Queen's University
35th Annual Anesthesiology Research Day

Scientific Program Directors and Residency Research Coordinators:

Ian Gilron, MD, MSc, FRCPC

Elizabeth VanDenKerkhof, RN, MSc, DrPH

Scientific Adjudicators:

Rob Tanzola
MD, FRCPC

Imelda Galvin
MB BaO BcH, MRCPCH, FRCA, MSc

Guest Lecturer: **Davy Cheng**, MD, MSc, FRCPC, FCAHS, CCPE

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Institutional support:

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SCIENTIFIC PROGRAM OUTLINE

0800 – 0810 **Opening Remarks and Introduction of Guest Lecturer – Dr. Joel Parlow**

0810 – 0910 ***Guest Lecture* Dr. Davy Cheng,** Distinguished Professor, University of Western Ontario

"Knowledge Translation - Evidence to Guidelines to Practice: The Road Less Traveled"

0910 – 0930 **Introduction of Research Day Presentations – Dr. Ian Gilron**

0930 – 1030 **Oral presentations (4)**

1030 – 1045 **Nutrition break**

1045 – 1130 **Oral presentations (3)**

1130 – 1230 *** LUNCH** (provided) *****

1230 – 1400 **Oral presentations (6)**

1400 – 1415 **Nutrition break**

1415 – 1530 **Oral presentations (5)**

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

The Judges will be:

Dr. Rob Tanzola, Assistant Professor, Queen's Department of Anesthesiology & Perioperative Medicine

Dr. Imelda Galvin, Assistant Professor, Queen's Department of Anesthesiology & Perioperative Medicine

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1530 **Wine & Cheese** to follow with *** Awards Presentation *** (Donald Gordon Center)

Oral Presentations

(*in alphabetical order, presentation order to be announced*) ---------- page 1/2

James CHENG, PGY2
"**Periarticular Versus Systemic Ketorolac in Total Knee Arthroplasty Patients: Is there a Difference?**" (proposal)

Tanya GRIFFITHS, PGY2
"**Prevalence of Thromboembolic Events in Surgical Patients Receiving Epidural Analgesia.**" (proposal)

David HE, MD Candidate, Queen's University
"**FINESSE: A pilot survey to assess the distinction between stimulus-dependent and stimulus-independent pain symptoms in neuropathic pain**" (update)

Darryl HOFFER, PGY3
"**Adverse effect reporting in RCTs of gabapentin and pregabalin for acute postoperative pain: A systematic review.**" (update)

Nicole KING, PGY3
"**A survey of scope of practice in Family Medicine Anesthesia**" (update)

Karmen KROL, PGY3
"**Measurement of cardiac output with the ultrasonic cardiac output monitor versus transthoracic echocardiography**" (update)

Mahmoud LABIB, PGY3
"**Determining the minimum degree of needle angulation towards the midline in thoracic epidurals using 3D CT imaging, a pilot study**" (update)

Judy MAROIS, PGY4
"**The Effect of Intraoperative Labetalol on Time to Discharge and Hemodynamic Stability in Laparoscopic Cholecystectomy**" (update)

Erika NGUYEN, PGY4
"**Resources Utilization in the Joint Room: Building a parallel processing model**" (proposal)

Nicole PROULX, BSc Eng 2014 Candidate, Queen's Faculty of Engineering & Applied Science
"**Microbubble Tracking for Patent Foramen Ovale Assessment**" (data presentation)

Gita RAGHAVAN, PGY2
"**Does systemic dexamethasone prolong analgesia after interscalene catheter removal? A randomized control trial.**" (proposal)

Frank SECRETAIN, PhD Candidate, Queen's Faculty of Engineering & Applied Science
"**Detection and Breakup of Potential Cerebral Air Emboli**" (data presentation)

Soniya SHARMA, MD Candidate, Queen's University
"**Adopting a flat operating room schedule: A Quality Improvement Audit**" (update)

Oral Presentations

(*in alphabetical order, presentation order to be announced*) ---------- page 2/2

Serena SHUM, PGY2
"**Faculty time distribution across Canadian academic medical centres**" (proposal)

Vanessa SWEET, PGY3
"**Electronic Anesthesia Records: Impact Upon Legibility, Accessibility, and Accuracy**" (update)

Josie XU, BHSc, MD Candidate, Queen's University
"Perioperative Management of Urgent Surgery: A Quality Improvement Initiative" (update)

Julie ZALAN, PGY2
"**Frailty indices as a predictor of postoperative complications: a systematic review**" (proposal)

Cheng ZHOU, MD Candidate, Queen's University
"**Time to discharge with ultrasound guided blocks versus general anesthesia in arthroscopic shoulder surgery**"

Periarticular Versus Systemic Ketorolac in Total Knee Arthroplasty Patients: Is there a Difference?

