suggested that BNP or NT-proBNP should routinely be measured before noncardiac surgery to optimize perioperative cardiac risk estimation in patients who are 65 years of age or older, are 45-64 years of age with significant cardiovascular disease, or have a Revised Cardiac Risk Index score ≥1[1]. The guidelines also recommended obtaining daily troponin levels in patients with positive NT-proBNP levels, as an elevated postoperative troponin is a known predictor of 30-day morbidity and mortality[2,3,4].

After these guidelines were released, the measurement of NT-proBNP levels was implemented as part of the presurgical screening process at Kingston Health Sciences Center (KHSC) and a protocol for the management and follow-up of patients with positive results was developed. It is currently unknown whether this protocol is being appropriately followed at KHSC and the proposed study aims to investigate this to ensure that the best possible care is provided to patients at this centre.

Study Design: This project is a prospective quality assurance plan-do-study-act (PDSA) cycle. 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 was implemented

Hypotheses: Despite the clear recommendations put forth by the Canadian Cardiovascular Society, it is hypothesized that the majority of patients at KHSC with positive preoperative NT-proBNP levels are not receiving the subsequent investigations and recommended follow-up care. Furthermore, it is hypothesized that taking measures to improve the ease of testing (i.e. adding testing/referral options to patient management forms) will improve compliance and result in more patients receiving postoperative care compliant with current guidelines.

References

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Effect of Sugammadex versus Neostigmine/Glycopyrrolate on postoperative cognitive dysfunction in elderly patients.

Jamei Eng, Nilufer Nourouzpour, Glenio Mizubuti, Dale Engen, Anthony Ho

Background:

Non-depolarizing neuromuscular blockers (e.g., rocuronium) have been generally favored over depolarizing agents such as succinylcholine. Some of the reasons for this include succinylcholine-induced: bradycardia/asystole, hyperkalemia, temporary intracranial/intraocular/intragastric pressure elevation, prolonged paralysis (in case of pseudocholinesterase deficiency), malignant hyperthermia, and myalgia (1). Additionally, its short duration of action makes succinylcholine unsuitable for surgical procedures requiring prolonged muscle relaxation. Yet, succinylcholine is classically used for rapid sequence tracheal intubation. (2)

Given its rapid onset of action, rocuronium is used as an alternative to facilitate rapid sequence intubation (3). Its prolonged clinical effect, however, has historically limited its application in situations where the need for prompt reestablishment of the neuromuscular function is anticipated. Typically, the effects of rocuronium are antagonized by cholinesterase enzyme inhibitors (AChEi) such as Neostigmine. More recently, however, a reversal agent that binds directly to rocuronium (namely, sugammadex) has been approved in Canada in 2016. (4)

Cholinergic crisis is an over-stimulation at the neuromuscular junction due to excess of acetylcholine (Ach), as of a result of the inactivity/inhibition of the AChE, which normally breaks down ACh. The clinical presentation spectrum goes from meiosis, restlessness and confusion, to unresponsiveness, increased pulmonary secretions/bronchospasm and muscle weakness/paralysis. Cholinergic crisis is mostly described in organophosphate intoxication and/or in patients with myasthenia gravis who take too high a dose of their AChEi. (5) However, there is a lack of literature in the context of reversal of paralysis with neostigmine. We suspect that higher (or even clinical) doses of neostigmine, especially in elderly patients, might stimulate central receptors resulting in postoperative cognitive dysfunction. We, therefore, hypothesize that sugammadex will be associated with better postoperative cognitive function than neostigmine in elderly patients.

Purpose of Study:

We plan to examine the occurrence of post-operative cognitive dysfunction/delirium in the elderly population and its relation to reversal with neostigmine. The study will consist of a randomized control trial by comparing reversal of neuromuscular blockade with rocuronium vs neostigmine versus sugammadex. Inclusion criteria will be age $\geq$ 70, patient had to be given rocuronium for any surgery and meet requirements to use reversal. In order to assess post-operative cognitive dysfunction/delirium, the scoring system for RASS and CAM-ICU will be used. Scoring will be conducted by nursing staff. Primary outcomes assessed will be a positive score for delirium at 30 min and 1, 3, 6 and 24 hours postoperative. Intravenous neostigmine 50mcg/kg along with glycopyrrolate 0.4-0.6 mg will be given at the end of surgical procedure. Dosing of sugammadex will be administered as suggested by the manufacturer based on train of four measurement, which is dependent on the value of the train of four nerve stimulation. The study will be double blind, i.e. neither the anesthesiologist nor the nursing staff responsible for the postoperative assessments will know which reversal agent was given.

References:

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4. Health Canada New Drug Authorizations 2016 Highlights https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/health-canada-new-drug-authorizations-2016-highlights.html
5. Anticholinesterase Poisoning: Rx – Open Anesthesia https://www.openanesthesia.org/anticholinesterase_poisoning_rx/

Spinal Anesthesia is Associated with Lower Recurrence Rates after Resection of Non-Muscle Invasive Bladder Cancer

Yuri Koumpan MD, Melanie Jaeger MD, FRCPC, Glenio Bitencourt Mizubuti MD, MSc, Rob Tanzola MD, FRCPC, Kunal Jain BMSc, Gregory Hosier MD, Wilma Hopman MSc, D. Robert Siemens MD, FRCSC

BACKGROUND:
The association between cancer recurrence and anesthetic technique has been an intriguing area of investigation in the past decade. Various perioperative factors have been implicated in negatively modulating the immune system to promote cancer cell growth, including surgical inflammation, volatile anesthetics, and opioid use. On the other hand, regional anesthesia has been suggested to reduce perioperative immunosuppression, improve the function of cancer-killing immune cells, and reduce the use of volatile anesthetics and opioids. The aim of our study was to determine if anesthetic type (general vs. subarachnoid block) would influence our primary outcome of cancer recurrence following transurethral resections of bladder cancer.

METHODS:
Following research ethics board approval, this observational, retrospective study reviewed 231 patients who underwent transurethral resection of bladder tumor (TURBT) surgery for non-muscle invasive urothelial bladder cancer (NMIBC) at a single center between 2011-2013. Variables collected included key factors influencing recurrence of NMIBC (stage, grade, size and number of tumors) as well as adjuvant anti-cancer therapies. Additional perioperative data included anesthetic type, age and ASA classification. Chi-Square tests were conducted to test for associations between patient characteristics and incidence of recurrence, progression and overall mortality, and Kaplan-Meier estimates were conducted for time to recurrence, time to progression, and time to mortality. Logistic regression and a Cox proportional hazards regression model were used to explore the association between anesthetic type and recurrence.

RESULTS:
In univariable analysis, patients under spinal anesthesia (n=135) had a longer median time to recurrence (42.1 months vs 17.2 months, p=0.014) compared to those who had general anesthesia (n=96). As anticipated, adjuvant therapies (p=0.003) and risk groupings (amalgam of stage, grade, CIS, number and size of tumors) (p=0.042) were all associated with recurrence rates. In multivariable analyses incorporating key a priori variables including cancer risk, adjuvant chemotherapy and immunotherapy, patients under general anesthesia had a higher incidence of recurrence (OR=2.062, 95% CI=1.14-3.74, p=0.017) and earlier time to recurrence (HR=1.57, 95% CI=1.13-2.19, p=0.008) compared to patients under spinal anesthesia. Anesthetic type was not associated with cancer progression or overall mortality.

CONCLUSION:
Patients receiving a general anesthetic had higher incidence of recurrence and earlier time to recurrence following TURBT for NMIBC. These findings should prompt large-scale, prospective studies to further delineate this association.

Randomized Control Trial of Novel Formulation Trigger Point Injections for Relief of Chronic Myofascial Pelvic Pain

J.Leitch, A.Webb, R.Nitsch, S.Chamberlain, J.Pudwell, R.Henry

Background:

Chronic pelvic pain is a common and disabling condition - it is estimated that 16% of women experience the debilitating functional, emotional, and sexual associated deficits. Practically, this is an extremely costly health care issue, accounting for one of every ten gynecologist visits, and is a frequent indication for surgery, despite little proven benefit.[1]

Current recommendations for the treatment of myofascial pain and trigger points according to the Society of Obstetricians and Gynecologists includes trigger point injections, physical therapy, and manual therapy. Various formulations have been trialed, including local anesthetics, steroids, and botulinum toxin.[3] Lidocaine formulations are the most commonly used, despite a paucity of robust research and sound study design demonstrating benefit. As such, there is no clear consensus or guidelines on the most appropriate injection formulation.

Trigger points account for the somatic pain experienced by patients, which can be either latent (painful when palpated) or active (unprovoked, spontaneous pain). Trigger points develop due to a failure of voluntary muscle to relax, resulting in a chronic state of contraction and a relative ATP (energy) crisis. Essentially, chronic contraction causes decreased tissue perfusion, which in turn results in a local decrease in energy production and increase in anaerobic cellular respiration. The hydrogen ions (lactic acid) produced during anaerobic metabolism stimulate peripheral nociceptors that cause pain.[2] The contraction is further perpetuated by a lack of inhibition of the ryanodine receptors (due to a deficiency of both ATP and magnesium) which results in an increase in the amount of calcium present in the sarcoplasm to facilitate muscle contraction.