Author: Dr. James Cheng PGY-2; Supervisor(s): Dr. John Murdoch

Background

In recent years, periarticular infiltration (PAI) has become a common mode of analgesia for the management of post-operative pain in arthroplasty patients. Many drugs have been investigated for potential use as part of a PAI mixture. Among these, Ketorolac was one of the first drugs incorporated into the mix.[1,2] The rationale for injecting ketorolac into traumatized tissue is because of its anti-inflammatory properties, which can block prostaglandin synthesis and decrease local inflammation.[3] This in turn will prevent the sensitization of peripheral neurons to nociceptive stimuli and decrease post-operative pain. Indeed, studies have shown that adding ketorolac to a PAI mix will result in lower post-op pain score.[4] What is unclear, however, is whether this is truly from ketorolac's local effect. Even when injected into local tissue with epinephrine, studies have shown that there is significant systemic absorption of ropivacaine after PAI.[5] It would not be surprising to find that ketorolac is being absorbed in a similar fashion.

Purpose/Hypothesis

The purpose of this investigation is to determine whether periarticular ketorolac exert its analgesic effects at the site of injection, or whether we are simply seeing the benefits of systemic ketorolac; and whether there is any actual benefit to adding ketorolac into a PAI injection mixture. We hypothesize that systemic ketorolac will provide the same analgesic effect as periarticular ketorolac in post-total knee arthroplasty patients.

Study Design

Single Center, blinded, randomized-controlled trial

Intervention

1. control group – PAI mixture of ropivacaine 300mg, ketorolac 30mg, epinephrine 0.3mg diluted with normal saline to 120mL
2. Intervention group – PAI mixture of ropivacaine 300mg, epinephrine 0.3mg diluted with normal saline to 120mL. At time of PAI, ketorolac 30mg IM.

Outcomes

The primary outcome will be post-operative visual analog scale (VAS) pain scores (at rest and with activity) in PACU, 4 hours post-op, POD-1, and POD-2. Secondary outcomes will include post-op PCA opioid use, VAS patient satisfaction score, length of hospital stay, and incidence of nausea/vomiting and constipation.

Reference

1. Busch CA, Shore BJ, Bhandari R, et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty: a randomized trial. *J Bone Joint Surg.* 2006;88-A:959-963.
2. Lamplot JD, Wagner ER, Manning DW. Multimodal pain management in total knee arthroplasty: a prospective randomized controlled trial. *J Arthroplasty.* 2014;29:329-334
3. Kerr DR, Kohan L. Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery. *Acta Orthop.* 2008;79(2):174-183
4. Kelley TC, Adams MJ, Mulliken BD, et al. Efficacy of multimodal perioperative analgesia protocol with periarticular medication injection in total knee arthroplasty: a randomized, double-blinded study. *J Arthroplasty.* 2013;28:1274-1277
5. Stringer et al. Serum and wound drain ropivacaine concentrations after wound infiltration in joint arthroplasty. *J Arthroplasty.* 2007;22(6):884-892

Prevalence of Thromboembolic Events in Surgical Patients Receiving Epidural Analgesia

Tanya Griffiths, MD, PhD, Rosemary Wilson, RN, PhD

Controversy exists at Kingston General Hospital (KGH) regarding the concomitant use of postoperative low molecular weight heparin (LMWH) and neuraxial analgesia, specifically, epidural anesthesia with an indwelling catheter. Our institutional guidelines recommend against using dalteparin, a LMWH, for thromboprophylaxis in patients with continuous neuraxial analgesia for a variety of reasons including the absence of an effective reversal agent for LMWH and the inability to monitor aberrancies in coagulation status should an epidural need to be removed expeditiously. This controversy exists because new findings and recommendations regarding the safety and perhaps even superiority of LMWH over UFH have reached the literature in the past several years.

The current ASRA Consensus Statement states that the use of once daily dosing of LMWH with an indwelling epidural catheter in the postoperative period is safe as long as no other hemostasis modifying drugs are given simultaneously.

The ACCP Guidelines on thromboprophylaxis describe a meta-analysis comparing LMWH with low dose unfractionated heparin (UFH) in more than 48,000 abdominal surgery and general surgery patients. The risk of clinical venous thromboembolic (VTE) events was found to be 30% lower in LMWH group, however most studies were open label and asymptomatic deep venous thromboses (DVTs) were also identified questioning the clinical relevance of these studies. When only blinded, placebo controlled studies were identified, there was no difference between LMWH and UFH on major outcomes such as pulmonary embolism (PE), mortality, or bleeding/hematoma at the wound site.