Study Design & Methods:

Our study is a single-center, double-blinded, randomized control superiority trial. The primary outcome is pain score 2 weeks after the final trigger point injections on the visual analog scale. We will also assess secondary outcomes including quality of life, functional movement, concomitant medication usage, procedural pain, time to resolution of pain, and adverse events. Participants will be recruited via referrals to our pain clinic, with 30 patients randomly assigned into either the lidocaine-only or the novel formulation arms. The novel formulation is comprised of magnesium, sodium bicarbonate, dextrose and lidocaine. A third arm will consist of 30 patients on the clinic waitlist and will serve as a control. Each participant in the treatment arms will have 9 visits (8 treatments) during which they are assessed, receive injections, and complete questionnaires.

Results:

We have recruited 23 patients to the intervention group and 12 patients into the control group (8 completed). The original stratification based on opioid use has been removed from the study design as there were not an adequate number of participants referred to the clinic who are managed on opioids to allow comparison. The study design has been shown to be feasible, with perhaps an ambitious timeline. Nonetheless, we are on track to complete the study by December 2019.

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A retrospective cohort study to examine the effectiveness of perioperative brachial plexus nerve block to reduce healthcare use after shoulder surgery: Targeting the Quality-Based Procedures program

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Staff Investigators: Louie Wang, MD, FRCPC; *Glenio Mizubuti* MD, MSc; *Elizabeth VanDenKerkhof*, RN, MSc, DrPH; *Monakshi Sawhney*, NP, PhD; *Stephen Mann*, MD, FRCPC

Background: Shoulder surgery can be performed under general anesthesia (GA), brachial plexus nerve block, or a combination of both. In addition, continuous brachial plexus nerve blocks can provide post-operative pain control for several days. Studies have demonstrated the benefits of brachial plexus nerve blocks in shoulder surgery to include improved post-operative pain control, greater passive shoulder movement, and the decreased incidence of side effects associated with opioid consumption.[1-4] Peripheral nerve blockade during rotator cuff surgery has also been shown to reduce the length of stay in postoperative anesthesia care units and reduce the rate of hospital admissions.[4,5]

Objective: To use population-level data to examine the effect of brachial plexus nerve block on the use of Emergency Department (ED) services, rate of unplanned hospital admissions, and length of hospital stay following elective shoulder surgery for degenerative disorders of the shoulder.

Methods: Administrative data, available through the Institute for Clinical Evaluative Sciences, was used to identify all Ontario residents who underwent elective surgery for degenerative disorders of the shoulder from 2009 to 2015, using predefined inclusion and exclusion criteria. Bivariate statistics is used to describe the relationship between brachial plexus block and study outcomes. Multiple regression analysis is used to identify patient and provider characteristics and control for confounding variables. Finally, reasons for post-operative health care utilization will be described and stratified by type of anesthetic.

Preliminary Results: We identified 62,959 elective shoulder surgery patients in Ontario between 2009 and 2015. 52.1% of patients had surgery under GA alone, 43.3% of patients received a single-shot brachial plexus block and 4.6% of patients had received a continuous brachial plexus block. 5.6% of patients utilized ED services and 2.6% of patients had an unplanned hospital admission during the 7 days following surgery. In comparison to GA alone, single shot brachial plexus block resulted in decreased ED utilization [adjusted relative risk (aRR) 0.93; 95% confidence interval (CI) 0.87-1.00 ($P = 0.044$)], decreased unplanned hospitalization [aRR 0.79; CI 0.72-0.88 ($P < 0.001$)], and decreased length of stay [aRR 0.78; CI 0.75-0.82 ($P < 0.001$)]. Continuous brachial plexus block resulted in increased ED utilization [aRR 1.23; CI 1.05-1.42 ($P = 0.008$)], increased length of stay [aRR 1.08; CI 1.03-1.12 ($P = 0.001$)], and no significant difference in unplanned hospitalization [aRR 1.04; CI 0.82-1.31 ($P = 0.760$)].

Conclusions: Information gathered from this study can help guide best practices and reduce unnecessary health care utilization. In comparison to GA alone, single-shot brachial plexus block is associated with lower health care utilization as measured by ED visits, unplanned admissions, and hospital length of stay. Conversely, continuous brachial plexus block has a higher risk of ED visit and increased hospital length of stay. Potential reasons for this difference, study limitations and next steps will be discussed during the presentation.

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Benefits and Barriers to use of Active Warming Methods during Cesarean Delivery

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Incidence of hypothermia can be as high as 90% in patients undergoing Cesarean section under spinal anesthesia. This can result in increased maternal and neonatal complications perioperatively. Despite known benefits of decreased incidence of hypothermia and shivering, neither fluid warmers nor forced air warmers are routinely used during Cesarean sections. The aim of this study will be to explore the benefits of active warming during Cesarean section as well as potential barriers to their routine use.

This study will be a randomized control trial comparing two active warming methods, the Bair Hugger and the Enflow warmer versus warm cotton blankets, on intraoperative temperature maintenance and shivering. Secondary outcomes will include maternal thermal comfort, anxiety and estimated blood loss, neonatal temperature and Apgar scores, and ability to perform unobstructed skin to skin. In addition, an anesthesiologists survey will explore routine practices across Canada and reasons for or against active warming during Cesarean section.

Previous studies have shown improved temperature maintenance during Cesarean section when active warming methods are used, yet no study has compared which warming modality is most effective. By comparing both benefits and barriers to each method, we hope to determine which commonly used active warming method is better during Cesarean section. As a result of this study, we hope to achieve better perioperative outcomes, an improved sense of maternal and neonatal wellbeing and an improved perioperative experience that will inspire other anesthesiologists to adopt active warming methods during Cesarean deliveries.

Addressing the shortage of rural and remote physicians: what are Canadian anaesthesiology training programs doing to combat the problem and how do these initiatives impact the future practice location of trainees?

Navroop Sandhu, PGY-3, Supervisor: Dr. Greg Klar

Background

Under the *Canada Health Act* of 1984, all residents of Canada should have "reasonable access to medically necessary hospital and physician health services without paying out of pocket"[1]. Like many other countries around the world, however, many inequities exist in health care delivery in Canada[2]. Approximately 29% of Canadians report having difficulties accessing necessary health care services. Many essential services including mental health, physiotherapy, and long-term care are not covered[3]. According to Statistics Canada[2], barriers to equal healthcare access in Canada include socioeconomic status, gender, education level, immigration status (likely due to language/cultural barriers), and geography.

As Dr. John Wooton, Health Canada's Special Advisor on Rural Health stated in 1999, "[if] there is two-tiered medicine in Canada, it's not rich and poor, it's urban versus rural"[4]. Geography is a major barrier to health care access in Canada. Over 95% of Canada's land mass is rural[5] and as of 2011, over 6.3 million Canadians (~19%) lived in areas with a population density below 400 people per square kilometer[6]. Studies conducted looking at health care disparities have found that geography is absolutely a determinant of health. Those in rural and remote areas have poorer health outcomes[5-7], are more likely to be in a lower socioeconomic class[5,8], have less healthy behaviours[5,8], and have a higher rate of disability[5,9], accidents[5,9] and suicide[5]. Those in rural and remote communities also have an overall lower life expectancy[7]. Even though a significant proportion of the Canadian population lives in rural and remote areas, only 8% of Canadian physicians serve this population[10]. It can be tremendously difficult for those in rural and remote communities to access primary care providers, let alone retain those physicians[9]. Services such as diagnostic imaging and specialist services are even harder to get in these communities. Needing specialist care often involves expensive travel to an urban center, time away from one's family and support systems, and the financial burden of meal and accommodation costs.[5-7].

Purpose

To determine whether accredited Canadian Anesthesiology training programs offer electives/mandatory rotations that serve to increase trainee awareness about the need for, and/or exposure to rural/remote health care and (2) if they do, how many residents actually take part in these initiatives and (3) what are individual programs doing to help facilitate these experiences for interested residents, and finally (4) do these experiences have an impact on future practice location?

Method

With Research Ethics Boards approval, a short survey will be developed by our group at Queen's University with adherence to the EQUATOR guidelines for online questionnaires (CHERRIES). The draft survey will be piloted for or expert feedback and revision. Once finalized, the survey will be distributed to program directors at each of the 14 English and 3 French accredited Canadian Anesthesiology residency training programs using the Queen's University supported online survey platform, Qualtrics.

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Neuroimmune mechanisms controlling circadian pain in experimental autoimmune encephalomyelitis

Julia Segal, BSc; Courtney Bannerman, BSc; Sarah Phillips; Jaqueline Silva, PhD; Ian Gilron, MSc, MD; Nader Ghasemlou, PhD

Up to 80% of multiple sclerosis (MS) patients experience chronic pain, and the most common type and most difficult to treat is neuropathic pain. Recent evidence shows that circadian rhythms can significantly affect chronic pain, inflammation, and nociceptor activity; both human and mouse models of neuropathic pain show a circadian rhythm to pain levels, and it has been extensively shown that the immune system is very tightly regulated by circadian rhythms. Neuroimmune mechanisms mediating neuropathic pain remain poorly characterized, and the role of circadian rhythms in MS pain has not been studied. We hypothesize that the circadian system modulates the neuroimmune responses underlying pain in MS and contributes directly to disease pathophysiology. This was investigated using actively-induced experimental autoimmune encephalomyelitis (EAE), a mouse model of MS.