A recent systematic review and meta-analysis from McMaster University looked at heparin thromboprophylaxis in medical/surgical critical care patients and concluded that LMWH compared with UFH BID decreased overall PE as well as symptomatic PE.

Heparin induced thrombocytopenia (HIT) is also a consideration when using heparin-based pharmacologic means for thromboprophylaxis and a recent Cochrane Review demonstrated a lower incidence of HIT in postoperative patients when LMWH was used instead of UFH.

As mentioned above, some disagreement exists at KGH between the Anesthesia Department, which has recommended avoiding LMWH in patients with indwelling epidural catheters and, for example, intensivists who feel that based on the current literature, it is standard of care and more cost effective to administer once daily LMWH instead of twice daily UFH to patients with indwelling catheters (personal communication).

The purpose of this preliminary descriptive study is to conduct a retrospective chart review using the hospital database and our APMS database to answer the question "What is the prevalence of diagnosed thromboembolic events in patients with epidural analgesia who have undergone general surgery with an abdominal incision and received standard UFH 5,000 U BID for DVT prophylaxis?" It is our hope that by determining the prevalence of diagnosed DVT and/or PE in a specific surgical population, we can ensure that our patients are receiving the highest standard of care and our findings can help to support or refute our current practice.

A query of the APMS database from January 2009 – December 2013 will be performed to identify all patients undergoing a general surgical procedure with an abdominal incision who had epidurals placed to provide analgesia. Using the CR numbers from the APMS database, patient data will be extracted from the hospital database and the subset of patients who had a radiographically diagnosed DVT or PE (ascertained from ICD codes) will have a full chart review performed covering the highest risk 12-week postoperative period. A data extraction tool will be developed to stratify our data based on important patient characteristics such as oncologic versus non-oncologic surgery, BMI, age, etc.

Once the initial database queries have been performed and the prevalence determined, further subgroup analyses can be performed to address a variety of research questions such as, "Does the duration of the indwelling catheter and continuous epidural analgesia confer any protective advantage with respect to development of VTEs in our patient population?"

FINESSE: A pilot survey to assess the distinction between stimulus-dependent and stimulus-independent pain symptoms in neuropathic pain

David He, Ph.D.[1], **Ian Gilron** M.D., M.Sc., FRCP(C)[2], Ronald R. Holden, Ph.D.[3], **Brian Grant**, M.D., FRCP(C)[4]

1. 2015 MD Candidate, Queen's University
2. Departments of Anesthesiology & Perioperative Medicine, Biomedical & Molecular Sciences and Center for Neuroscience Studies, Queen's University
3. Department of Psychology, Queen's University
4. Department of Anesthesiology & Perioperative Medicine, Queen's University

Background: Patients with neuropathic pain conditions often present with some combination of stimulus-dependent and stimulus-independent pain symptoms. Stimulus-dependent, "evoked pain", is caused by an identifiable external stimulus (e.g. skin touch, walking), while stimulus-independent, "spontaneous pain", is experienced without an apparent trigger (e.g. pain at rest). In theory, these two categories of pain symptoms are distinct and readily identifiable; however, in practice they are often difficult to distinguish. Current research approaches to understanding neuropathic pain pathophysiology and treatment response focus largely on stimulus-dependent responses, both in the laboratory (e.g. withdrawal responses to tactile stimulation) and in human neuropathic pain (e.g. quantitative sensory testing). Thus, the relative contributions of "evoked" versus "spontaneous" pain to overall neuropathic pain symptom burden remains unclear. In the setting of human neuropathic pain, this emphasizes the need for assessment tools that concurrently evaluate both "evoked" and "spontaneous" pain experiences.

Methods: To address these concerns, we have developed The Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation (FINESSE) Pain Pilot Questionnaire – a 10-question survey that explores participants' pain, in response to direct stimuli (e.g., skin contact), during passive experiences (e.g., lying in bed, watching TV), and active experiences (e.g., walking). In this Queen's Ethics Board-approved pilot study, 78 consenting participants who self-identified as having neuropathic pain were asked to complete the FINESSE survey, along with the Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) pain score, and a Modified Brief Pain Inventory (mBPI).

Results: Preliminary results indicate that, among patients with self-reported neuropathic pain, 45% frequently exhibited both stimulus-dependent and stimulus-independent symptoms; 10% frequently exhibited only stimulus-dependent pain; 23% frequently exhibited only stimulus-independent pain; and 22% rarely exhibited either type. By comparing these results to the mBPI responses, this pilot study found that patients reporting both pain symptoms reported higher interference in nearly all pain interference subscales; but patients reporting only stimulus-independent pain reported more interference with sleep, and enjoyment of life than those reporting only stimulus-dependent pain.

Discussion: Continued development of this pain assessment strategy will be required to strengthen its applicability, but the findings of this pilot study are promising, and suggest that FINESSE is a simple tool which may distinguish between the stimulus-dependent and stimulus-independent components neuropathic pain.

Adverse effect reporting in RCTs of gabapentin and pregabalin for acute postoperative pain

Darryl Hoffer PGY3, Supervisor: **Ian Gilron**

Background: Numerous RCT's and systematic reviews have studied the efficacy of gabapentin and pregabalin for post-operative analgesia. It is equally important to know the safety and tolerability of these medications when used peri-operatively. A recent study showed that randomized controlled trials (RCTs) in three major pain journals frequently failed to meet the recommendations for adverse effect reporting set out in the extension to the Consolidated Standards of Reporting Trials (CONSORT) in 2004.

Purpose: To evaluate the completeness of adverse effect reporting in randomized controlled trials of pregabalin/gabapentin for acute postoperative pain

Methods: Three major electronic medical databases (MEDLINE, Cochrane, and EMBASE) were searched for randomized placebo-controlled trials for use of gabapentin and/or pregabalin in the treatment of acute postoperative pain. Included articles were coded using descriptors from the CONSORT harms recommendation checklist

Preliminary results: Database search yielded 86 RCT's including 25 pregabalin articles, 59 gabapentin articles and two with both gabapentin and pregabalin. The average number of CONSORT recommendations met was 6.2 out of 10.

Conclusion: Reporting in gabapentin and pregabalin RCTs for acute postoperative pain need improvement.

A Survey of Scope of Practice in Family Medicine Anesthesia

Dr. Nicole King and Supervisors: Dr. Mike Cummings, Dr. Brian Mahoney.
Thanks to Dr. Chris Richardson

Background

Modern advances in healthcare provision involve specialized training and resources only available in tertiary centers. It is not practical, however, for all surgical, anesthesia, and obstetric services to be provided by specialists in referral centers. Many of these services can safely be provided in smaller hospitals, keeping wait lists more manageable and allowing local access to healthcare for more Canadians1. For many years these services have been provided by family physicians with additional training in anesthesia. Currently, however, there are few national regulations for family practice anesthesia. There is no standardized national curriculum and no end-of-training examination. There is no assessment of competence process for physicians trained outside of Canada. There are no requirements for continuing medical education and a lack of relevant CME opportunities. It is well recognized that FPAs help maintain a higher standard of healthcare in many underserviced areas by providing emergency, surgical, and obstetric services as well as special skills in airway management and resuscitation3. Without further advancements in their training, regulation, and support in practice, however, the sustainability of family practice anesthesia and the care they provide for thousands of Canadians is at risk.

Study Design

We propose to survey current Family Practice Anesthetists (FPAs) about their scope of practice to provide valuable data on which to base further curriculum development, evaluation and assessment, and continuing education.

Update: We have developed a survey to assess FPA scope of practice including questions on demographic information, site characteristics of the facilities they work in, scope of case work, airway management, technical skills, and CME. We have created an online version of this survey for electronic distribution and ease of response and data analysis. We are currently in the process of obtaining ethics approval. As there is currently no comprehensive list of practicing FPAs, we plan to distribute the survey widely via email using a combination of existing mailing lists. Responses will be kept anonymous and electronically coded to ensure no duplication. After the deadline for survey completion, data will be analyzed to establish the scope of practice and range of variation across Canada.

References

1. Barry AW. Meeting the challenge: Providing anesthesia services in rural hospitals. Can Med Assoc J. 1995; 153(10):1455-6.
2. Working group on rural anesthesiology practice. Determining and sustaining a maintenance of competence program for family physician anesthesiology practice in rural Canada. 2002.
3. Working Group: Society of Rural Physicians of Canada, College of Family Physicians of Canada, Canadian Anesthesiologists Society. Joint position paper on training for rural family physicians in anesthesia. 2001.