To determine the role of circadian rhythm in pain and disease progression, EAE was induced using a modified model that produces low clinical symptoms but a high pain phenotype. Pain outcomes were measured using behavioural tests that assess mechanical, thermal and cold sensitivity at 9am, 3pm, and 9pm at specific days post-EAE induction to determine whether pain follows a circadian rhythm, as has been shown in other models. It was found that EAE mice experience lower mechanical and cold sensitivity at 9pm compared to 9am and 3pm, and that there is no heat sensitivity associated with this particular EAE model.

The long-term goal of these studies is not only to characterize the circadian control of pain in EAE but also to identify mediators of pain that may be used to identify new pharmacological targets for chronic pain in MS.

Quantitative predictors of post-operative neurological impairment in cardiac surgery patients

Joanna S. Semrau, Stephen H. Scott, Andrew Hamilton, Dimitri Petsikas, Darrin Payne, Gianluigi Bisleri, Tarit Saha, and J. Gordon Boyd.

Background: Coronary artery bypass grafting (CABG) surgery may be associated with subsequent neurological complications. Decreases in regional cerebral oxygen saturation (rSO_2) during surgery may be associated with post-operative cognitive decline (Slater, JP et al. Ann Thorac Surg. 2009; de Tournay Jette, E et al. J. Cardiothorac. Anes. 2011). However, the lack of robust and quantitative neurological assessments has led to variable results (Zheng, F et al. Anesth Analg. 2013). We have used robotic technology called the Kinesiological Instrument for Normal and Altered Reaching (KINARM, Bkin Technologies) to generate a comprehensive and quantitative neurological profile for patients undergoing CABG surgery. The KINARM assesses the sensorimotor and neurocognitive control of upper limbs in humans. **Our objective is to quantify neurological function in CABG patients, and determine whether intraoperative rSO_2 can predict post-operative outcome. We aim to test the hypothesis that low rSO_2 is associated with poor post-operative neurological function, as measured by the KINARM.**

Methods: Adult patients undergoing elective on-pump CABG were recruited for this study. Patients with a history of cognitive and/or neurological problems were excluded. Participants were assessed prior to and 3 months following their CABG surgery using 7 standardized KINARM robotic tasks. Intraoperatively, rSO_2 was recorded for each patient using the FORESIGHT cerebral oximeter (Casmed, Caster Medical, CAN). Linear regression was used to assess the ability of the following 2 variables to predict post-operative cognitive dysfunction: % drop of rSO_2 from baseline (delta-rSO_2), and pre-operative task score. A Bonferroni correction was performed for all seven models to reduce the over-inflation of p-values due to multiple comparisons.

Results: Perioperative data from a total of 41 CABG surgery patients was used for this analysis. For a number of tasks (arm position matching, ball on bar, object hit, visually guided reaching, and reverse visually guided reaching), the greatest predictor of post-operative neurological impairment was existing impairment detected prior to surgery. Our second predictor, delta-rSO_2, did not significantly predict impairment following Bonferroni correction. The highest rate of impairment was observed on the reverse visually guided reaching task, with 27.4% of participants scoring outside the normal range 3 months after their surgery. The two chosen predictors accounted for 82.2% of the variance in post-operative scores (R^2=0.822, p=1.37e-14) for this task, the largest explained variance out of all models.

Clinical Implications & Future Directions: Our results suggest that subclinical or undiagnosed neurological dysfunction, rather than intraoperative variables, may be the strongest predictor of post-operative neurological outcomes. Pre-surgical neurological assessment may provide valuable information about a patient's recovery process. These findings suggest that patient cognitive reserve may be crucial in determining the success of their recovery process following surgery. This hypothesis is to be explored further as we expand to other cardiac surgeries.

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 Over the Span of a Residency Program with the Transition to Competency-Based Medical Education

D. Vautour, Co-Authors: M. Fleming, G. Mizubuti, M. McMullen, R. Egan, J. Baumhour.

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). Competency Based Medical Education (CBME) is a curricular shift that calls for structured and iterative assessment across pre-determined and distinct professional activities, with granulized requirements clearly outlined with enabling competencies and milestones. As such, there is a unique opportunity to assess, develop, and refine systematized mechanisms of synchronous and blinded assessment between residents and supervisors, with subsequent calibration through written and/or verbal feedback. As a leader in CBME, Queen's University has a unique opportunity to evaluate the effectiveness of self-assessment as an important measure of resident entrustment. Entrustment based on self-assessment transcends the current state of training by honing residents' ability to accurately determine the limits and extent of their ability, a skill that is essential for continuing professional development and has the potential to enhance patient safety and care quality into the future.

As of April 2018, data collection and entry for the pilot study within the residents of the Anesthesiology Department has been completed. Analysis of this raw data is underway but general tendencies have been observed.

Methodology

Phase 1- Instrument Design **-Completed**
Development of a self-assessment tool
Phase 2 – Pilot Study Data Collection**-Completed**
Participating sub-specialties will begin pilot data collection of daily faculty and resident paper assessments. Qualitative data will subsequently be compiled, analyzed, and triangulated by research assistants working with the OHSE
Phase 3 – Data Collection, Analysis & Results Communication**-In Progress**
Entrada Project©, the integrated teaching and learning platform tool, will be used in the consistent design of online distribution, collection, and analysis of self-assessment forms/data. Postdoctoral fellows with the OHSE will collect, conduct and analyse the quantitative data.
Phase 4 – Qualitative Interview
Interview investigating resident and staff perspective from a lived experience lens and also evaluate if/how residents' used the trends in their self-assessment to inform their perspectives on practice.

Outcomes

Through this project we will:

1. Establish a shared vision and approach to self-assessment within the Queens CBME context.
2. Establish an evidenced based approach to Entrada self-assessment design.
3. Collect data on self-awareness accuracy trajectory across residents at different stages and within different (sub) specialties over 1.5 years of their programs.
4. We will provide the literature with one of the first longitudinal self-assessment studies concentrating not on *if* self-assessment is accurate, but rather *how* accuracy can be approved over time and across contexts.

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Postoperative pain in patients post hospital discharge: A systematic review

Authors: Samuel Walsh, Elizabeth VanDenKerkhof , Amanda Ross-White, Ian Gilron

Clinical Need: Major advances have been made in the treatment of pain in patients admitted to hospital postoperatively; however, patients continue to report high levels of pain after discharge to the community. (1). A 2013 survey in the United States found that of a random sample of 300 patients, 74% experienced moderate to major pain after being discharged from hospital (2). These findings are consistent with a Canadian study which reported that 68% of inpatient and 49% of outpatient surgery patients had high levels of pain (3). Poorly controlled postoperative pain has a major impact on quality of life during the recovery process and may delay return to work. Unplanned health care visits related to poorly controlled pain places additional strain on health care systems. A multicenter randomized controlled trial studying pain in 171 patients post total knee replacement found that 60% had to seek additional medical attention from a primary care provider and 3 patients returned to hospital for pain management (4). Acute pain is also related to chronic pain. A recent expert review by Katz and Seltzer identifies moderate to severe acute pain as a major risk factor for the development of chronic pain (5).
Current gaps in knowledge: A majority of studies focusing on postoperative pain are conducted on ambulatory surgery patients or on inpatient surgery patients only while they are in hospital. There is a small, but growing body of literature about postoperative pain at home after discharge from inpatient surgery. Surgeries requiring admission are often more painful and extensive than ambulatory surgery. Transitioning from inpatient pain management with nursing and physician help to outpatient care can be stressful and difficult (6). A review of the existing literature could help guide optimal management for larger more painful procedures and improve patient experiences and outcomes at home. We chose to focus only on acute pain, as chronic pain has a large and well-reviewed body of literature.
Study question: What is the pain experience of surgical inpatients as they transition from an intensive pain management regime under the care of doctors and nurses to self-administered analgesia post discharge.
Study design: A two-step strategy was utilized to develop a comprehensive search. Initially three search strategies predicted to return studies of interest were developed by combining relevant keywords and excluding other terms. We limited our search to adults and English language studies. A cut off of 3 months was chosen to define acute pain based on our scoping review. We also excluded procedures focused on the resolution of preoperative pain, such as spine surgery. These searches returned 2527 abstracts, which were reviewed to find articles which addressed our study question. Articles which met our inclusion criteria were used to develop a gold standard search to ensure a complete list of keywords and subject headings were used.
Progress: Since last year 201 articles identified as potentially relevant by an abstract review were hand reviewed yielding 65 papers. These papers were used to reverse engineer a gold standard search strategy valid for systematic review as described by Booth (7) and Golder (8). Of note, upon exploring the 4th strategy from last year it was found that a majority of the studies dealt with ambulatory surgery and therefore were not appropriate to answer our question.
Limitations: The large amount of heterogeneity between the time points and pain measures used make direct comparison between studies and statistical analysis difficult. The elimination of certain types of surgery and studies addressing chronic pain will limit the generalizability of this review. Lastly the changing terms and definitions associated with ambulatory and inpatient surgery make finding an effective but exhaustive search strategy very difficult. Our two-stage search strategy attempts to reconcile this but it is still possible that some valid and important studies were missed.