Measurement of cardiac output with the ultrasound cardiac output monitor versus transthoracic echocardiography: a data update

Karmen Krol, MD; John Murdoch MD; Michael McMullen MD

Reliable measurements of cardiac output (CO) have been achieved typically using invasive procedures such as pulmonary artery catheter insertion, transesophageal echocardiography, and more recently, placement of esophageal doppler probes. Intermittent, though non-invasive, methods like transthoracic echocardiography (TTE) remain valid, though impractical for intraoperative determinations of CO given surgical constraints on patient positioning limiting precordial access for image acquisition. With considerations like the invasiveness of a CO measuring method (and the attendant risks involved), and the cost of disposable components of devices, regular use of these methods tends to be more strictly reserved for strong patient and surgical factors informing an appropriate indication for their use. There is extensive utility, however, in the ability to perform perioperative CO measurements in order to develop and facilitate the safe hemodynamic management of surgical patients, particularly those whose status is unstable. The Ultrasonic Cardiac Output Monitor (USCOM) is a handheld, non-invasive device designed to measure direct and generate derived hemodynamic parameters, with no disposable components. It has been clinically validated for the hemodynamic management of patients preoperatively and in critical care settings. We have proposed a clinical pilot study to assess the utility of USCOM in measuring the cardiac output in patients undergoing elective lower extremity orthopedic procedures under spinal anesthesia. The intent was twofold: 1) to compare USCOM data with those acquired with the use of TTE for patients prior to, and following the induction of spinal anesthesia for their procedure, as well as during significant intraoperative events, and in the post-anesthetic care unit; and 2) to ascertain the utility of USCOM as a method to inform goal-directed use of intravenous fluids and vasoactive agents. The very early data from the initial 5 enrolled patients will be reviewed and presented for potential discussion; however, interpretation is necessarily constrained with due consideration to the frank immaturity of the data set.

Determining the minimum angle of needle angulation towards the midline while placing thoracic epidurals using the classic paramedian approach, a pilot study

Mahmoud Labib PGY2

Supervisor: Dr. Ronald Seegobin

Background

Thoracic epidurals offer an effective post operative analgesia in major abdominal and thoracic surgeries. Success rates are variable as is the time taken for catheter placement. Any aids to maximizing success rate and minimizing insertion time would be useful. Reaching the epidural space is technically more challenging for thoracic epidurals than for lumbar epidurals. The acute caudal angulation of the spinous process, especially at the high-thoracic spine, makes the midline approach more difficult. The classic paramedian approach is favored by many clinicians for thoracic epidurals.

Determining the minimum angle of needle angulation to midline could be challenging and is vital for reaching the interlaminar space. The angle quoted in the literature is 10-24 degrees. However, to our knowledge, no one has used spine imaging of any modality to measure this angle. Visualisation of a digital model immediately prior to or during needle /catheter placement and a review of the optimal angle of needle approach may be of value.

Objective

1. Generate digital 3D models of the spine developed from an age related archive of CT scans at the KGH.
2. Determine the minimum degrees of needle angulation towards the midline to reach the interlaminar space in the classic paramedian thoracic epidurals.

Methods

For our pilot study, we plan to use forty subjects. Twenty males and twenty females, both with ages 18-30 years old. We will examine six vertebrae for each subject, T4-T9, a total of 240 vertebrae. The CT would have been done originally for abdominal/pelvis pathology rather than spine pathology. This will help us exclude obvious or subtle spine pathology that may effects our results. Subjects with obvious spine abnormality will be excluded and replaced to adhere to our sample size. The CT images of the abdomen/pelvis will be extracted and formatted into the spine protocol then volume-rendered. After determining the orientation of the 3D spine in space which allows sufficient visualization of the interlaminar space, the angle in question will be measured:

A horizontal line (A) will be drawn from the mid tip of the spinous process and to the right parallel to the coronal plane. This will be the presumed insertion site used by most clinicians. A second line (B) will be drawn from the end of line A and into the transverse plane (posterior to anterior) reaching the most superior aspect of the lamina. Line B can be thought of as the virtual Touhy, will then be incrementally angulated towards the sagittal plane till the obstructing bony structures to the right are cleared, and a clear path is established between the insertion point and the interlaminar space. The minimum angle to achieve an unobstructed path to the interlaminar space will be recorded.

Update: The Effect of Intraoperative Labetalol on Time to Discharge and Hemodynamic Stability in Laparoscopic Cholecystectomy

Investigators: Judith Marois, Rob Tanzola, Dale Engen, Elizabeth VanDenKerkhof

Background: Surgical stimuli such as incisional pain or pneumoperitoneum from abdominal insufflation, can provoke increases in intraoperative heart rate (HR) and blood pressure (BP). These increases in HR and BP are thought to be indicative of pain and are often treated with opioids such as fentanyl. Pneumoperitoneum alters hemodynamic stability by rapidly increasing HR, BP, as well as systemic and central venous pressure. These changes are partially due to acute autonomic/sympathoadrenal responses. It has been shown that pneumoperitoneum (and the applied CO2 in particular) evoked sympathoadrenal responses only in patients who received intraoperative opioids but not esmolol. These data suggest that intraoperative beta-blockade may be superior for the management of hemodynamic changes associated with abdominal insufflation as required for laparoscopic cholecystectomy. Several studies indicate that intraoperative esmolol administration may also be associated with reduced opioid consumption, improved analgesia, reduced PONV, expedited patient recovery and a reduced time to discharge following laparoscopic cholecystectomy. Labetalol has a mode of action similar to esmolol but is cheaper, easier to administer, and clinical experience would suggest that labetalol may be more effective than esmolol for hemodynamic control.

Purpose/Hypothesis: The purpose of the current investigation is to assess whether labetalol and esmolol compared to fentanyl provide sufficient hemodynamic control during laparoscopic cholecystectomy; whether they have opioid-sparing effects; and whether they result in decreased side effects and reduced time to discharge from PACU. The current investigation examines the efficacy of labetalol which clinical experience may suggest is superior to esmolol for hemodynamic control. We hypothesize that labetalol will be ***at least*** as effective as esmolol for hemodynamic control; will reduce the length of stay in PACU and will reduce time to discharge.

Outcomes: The primary outcome will be the time from arrival in PACU until readiness to discharge from PACU. Secondary outcomes will include intraoperative hemodynamics measured by HR, mean arterial pressure (MAP), systolic BP and diastolic BP, incidence and required treatment of PONV in PACU, pain scores in PACU as measured by the VAS (0-10), fentanyl used in PACU, fentanyl, labetalol, and esmolol administered intraoperatively. Participants will receive a 24 hour follow-up phone call inquiring as to pain scores, analgesics used, satisfaction with postoperative care, and adverse events.

Study Design: Following signed informed consent, patients presenting for ambulatory laparoscopic gallbladder surgery will be randomly assigned to one of 3 groups: 1) will receive intravenous (iv) fentanyl bolus 50 mcg q5minutes; 2) will receive iv labetalol (bolus 5mg q5minutes) and 3) will receive iv esmolol (bolus 0.25mg/kg then titrated infusion 5-15mcg/kg/min) for intraoperative hemodynamic control if necessary. Participants will be monitored until discharge for the outcome measures.

Update: This prospective, randomized, double-blinded clinical trial has been approved by the Queen's University and Affiliated Teaching Hospitals' Research Ethics Board. It is currently underway with 56 patients recruited so far. We anticipate completion of data collection within 1.5 years.

Resources Utilization in the Joint Room: Building a parallel processing model

Erika Nguyen PGY4

Supervisors: Dr. Christina Godfrey and Dr. Jennifer Medves

Background:

In Ontario, the wait times for hip replacement surgery and for knee replacement surgery average 186 days and 220 days respectively (Ministry of Health and Long-Term Care). With an aging population and an increased prevalence of obesity and osteoarthritis, the need for joint replacement surgery is expected to grow and exacerbate the problem of timely access to adequate care. Finding ways to provide a safe anesthetic while minimizing OR utilization can allow a hospital to provide more surgical services relatively to the human resources available. The purpose of this study is to explore parallel processing as a workflow design for joint replacement surgery in our organization. Ultimately, the goal is to improve efficient resources utilization in the operating room.

Methods:

The study population consists of the orthopedic population who underwent elective total hip or total knee replacement in our institution between October 1st 2012 and October 31st 2012. Through retrospective chart reviews, patients' journey through the OR suite will be broken down into several procedural times: anesthesia-controlled time, surgeon-controlled time and between-case time. Those procedural times will then be used to build a parallel processing workflow model that minimizes anesthesia-controlled time by using a separate room from the OR to initiate the anesthetic. Information on the anesthetic technique (neuraxial or general anesthesia), the American Society of Anesthesiology (ASA) class, the body mass index, the presence of trainees, the hospital site and the type of surgery (hip or knee) will also be collected in order to analyze whether or not they significantly influence procedural times.

Microbubble Tracking for Patent Foramen Ovale Assessment

N.Proulx*, F. Secretain*, B. Milne, A. Pollard* and R. Tanzola
Department of Anesthesiology and Perioperative Medicine,
*Department of Mechanical and Materials Engineering
Queen's University at Kingston

The foramen ovale is a hole between the left and right atria of the heart. When this flap-like hole fails to close after birth, it is named a patent foramen ovale (PFO). Under high-pressure conditions, the flap may open allowing blood to travel from the right atrium to the left atrium. The severity of a PFO is currently qualitatively determined by injecting microbubbles into the patient's venous system. The microbubbles passing through the PFO from the right atrium to the left are observed using a transesophageal echography (TEE) probe. The size and severity of the PFO is examined qualitatively.