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Critical Appraisal Essay – Daenis Camiré, PGY1, Anesthesiology & Perioperative Medicine

Publication title: "***Comparison of reversal with neostigmine of low-dose rocuronium vs. reversal with sugammadex of high-dose rocuronium for a short procedure.***"

Authors: Choi ES, Oh AY, Koo BW, Hwang JW, Han JW, Seo KS, Ahn SH, Jeong WJ
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Introduction

Laryngeal micro-surgery is described as a brief procedure with insufficient time for titration of the level of neuromuscular blockade; however, it requires deep levels of neuromuscular blockade for tracheal intubation and direct laryngeal manipulations. Until recently, anaesthetists preferred to maintain a moderate level of neuromuscular blockade to allow rapid reversal and avoid residual paralysis at the end of surgery. With only moderate levels of neuromuscular blockade, however, intra-operative patient movement and the need for additional doses of neuromuscular blockers are not infrequent.

The laryngeal muscles are relatively resistant to neuromuscular blockade and can move even when there is no movement in the adductor pollicis muscle [1]. With the use of sugammadex, rapid reversal from even a deep level of neuromuscular blockade is possible [2]. Therefore, in the present study, two commonly used doses of rocuronium was chosen for induction (0.45 mg/kg and 0.90 mg/kg), which the study considered to represent moderate and deep neuromuscular blockade, and reversed residual the blockade with neostigmine (50 ug/kg with glycopyrrolate 10 ug/kg) and sugammadex (4 mg/kg), respectively.

The purpose of the study was to evaluate and compare surgical conditions and recovery profile after moderate neuromuscular blockade reversed with neostigmine and with deep neuromuscular blockade reversed with sugammadex. The effect of deep neuromuscular blockade on the surgical conditions during laryngeal micro-surgery had not been previously reported at the time of the study.

It was found, in laryngeal micro-surgery, the use of rocuronium 0.9 mg/kg with sugammadex for reversal was associated with better surgical conditions and a shorter recovery time than rocuronium 0.45 mg/kg with neostigmine. The onset of neuromuscular block was more rapid, and intubation conditions and ease of intra-operative laryngoscopy were more favourable, and the satisfaction score was lower in the moderate block group compared with the deep block group. No difference was found in the incidence of postoperative sore throat.

Methodology

This is a prospective, parallel-interventional, randomised controlled trial with human patients randomly allocated to moderate (comparator) or deep block (experimental) using a computer-generated table. All patients enrolled in the study gave written consent. Patients and evaluating investigators were blinded, however the attending anesthesiologist was not. The demographics were healthy patients aged 18-70 years old, ASA status I to II, with a BMI 18.5 to 25 kg.m2 undergoing elective laryngeal micro-surgery and tracheal intubation. Exclusion criteria included were age < 18 or > 70 years old; ASA physical status of ≥ 3; were underweight (body mass index < 18.5 kg/m2); overweight (BMI > 25 kg/m2); receiving medications known to affect neuromuscular function; hepatic or renal disease; or moderate to severe respiratory or cardiac disease. In this study, moderate blockade was defined as a level of neuromuscular block showing > 1 TOF response, deep blockade was defined as the presence of > 1 PTC count and before the first response to TOF stimulation, and intense blockade was defined as no response to any pattern of nerve stimulation.

This interventional clinical trial is ethically sound, approved by the Review Board at Seoul National University in the Republic of Korea. There were no conflicts of interest disclosed. All patients received standardized treatment according to strict protocol and were not denied appropriate interventions. Randomization was close to 1:1 (Figure 1), n=19 in moderate block group and n=21 in deep block group as some patients were disqualified from the study due to monitoring failure. Although the sample size is small as a result of rigid exclusion criteria, the methodology reflects valid recommendations from the international consensus on safe neuromuscular blocker agent research published in 2007. Monitoring used in the study fits within CAS standards, with the addition of bispectral index and objective neuromuscular blockade monitoring that was calibrated and performed in accordance with Good Clinical Research Practice guidelines [5].

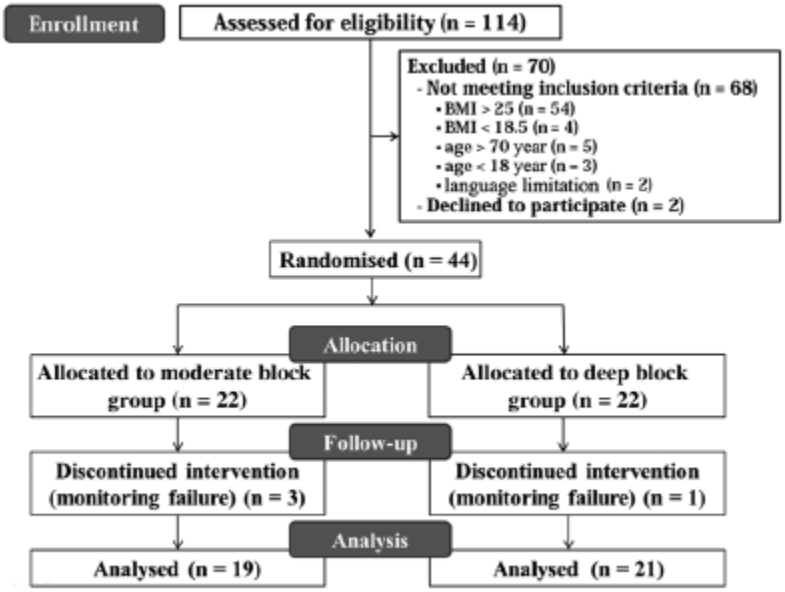


Figure 1 CONSORT diagram.

The primary outcome was the intubation conditions during laryngoscopy. Secondary outcomes were recovery of neuromuscular block; conditions for tracheal intubation; satisfaction score as determined by the surgeon; onset of neuromuscular block; postoperative sore throat; and symptoms or signs of PORC. To calculate the sample size, the researchers assumed that a > 40% increase in the ratio of easy intra-operative laryngoscopy conditions would be clinically significant. Twenty patients were needed in each group with power = 0.8 and a = 0.05. They decided to include 22 patients per group to allow for a 10% dropout rate.

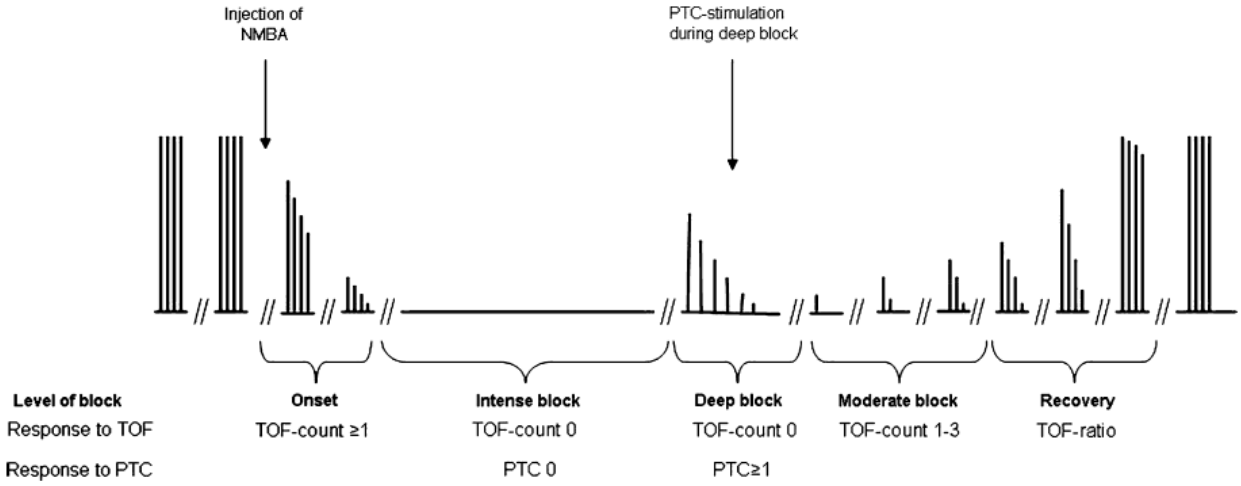
Limited detail was provided in regards to the peri-operative anesthetic drugs and dosages delivered. All patients were premedicated with intravenous midazolam 0.03 mg/kg. On arrival in the operating room, monitoring with pulse oximetry, non-invasive blood pressure, bispectral index and electrocardiography was started. Anesthesia was induced and maintained with a target-controlled infusion of remifentanil and propofol. All patient's were intubated, mechanically ventilated, and ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.7–5.3 kPa (35-40 mmHg). Central and peripheral temperatures were maintained at ≥ 35° C and ≥ 32° C, respectively.

The dose of remifentanil was adjusted to maintain blood pressure and heart rate within 20% of pre-operative values and propofol to maintain BIS 40–60. After induction of anesthesia, an objective neuromuscular function monitor was set up on the adductor pollicis muscle, calibrated and stabilised. Next, a predetermined dose of rocuronium (0.45 mg/kg, moderate block group; 0.90 mg/kg, deep block group) was administered and tracheal intubation was undertaken after confirming > 95% twitch depression.