A potential gaseous emboli detection software package named DETECTS™ has been developed to determine the number and size of potential gaseous emboli using real-time data from TEE images [HYPERLINK \l "Fra" 1]. A bubble tracking capability has been added to the DETECTS™ software package for PFO quantitative assessment. The microbubbles in the TEE image are tracked to measure the number and volume of microbubbles passing through the PFO.

The number and size of microbubbles in each frame are detected with a region of interest and threshold algorithm. Once the region of interest is defined, the microbubble velocities are calculated using the change in microbubble positions between each frame. The microbubble positions in the next frame are estimated using the current microbubble positions and the calculated velocities. The minimum Euclidian distances are determined between the estimated and actual microbubble positions to track the microbubbles from frame to frame.

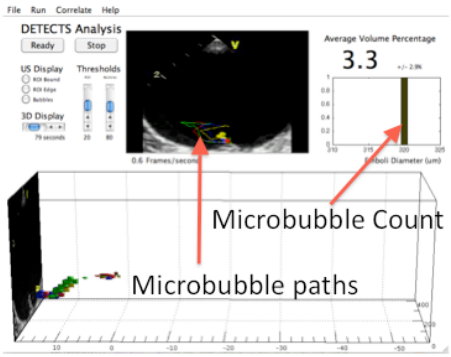

Figure 1: Screenshot of offline bubble tracking using DETECTS™

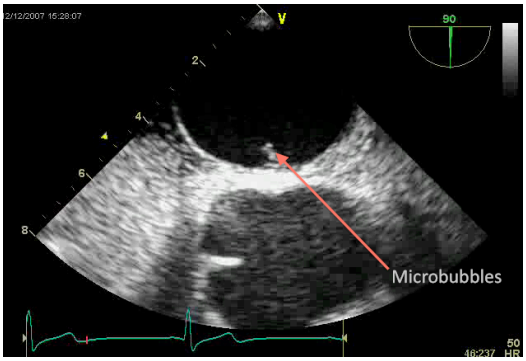

Figure 2: TEE image of microbubbles in the left atrium after passing through the PFO

The microbubble tracking capability included in the DETECTS™ software package will allow physicians to quantitatively assess the size and severity of a PFO by measuring the number and volume of microbubbles passing through the PFO from the right atrium to the left.

Reference

[1] Frank Secretain, "Investigation of Multi-Frequency Acoustic Breakup of Potential Cerebral Emboli," Queen's University, Ph.D.Thesis In preparation.

Does systemic dexamethasone prolong analgesia after interscalene catheter removal? A randomized control trial.

Gita Raghavan, John Murdoch, Vidur Shyam

Background:
Effective intraoperative anesthesia and analgesia for shoulder arthroplasty can be achieved with the use of continuous interscalene nerve block. Major advantages of this technique include continuous intraoperative and prolonged post-operative analgesia, decreased opioid requirements, and accelerated resumption of passive joint range of motion. Previous studies investigating peripheral nerve block adjuvants such as epinephrine and clonidine have demonstrated block prolongation and enhanced analgesia. Recent studies have specifically investigated the effects of adding dexamethasone to various peripheral nerve blocks and have also demonstrated prolonged analgesia.[1] The underlying mechanism of this off-label use of perineural dexamethasone is poorly understood, and there is debate in the literature regarding whether this observed enhanced analgesia is a result of a regional versus systemic effect.[2]

Study Objective and Rationale:
To determine if systemic dexamethasone provides prolonged analgesia following the removal of interscalene catheters. This could provide a cost-effective strategy for improving patient satisfaction as hospital discharge could be potentially expedited with prolonged analgesia, but without the need for costly ambulatory pumps.

Study Design:
Following Research Ethics Board approval, patients undergoing shoulder arthroplasty with interscalene catheters established preoperatively under ultrasound guidance will be randomized into two groups. Twenty-four hours after catheter placement, patients in Group A will receive a 10 cc 0.25% ropivacaine bolus and 4 mg dexamethasone IV, while patients in Group B will receive a 10 cc 0.25% ropivacaine bolus and 0.9% normal saline IV. Catheters will then be removed and all patients will receive a standardized, multimodal analgesia regimen in the form of acetaminophen, NSAIDs, Hydromorph Contin, and hydromorphone for breakthrough pain.

Primary End Point:
Time to first breakthrough analgesia request following interscalene catheter removal.

Secondary End Points:
Total opioid consumption and patient reported pain scores in the 24 hours following catheter removal.