Rocuronium at 0.45 mg/kg for the moderate block group was chosen based on the researchers current routine practice attributed to a study showing that 1.5 times the ED95 of rocuronium is sufficient for routine tracheal intubation [3]. The dose of 0.90 mg/kg rocuronium for the deep block group was based on a previous study showing that intubation conditions at 60 s did not differ if 0.9 mg/kg or 1.2 mg/kg were used, and because the mean time from rocuronium administration to the first appearance of T1 was 33.8 min (range 16.2–52.9 min) after 0.9 mg/kg of rocuronium [4]. Mean surgical and anesthesia times are represented below (Table 2).

The TOF-Watch SX monitoring software (v. 2.1; Organon) was used to automatically collect train-of four data. The onset of neuromuscular blockade was defined as the time from the start of intravenous administration of rocuronium to > 95% twitch depression. Intubation conditions were evaluated using the scoring system described in the Good Clinical Research Practice guidelines (Table 2) [5]. Immediately after tracheal intubation, the train-of-four (TOF) ratio was checked; the post-tetanic count (PTC) was also checked when no TOF count was obtained. The TOF ratio was then checked every 15 s to maintain a TOF count of 1 to 2 in the moderate block group, and the PTC was checked every 3 min to maintain a PTC count of 1 to 2 in the deep block group. Bolus doses of 5 to 10 mg of rocuronium were used as appropriate to maintain these TOF or PTC targets (Figure 2) [5].

Figure 2



Levels of block after a normal intubating dose of a non-depolarizing neuromuscular blocking agent (NMBA), as classified using post-tetanic count (PTC) and train-of-four (TOF) stimulation. During intense (profound) block, there are no responses to either TOF or PTC stimulation. During deep block, there is response to PTC, but not to TOF stimulation. Intense (profound) block and deep block together constitutes the 'Period of no response to TOF stimulation'. The reappearance of the response to TOF stimulation heralds the start of moderate block. Finally, when all four responses to TOF stimulation are present and a TOF ratio can be measured, the recovery period has started.

At the end of surgery, residual neuromuscular blockade was reversed with neostigmine at 50 ug/kg combined with glycopyrrolate 10 ug/kg in the moderate block group and with sugammadex 4 mg/kg in the deep block group. The patients' tracheas were extubated in the operating room after confirming a TOF ratio of 0.9. The blockade level just before administration of the reversal agents and the recovery time, defined as the time from administration of the reversal agent to the achievement of a TOF ratio of 0.9, were recorded. At the beginning of surgery, the surgeon rated the laryngoscopy conditions as easy, fair, or difficult (Table 1) [5].

Table 1 Definitions for evaluation of intubation conditions.

Variables	Excellent	Good	Poor
Laryngoscopy	Easy	Fair	Difficult
Vocal cords position	Abducted	Intermediate/moving	Closed
Reaction to insertion of the tracheal tube and cuff inflation (diaphragmatic movement/coughing)	None	Slight*	Vigorous/sustained**

*One or two weak contractions or movement for < 5 s.
**> 2 contractions and/or movement for > 5 s.
Excellent, all qualities are excellent; good, all qualities are either excellent or good; poor, the presence of a single quality listed under poor. Laryngoscopy: easy, jaw relaxed, no resistance to blade insertion; fair, jaw not fully relaxed, slight resistance to blade insertion; difficult, poor jaw relaxation, active resistance of the patient to laryngoscopy.

At the end of surgery, the surgeon rated their satisfaction score using a 7-point Likert scale as follows:
1 = extremely dissatisfied; 2 = dissatisfied; 3 = somewhat dissatisfied; 4 = undecided; 5 = somewhat satisfied; 6 = satisfied; and 7 = extremely satisfied. Symptoms and signs of postoperative residual curarisation (PORC), presence of hypoxia (SpO2 < 95%), inability to sustain headlifting for > 5 s, and presence of diplopia were evaluated before discharge from the recovery room. Sore throat was also evaluated: 0 = none; 1 = mild with pain only on deglutition; 2 = moderate with pain present constantly and increasing with deglutition; and 3 = severe with pain requiring analgesic medication.
Baseline characteristics (age, weight, and height), operation time, anesthesia time, onset time, and recovery time were compared with Student's t-test (SPSS ver. 22, IBM Corp., Armonk, NY, USA). Satisfaction scores, intubation and intra-operative laryngoscopy conditions, blockade level, and postoperative sore throat between the two groups were compared with chi-squared test, Fisher's exact test, and Mann–Whitney U-test. $P < 0.05$ was considered statistically significant.

Results

Of 114 patients assessed for eligibility, 44 patients were randomly allocated to one group or the other and data from 40 patients were analysed. Reasons for exclusion were BMI in 58 patients (54 overweight and four underweight), age in 8

patients, foreign nationality in 2 patients and not consenting to participate in 2 patients (Figure 1). Baseline characteristics were similar in both groups (Table 2).

Table 2 Baseline characteristics. Values are mean (SD) or number.

	Moderate n = 21	Deep n = 19
Age; years	52 (12)	48 (14)
Sex; men	16	12
Weight; kg	64 (6)	63 (6)
Height; cm	169 (6)	167 (8)
BMI; $m.kg^{-2}$	21 (5)	22 (1)
ASA physical status 1/2	17/4	15/4
Surgery time; min	20 (9)	18 (10)
Anaesthesia time; min	45 (9)	40 (13)

After injection of rocuronium, the onset of neuromuscular blockade was significantly slower in the moderate block group compared with the deep block group ($p < 0.001$). When the degree of neuromuscular blockade was checked immediately after tracheal intubation, most patients in the moderate block group (85.7%) had moderate to deep blockade while all patients (100%) in the deep block group had intense blockade. Overall, more patients in the moderate block group needed an additional dose of rocuronium than those in the deep block group ($p = 0.034$).

When the degree of neuromuscular blockade was checked just before the administration of the reversal agent, all except one patient in the moderate block group were in moderate blockade and all patients in the deep block group were in deep (5/19, 26.3%) or intense (14/ 19, 73.7%) blockade. Yet, the recovery time was slower in the moderate block group than in the deep block group ($p < 0.001$). Train-of-four ratio did not reach 0.9 in 9 patients (43%) after 10 min and in 4 patients (19%) after 15 min in the moderate block group. In contrast, all patients in the deep block group recovered to a TOF ratio of ≥ 0.9 within 4 min (Table 3).

Table 3 Variables related to the degree of neuromuscular blockade. Values are mean (SD) or number.

	Moderate n = 21	Deep n = 19	p value
Onset time; min	2.0 (0.5)	1.3 (0.3)	<0.001
Block level immediately after intubation; moderate/deep/intense	8/10/3	0/0/19	<0.001
Additional dose of rocuronium; %	9 (42.8)	2 (10.5)	0.034
Block level at administration of reversal; moderate/deep/intense	20/1/0	0/5/14	<0.001
Recovery time; min	9.9 (4.0)	2.1 (0.6)	<0.001

Block level, moderate when ≥ TOF 1, deep when ≥ post-tetanic count (PTC) 1, intense when PTC 0.

Table 4 Outcome variables. Values are number.

	Moderate n = 21	Deep n = 19	p value
Intubation conditions; poor/good/excellent	2/15/4	0/0/19	<0.001
Intra-operative laryngoscopy conditions; difficult/ fair/easy	1/11/9	0/0/19	<0.001
Surgical rating scale; 3/4/5/6/7	1/0/5/14/1	0/0/0/3/16	<0.001
Sore throat; 0/1/2/3	3/6/6/6	5/8/3/3	0.198

Surgical rating scale: 1–7 extremely dissatisfied to extremely satisfied. A clinically acceptable surgical condition was 6–7. Sore throat: 0, none; 1, mild; 2, moderate; 3, severe.

Intubation conditions were worse in the moderate block group than in the deep block group (excellent intubation condition, 19% in moderate vs. 100% in deep, $p < 0.001$). Laryngoscopy conditions as checked by the surgeon at the beginning of surgery were also worse in the moderate block group than in the deep block group (easy conditions 43% in moderate vs. 100% in deep, $p < 0.001$). Satisfaction scores as checked by the surgeon at the end of surgery were lower in the moderate block group compared with the deep block group ($p = 0.021$).

No significant difference was found in the incidence or severity of postoperative sore throat ($p = 0.198$) (Table 4). No patient in recovery showed symptoms or signs of PORC such as hypoxia ($SpO2 < 95\%$), an inability to sustain a head lift for 5 s, or diplopia.

Discussion

This study has shown that reversal with sugammadex facilitates the administration of a higher dose of rocuronium, with attendant improved surgical conditions for short surgery, and faster recovery times as compared with using neostigmine after a smaller dose of rocuronium. Statistical analysis techniques were valid in comparing similar baseline characteristic between the two groups. The study however failed to disclose if the surgeons evaluating surgical conditions and the participating anesthesiologist were the same throughout.

Overall, I believe laryngeal micro-surgery to be a good candidate for deep neuromuscular blockade because the larynx is near centrally located muscles such as the jaw and diaphragmatic musculature, which are relatively resistant to neuromuscular blockade compared with peripherally-located muscles such as the adductor pollicis muscle [1]. The authors describe only one study evaluating deep neuromuscular blockade in laryngeal micro-surgery; the results were similar to this study and suggested that deep neuromuscular blockade improved surgical conditions compared with moderate blockade. The researchers divided the patients into two groups according to the degree of neuromuscular blockade (TOF 1–2 and PTC 1–2), and they used larger doses of rocuronium, (0.5 mg/kg and 1.2 mg/kg) at the induction of anesthesia and hence reported longer recovery times than the current study in both groups [8].

This study has several limitations. First, the attending anesthetist was not blinded to the patient group. However, objective neuromuscular monitoring mitigated against bias. The use of bispectral index and cardiovascular measures also minimised the possibility that an anesthetist might compensate for any light neuromuscular block by deepening anesthesia. Although physiologic parameters were utilized to adjust for remifentanil and propofol dosages, it would be useful to obtain the range of dosages used for induction, maintenance, emergence of anesthesia and effect on blockage/reversal. Surgeon evaluation of intubating conditions is essentially subjective. However, the use of scoring systems allows some standardization of assessments; the scoring systems used are supported by Good Clinical Research Practice guidelines [5].

One reason why no patient showed PORC in the recovery area in this study is that neuromuscular monitoring was continued until reaching a TOF of 0.9 objectively before tracheal extubation was performed in the operating room. However, if they had not continued monitoring after administration of the reversal agent, the possibility of PORC would have still existed. On an important note, all of the patients reversed with sugammadex irrespective of block depth recovered a TOF$\geq$ 0.9 within 4 min. I find it interesting even when the lower dose of rocuronium (0.45mg/kg) was reversed appropriately, 19% of these healthy patients did not have a TOF $\geq$ 0.9 after 15 minutes. The authors acknowledged a recent survey indicating that 26.7% of patients had PORC after the use of a non-depolarising neuromuscular blocker [6]. This data supports the use of neuromuscular monitoring is now mandatory whenever neuromuscular blockade is used in many countries like the UK and Canada [7].

An important limitation in the study is that it did not include any financial analysis. Several reports suggest sugammadex is cost effective by reducing recovery time and risk of PORC [9, 10], although this remains a matter of debate [11]. Although these anesthetic practices and patient populations can be utilized and reproduced at Hotel Dieu Hospital and/or Kingston General Hospital (exception of objective neuromuscular blockage monitoring), an extensive evaluation of the impact of financial feasibility and how it applies to systemic savings is crucial in supporting this practice locally. Arguably, the recent literature suggests resource savings from faster recovery of NMB in the operating room and reduced rate of PORC when compared with neostigmine; however, these results warrant careful interpretation owing to shortcomings in the economic model and industry affiliation [12].

A 2017 study focusing on an economic assessment of the use of sugammadex in North America illustrates an evaluation of ‘value of each minute of OR time saved' [14]. In the evaluations below, they calculated conservatively the expense considering that each OR minutes costs $10 CAD (or $30 US).

A) In patients with superficial blockade (reappearance of the fourth twitch): Sugammadex could reduce the mean time to reach a TOF ratio of 0.9 by 17 min [9]. Patients with shallow NMB need 2 mg.kg-1 sugammadex to reverse rocuronium-induced blockade, which, on average, corresponds to 150 mg. The dose is obtained using 1 vial.

y=100 $Can-17 min x 10 $Can, y'=100 $US-17 min x 30 $US

y=100 $Can-170 $Can, y'=100 $US-510 $US,

y=-70 $Can, y'=-410 $US

In this case the OR time saved will lower the cost related to surgery by 70 $Can and 410 $US in Canada and in the United States, respectively.

B) In patients with moderate NMB (TOF count=1-3): Randomized controlled trials comparing rocuronium and sugammadex with rocuronium and neostigmine suggested that sugammadex reduces the mean time to reach a TOF ratio of 0.9 by 18.6 min [11]. Patients with moderate NMB should be given 2-4 mg.kg-1 sugammadex to reverse rocuronium-induced blockade, which, on average, corresponds to 225 mg. The last dose is obtained with 2 vials (200 $Can and 200 $US).

y=200 $Can-18.6 min x 10 $Can, y'=200 $US-18.6 min x 30 $US

y=200 $Can-186 $Can, y'=200 $US-558 $US

y=14 $Can, y'=-358 $US

In this case the OR time saved will not lower the cost related to the surgery but increase it by 14 $Can. On the contrary, in the United States, it might save up to 358 $US.

y=z - k - x

y=cost of a case using sugammadex

z=sugammadex cost per case

k=time saved per case

x=operation staff value per minute

C) In patients with deep NMB (PTC=1-2): Patients with deep NMB require 4 mg.kg-1 sugammadex to reverse rocuronium-induced blockade, which corresponds to 300 mg. The dose is obtained with 2 vials. Sugammadex reduces the mean time to obtain a TOF ratio ≥ 0.9 by 47.5 min in this clinical condition (50.4 min reversing with neostigmine–2.9 min reversing with sugammadex) [9].

y=200 $Can- 47.5 min x 10 $Can, y'=200 $Can-47.5 min x 30 $US

y=200 $Can-475 $Can, y'=200 $US-1425 $US

y=-275 $Can, y'=1225 $US

In this case, the OR time saved will lower the cost related to the surgery by 275 $Can and by 1225 $US in Canada and in the United States, respectively.

The study in question states that the cost-effectiveness of sugammadex relies on two concepts. The first concept is that faster recovery time can be achieved using sugammadex compared to neostigmine. The second concept is that time saving could be converted into valuable activities. Rapid NMB reversal can lower the operating room (OR) occupancy with the consequential potential to increase the OR workflow especially for short cases [14].

Upon reviewing the literature, in Canada, the cost for each OR minute has been estimated, on a per-minute basis, to range from 10 to 40 $CAD in 2016 [15]. In the United States, it has been previously estimated to be of 2000 $US per hour (30 $US per minute) [16]. The vials of sugammadex provided at Kingston Health Sciences Center are 500 mg single dose vials for injection. Economic evaluation study in 2017 describes states a vial with the smallest dose of sugammadex contains 200 mg and corresponds to approximately 100 $ Can; vials containing 500mg corresponds to approximately 200$ [14]. The average dose used in this study is 4 mg/kg = 256mg (mean weight of 64kg). This would equal $200 per patient (2 vials). The average minutes gained on recovery time in this study is 7.8 (19% of moderate block patients did not recover TOF after 15 minutes = 9 minutes gained). 7.8 minutes x $10-40/min = $78 to 312$, further subtracted from the cost of sugammadex at $200 = net deficit of $122 to a profit of $112.

Furthermore, it is important to consider if improved surgical conditions result in fewer complications and cost savings to the system as well? How about PACU length of stay? Changes in rate of post-op pulmonary complications? How teaching may influence time spent in operating room and associated costs; how are we able to justify increased costs to the system for teaching purposes but are hesitant when it may improve patient safety and outcomes?

A very high proportion (~60%) of participants screened were excluded from the study, with the main reason being a high BMI (54/114, 47%), so the results may not apply to all patients. There was no mention of any other adverse effects as a result of the pharmacologic agents used such as awareness, nausea & vomiting, hypersensitivities, arrhythmias, aspiration, atelectasis or other factors that may have influenced prolonged recovery room stay. Although there is an earlier tracheal extubation time, this may not necessarily translate to time savings in the OR or PACU length of stay. Additionally, there is no mention on complexity of the surgical procedure, underlying pathology, and any differences in surgical complication rates due to improved surgical conditions.

In conclusion, in patients undergoing elective laryngeal micro-surgery, deep neuromuscular blockade with sugammadex as the reversal agent significantly improved surgical conditions and reduced recovery time compared with a reduced dose of rocuronium with neostigmine reversal. The primary outcome was the intubation conditions during laryngoscopy. Secondary

outcomes were recovery of neuromuscular block; conditions for tracheal intubation; satisfaction score as determined by the surgeon; onset of neuromuscular block; postoperative sore throat; and symptoms or signs of PORC. Both primary outcomes and secondary outcomes (except for postoperative sore throat and PORC) had statistically ($P < 0.05$) and clinically (>40%) significant differences in favour of sugammadex. Further research is needed to evaluate systems savings/costs and how it relates to improved patient safety and postoperative outcomes in short surgical procedures.

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Critical Appraisal Article

By : **Rosy Sylvie Fournier**, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication title: ***"Association between preoperative pulse pressure and perioperative myocardial injury: an international observational cohort study of patients undergoing non-cardiac surgery"***

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Myocardial infarction after noncardiac surgery (MINS) occurs commonly in the adult population with a reported incidence of 8 percent and resulting mortality rates that are substantial.[1] In January 2017, the Canadian Cardiovascular Society (CCS) elaborated evidence-based guidelines that emphasize the value of early recognition of at risk patients in order to guide management and therapeutic goals.[2] Strong recommendations were made based on numerous studies that identified various predictors of adverse cardiovascular events in the perioperative setting.[3,4,5] Included in these is the VISION study. This large prospective international cohort study (N = 15,133) investigated a wide selection of variables relating to prognostically relevant myocardial injury, incidentally building a sizeable database.[5]

"Association between preoperative pulse pressure and perioperative myocardial injury: an international observational cohort study of patients undergoing non-cardiac surgery" by Abbott et al intended to refine risk assessment in regards to perioperative myocardial injury.[6] The concept of linking pulse pressure and adverse cardiovascular events was introduced in earlier studies in the non-surgical patient population.[7,8] The aforementioned study aims to establish this association independently of systolic blood pressure and age in the perioperative setting. The specific physiological relationship and causality of MINS by pulse pressure is still undetermined, but various mechanisms have been hypothesized. This study by Abbott et al attempts to explore the validity of this relationship with the goal of potentially creating a new tool for the prediction of MINS.

METHODOLOGY - This is a secondary analysis of the existing database produced by the VISION study, a prospective international observational cohort study. Review of this existing database offers several advantages. Firstly, access to a complete set of data from a multicenter international study allows large, representative sampling of a target population. Moreover, this design is inexpensive, convenient and efficient. As the authorship is, in majority, the same in both studies one can assume that the downfalls traditionally associated with a secondary analysis may not apply. Namely, the authors would have been both aware of the study-specific nuances and have the entirety of the database available, eliminating the confounding factors associated with using a partial public database. Despite the fact that a majority of the authors co-wrote these published works, this remains a secondary analysis as it was executed to answer a new question.[9] It is likely that this research was both question-driven and data-driven due to privileged access to this database, although mention is made of planning the statistical analysis prior to taking custody of the data.

The initial VISION study design does affect this secondary analysis. This cohort study is appropriate to examine the effect of risk factors, such as pulse pressure, on the incidence of an outcome (i.e. MINS) and demonstrate direction of causality. The prospective quality of the study avoided a selection bias, but misclassification and loss to follow up bias remained. The large sample size did facilitate use of a multivariate regression to control for the numerous identified confounding variables.

The study population consisted of patients 45 years or older undergoing non-cardiac surgery with regional or general anesthesia and at least one expected overnight hospital stay. The exclusion criteria included refusal to consent or previous enrolment in the study. These criteria confer strong external validity making them applicable to a broad population and useful for the author's probable goal of incorporating pulse pressure as a new predictor of MINS. Consent was obtained prior to surgery or within 24 hours after, and occasionally deferred if no next of kin was identified.

EXPERIMENTAL PROTOCOL - The VISION study database includes standardised and detailed information on potential preoperative predictors of MINS collected via interviews, physical examination and chart reviews recorded by trained research professionals. Roche fourth-generation Elecsys TnT assay was done 6 to 12 hours postoperatively and daily for three consecutive days and considered positive if 0.04 ng/ml or greater. Positive values would indicate a need for ischemic symptoms assessment, serial electrocardiograms and additional measurements of the TnT. MINS, in this study,

was strictly defined as: “Myocardial injury caused by ischemia (that may or may not result in necrosis), has prognostic relevance, and occurs during or within 30 days after noncardiac surgery.”[1] (p.565)

Abbott et al used the VISION study database to evaluate the prognostic value of pulse pressure. The last arterial blood pressures prior the induction of anesthesia were selected and used to calculate the preoperative pulse pressure. No standard measurement method was enforced. No reference group was needed but rather a deviation contrasts approach. The primary outcome was MINS as defined in the VISION study. No secondary outcomes were examined.

Since this is a secondary data analysis, the appraisal of the experimental protocol is brief. The design allows an adequate study of the hypothesis. The data collection was not tailored to this study allowing for possible improvements, such as a standardised method of measuring the arterial blood pressure and a specific pre-induction time of measurement. However, the selection of the database was adequate to answer the research question, but most likely opportunistic.

“The study was approved by institutional review boards or ethics committees at each site, and was registered with ClinicalTrials.gov (NCT00512109).” [4] (p.79) A complete declaration of interest and funding statement can be found in the article.

STATISTICAL ANALYSIS AND RESULTS - A comprehensive explanation of the data analysis can be found in the article. First, the preoperative pulse pressures were divided into quintiles to facilitate their analysis. Then, a multivariable logistic regression was used to test their association to MINS while controlling for various covariates. These confounding variables were associated to perioperative cardiac complications in previous publications and included coronary artery disease, atrial fibrillation, heart failure, peripheral vascular disease, diabetes, age, previous stroke or transient ischemic attack, chronic obstructive pulmonary disease, estimated glomerular filtration rate, neurosurgery, urgent or emergent surgery and major surgery. As an alternative to using a control group, Abbott et al compared each quintile with the unweighted average effect of pulse pressure on the occurrence of MINS through deviation contrasts. In the absence of a verified optimal pulse pressure in the literature, this seems appropriate.

Of 16,079 patients initially recruited in the study, 15,057 remained after exclusion criteria were applied. An additional 966 patients with missing outcome data were excluded, demonstrating a loss to follow up bias. The mean age was 65 years old and 48% of patients were male. MINS was found to occur more often in the two highest pulse pressure quintiles, quintile 4 (63-75 mm Hg, RR 1.14 [95% CI 1.01-1.28] P = 0.03) and quintile 5 (>75 mm Hg, RR 1.15 [95% CI: 1.03-1.29] P = 0.02).

Both sensitivity analyses were a repetition of the primary multivariable analysis with pulse pressure considered firstly as an ordered categorical variable and secondly as a continuous variable. These analyses were adjusted for systolic blood pressure. It was demonstrated that an elevated pulse pressure of >62 mm Hg was associated with MINS independently of the systolic blood pressure.

DISCUSSION - This study by Abbott et al provides evidence that preoperative pulse pressure is a better predictor of MINS than systolic blood pressure. It demonstrates that two out of five patients will present with an increased preoperative pulse pressure greater than 62 mmHg and will be at higher risk of MINS, as previously defined. While these results are statistically significant, the reported risk ratios were modest. The authors recognize that, while the risk ratios are modest, the number of patients undergoing non-cardiac surgery results in a clinically significant number of affected patients.

The initial goal of this study was to explore the hypothesis that there is an association between pulse pressure and MINS. The design and statistical analysis have adequately addressed this question. While it is true that the results showed only a modest relationship between the exposure and the outcome, this does serve to initiate a discussion surrounding this relationship. These preliminary results could serve to entice a future randomized control trial to better assess the correlation.

In order to for the VISION study to capture a significant incidence of MINS, a large population was surveyed. The enormous sample size of this database improved the precision of the statistical analysis and permitted the control of many confounding variables. The authors used appropriate statistical data analysis such as a multivariate logistic regression and researched in primary literature for the validity of their chosen covariates. However, the authors identified that there may be unmeasured residual confounding factors, such as use of premedication, anti-hypertensives, or the presence of undiagnosed aortic regurgitation. These residual confounders may limit the application of these findings to a wider population. Nonetheless, the external validity of this study is remains strong and offers a good starting point for further studies.

The authors dealt with the biases in this study in an elegant fashion. The multiple comparison bias associated with secondary data analysis was mitigated by announcing the hypothesis and study design prior to acquiring the dataset. Observer bias in diagnosing a myocardial infarct was avoided through the use of a standard definition provided by the initial VISION study. The measurements of the arterial blood pressure were not standardized in terms of method and timing. However, multiple sources were used during data collection to help reduce measurement bias. Interestingly, the selection and sampling biases were not prominent due to the clearly defined inclusion and exclusion criteria. Finally, including only inpatients during the perioperative period limited transfer bias from loss to follow up.

It would be reasonable to agree with the author's conclusion that, pulse pressure does provide prognostic information with regards to MINS. While this association does necessitate further exploration, this is the first study to assess the correlation in perioperative patients. This secondary data analysis encourages us to consider the future use of perioperative pulse pressure as a predictive tool rather than systolic blood pressure. Results were statistically significant through a suitable analysis and biases were properly addressed.

SUMMARY - The secondary data analysis of the VISION study database by Abbott et al highlights the association between elevated pulse pressure and increased risk of developing a myocardial infarct after non-cardiac surgery. Pulse pressure greater than 62 mm Hg was found to offer prognostic information towards predicting MINS, while systolic blood pressure was not independently associated with adverse cardiac outcomes. The design and statistical analysis adequately addressed the hypothesis and biases were appropriately managed.

As explicitly stated by the authors, this study allowed the identification of a simple exposure. I believe that this study generates new insight on the use of pulse pressure in the perioperative setting. Considering the high potential for confounding variables, this question would benefit from a randomized control trial. Until further exploration is completed, anaesthesiologists should refrain from making clinical decisions solely based on these results.

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Critical Appraisal Essay

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Publication: ***Cuffed vs. uncuffed tracheal tubes in children: a randomised controlled trial comparing leak, tidal volume and complications***

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Introduction

Airway management in pediatric patients has long been an area of research with debate about whether a cuffed or uncuffed endotracheal tube should be placed. This debate has long been fuelled by the anatomical differences in the pediatric airway anatomy with the narrowest point being the subglottic airway.[1] It is this subglottic airway narrowing and the fear that cuffed tubes lead to mucosal damage and subsequent stenosis that has led to uncuffed endotracheal tubes being the tube of choice. There have been recent studies in the past decade that have shown that the use of cuffed endotracheal tubes is not associated with post-extubation stridor or long-term complication.[2,3] Chambers et al compared the leakage around, tidal volumes, and complications associated with cuffed and uncuffed endotracheal tubes in children that required mechanical positive-pressure ventilation in the operating room. The study involved children aged 0-16 years who were randomized to receive a cuffed or uncuffed endotracheal tube. The children were ventilated using both pressure controlled and volume-controlled ventilation and measurements were taken at five standardized time points. The primary end-point of the study was air leakage around the endotracheal tube, which the authors have defined as the difference between the inspiratory and expiratory tidal volumes. The secondary outcomes included: inspiratory tidal volumes, expiratory tidal volumes, number of attempts at intubation, number of attempts to correctly size the endotracheal tube, adverse events, sore throat, and hoarse voice. The conclusions of this study are such that the cuffed endotracheal tubes provided better ventilation and had a lower rate of adverse outcomes when compared to the uncuffed tubes.

Methodology

This is a single-centre, randomised, parallel-group study. This study was carried out at the Princess Margaret Hospital for Children in Perth, Australia. Approval for this study was obtained through the Princess Margaret Hospital for Children Ethics Committee and the University of Western Australia Committee. They recruited participants and obtained informed consent (from parents) for participation from February 2012 through January 2014. In order to be considered for the study they must have been children between the age of 0 – 16 years old, weight >5kg and be undergoing elective surgery. Once enrolled the children were randomly assigned to one of the two study groups, cuffed or uncuffed endotracheal tubes. The randomisation was determined by using a computer-generated block randomisation in a 1:1 ratio in equal numbers. Those children who chose to withdraw from the study were not replaced. Exclusion criteria included children with airway abnormalities, upper airway surgery, contraindications to either a cuffed or uncuffed endotracheal tube or the requirement for postoperative ventilation.

For their elective surgical procedures, the participants were provided anesthesia guided by the standards of the Department of Anaesthesia and Pain Management at the Princess Margaret Hospital for Children and the Australian and New Zealand College of Anaesthetists. Induction, use of muscle relaxants, endotracheal tube size, maintenance (Sevoflurane or IV Propofol) were all performed as per the attending anesthetists usual practice.

Endotracheal tubes used were of varying manufacturers. Regarding cuffed tubes smaller than size 5 had low volume cuffs and tubes sized >5 had high-volume low-pressure cuffs. Following intubation, the cuffs were inflated and continuously monitored with a manometer to keep pressure $\leq$20 cmH_2O.

Five measurements of inspiratory and expiratory tidal volumes were measured initially under volume-controlled ventilation, then again under pressure-controlled ventilation. Following these measurements, a standardized recruitment manoeuver was carried out and subsequent measurements were recorded immediately, at 10 minutes, and at the 30-minute time point.
Extubation was performed at the discretion of the attending anesthetist. Oxygen saturation levels, laryngospasm, airway obstruction, severe coughing, and stridor were recorded in the post-anesthetic care unit. Finally, families were interviewed just prior to discharge regarding sore throats and then were monitored for 3 years for any participant that required further airway management.

The study's methodology was nicely outlined in a very concise, easy to understand table.

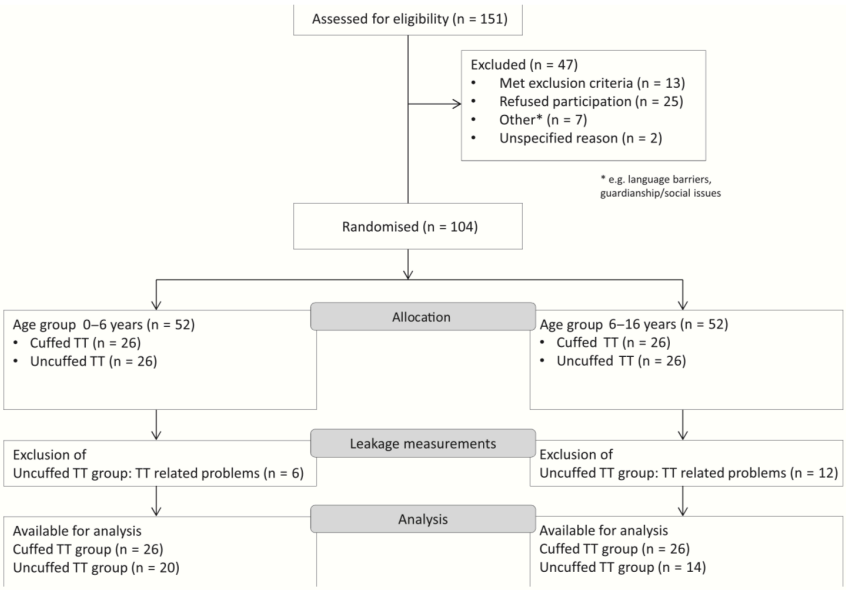

Figure 1 CONSORT diagram. TT, tracheal tube.

Using pilot studies at the Princess Margaret Hospital for Children they were able to assume that with their sample size of 52 participants per group and a standard deviation of 0.23, that this study had 90% power to detect a difference in leakage. Statistical analysis was carried out using the Mann-Whitney's Test and a significance level of 0.05.

Results
In all 104 children between the 0 and 16 years old were recruited into the study. 52 patients were aged <6 years, 52 ages 6-16 years old, and 26 patients from each age group made up the comparison groups of cuffed or uncuffed endotracheal tubes. The study groups appeared similar in characteristic (gender, weight) as well as risk factors for adverse respiratory events (wheeze, wheeze w/ exercise, dry cough at night).

In the end, data from 6 (<6 years old) and 12 (6-16 years old) could not be collected because of issues with the endotracheal tubes. Several tables outlined the numerical results and the associated p-values. The results compared leakage volumes between uncuffed and cuffed endotracheal tubes as well as results in the above-mentioned age categories.
Cuffed vs. Uncuffed (age independent) showed a significant difference in leakage volumes with the cuffed tubes having a lower leakage volume (ml/kg) at every measurement time point. This reduced leakage volumes with cuffed tubes was also present within each age groups (statistically significant $p<0.001$).

The numbers for adverse events are reported as proportions or events represented as a percentage of the study group. The data shows that the number of tube insertions, number of size changes, and excessive leaking were all more common in the uncuffed group regardless of age. With respect to peri-operative and post-operative respiratory complications, the cuffed group had statistically significant fewer number of patients with severe

persistent coughing and sore throat, but, failed to show a difference in occurrence of desaturation <95%, or hoarse voice.

Discussion

The primary conclusion of the study was that cuffed endotracheal tubes provided better ventilation. This outcome was supported by objective data from measurement of inspiratory and expiratory tidal volumes and using this data to calculate the leakage around the endotracheal tubes. The numerical data was collected using standardized anesthetic machines and as such was not subject to measurement bias. For example, when using Volume Controlled Ventilation, the median leak in the cuffed group was 0.2 ml/kg vs the 0.82 ml.kg in the uncuffed group. Similar findings were present at all the standardized measurement points. The Mann-Whitney's test used to analyse the data appeared to be adequate as the two groups were completely independent and the data was ordinal, using a significance level of 0.05. Though the authors never explicitly state a hypothesis they do state that this was the first study to compare leakage around cuffed and uncuffed endotracheal tubes and the conclusions do not come as a surprise.

The secondary outcomes of the study consisted of largely subjective measurements. The number of tube changes was lower in the cuffed endotracheal group. The other secondary outcomes, severe coughing and sore throat, were higher in the uncuffed group. The authors hypothesize that this was due to the need for multiple looks under direct laryngoscopy and multiple intubations in the uncuffed group. Having to change endotracheal tubes and take multiple looks would likely lead to irritation/trauma to the oral mucosa and vocal cords.
This is the first study that looks at, and compares, the leakage around cuffed and uncuffed endotracheal tubes in children, so it is not possible to compare the primary outcomes to existing literature. Many of the secondary outcomes have been studied in the past. One meta-analysis from 2016 found that the use of a cuffed endotracheal tubes reduces the need for tube exchanges and did not increase the risk of stridor post-extubation.[2,3,4]

The subjects in this study were children but they were all required to weigh >5kg, although one child who weighed less that 5 kilograms was accidentally included. Uncuffed endotracheal tubes are commonly used in the very small and very young and further study is needed to see if the use of uncuffed tubes is appropriate. There were limitations in this study relating to the various manufactures of the endotracheal tubes used and the non-standardized use of neuromuscular blockers. These unmeasured covariates may have influenced the amount of leakage around the endotracheal tubes and further study with more standardization is necessary. Moreover, due to the selection bias in this study these results can only be applied to healthy children presenting for elective surgery.

The applicability of this study is wide reaching as there are several dedicated pediatric hospitals in Canada and many academic and community centres see large volumes of pediatrics for lower-risk, elective procedures. Discussion and uncertainty surrounding the subject of endotracheal tubes in the pediatric population is quite frequent and this study allows us to contemplate this question with more assertion.

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