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Detection and Breakup of Potential Cerebral Air Emboli

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Abstract
Neurological dysfunction ranging from stroke or coma to cognitive deficits that arise from open heart surgery is still one of the most common negative outcomes after a successful operation [2]. Presently, there is no standardized method of detecting, quantifying or eliminating potential cerebral emboli. Studies have shown neurological dysfunction in 30-45% of all patients that undergo open heart surgery and a fatality rate up to 4% post cardiac surgery associated with cerebral emboli [1].

DETECTS™

Software has been created (figure 1) that can identify and measure potential emboli during the deaeration process of the surgery. This patent pending software, appropriately named DETECTS™ (Detection of Emboli using Transesophageal Echocardiography for Counting, Total volume, and Size estimation) uses existing TEE technology to quantify the amount of potential emboli and displays this to the operative team. Calibration of the DETECTS™ software was accomplished using optical measurements within an *in-vitro* experimental rig (figure 2). A reliable software program that could quantify the potential air emboli could standardize deaeration techniques for open heart cardiac surgeries.

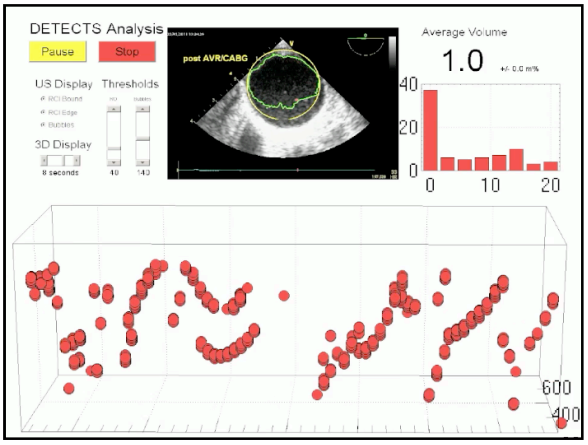

Figure 1: Screenshot of DETECTS™ being used on offline TEE data during the deaeration process of an open heart surgery.

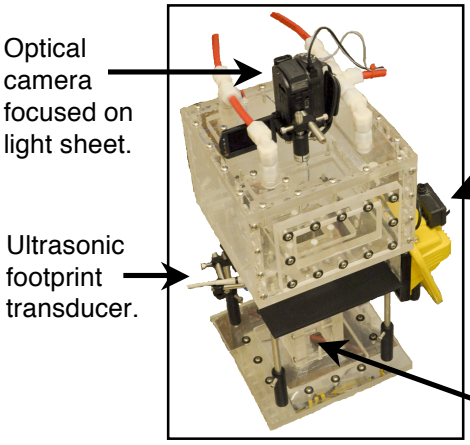

Figure 2: Experimental rig used to calibrate the DETECTS™ software *in-vitro*.

Bubble Breakup

The focus of this work is on the relationship between large band acoustic signals, surface oscillation and instabilities of collapsing bubbles. We hypothesize that we will be able to collapse larger potential air emboli within the arterial system using acoustic methods to produce smaller (micro) potential emboli. These microbubbles should then theoretically travel harmlessly through the body until being absorbed. The non-intrusive breakup of air emboli would completely change the current deaeration procedures.

References

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Adopting a flat operating room schedule: a Quality Improvement Audit

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Background: In the context of ongoing cost reduction efforts, a flat operating room (OR) schedule was introduced at Kingston General Hospital in September 2011. The previous OR schedule involved a heavier fall and winter schedule (40 weeks) and a slow down in the summer, Christmas and March break schedule (12 weeks). The new OR schedule was designed to enhance the efficiency of bed utilization by decreasing surgical beds but maintaining elective surgical volumes by leveling them throughout the year. Through the new schedule, there was a total reduction of 66 OR days shared by Orthopedics and General Surgery. The purpose of this audit was to assess the effectiveness of the new OR schedule in maintaining access for elective cases by measuring surgical volume, wait times, and case cancellations in the years before and after implementation.

Methods: After obtaining local institutional ethics approval we conducted a retrospective cohort study utilizing OR room records compared by service during two distinct periods (June 2010 to May 2011 and June 2012 to May 2013). The outcomes selected for this quality improvement audit were elective surgical volumes, surgery wait times, and case cancellations. Wait time data were assessed using independent samples t-tests and case cancellation data were assessed using χ^2 tests.

Results: The total surgical volume was 8048 cases from June 2010 to May 2011 cases and 8025 cases for June 2012 to May 2013. There was a significant increase in average adult wait times in Neurosurgery, General Surgery, and Gynecology ($p<0.0001$) and a significant decrease in Oral Surgery, Urology, and Vascular Surgery ($p<0.003$). The total wait times decreased from a mean of 73.1 (SD 23.3) to 70.4 (SD 30.6) days ($p<0.0001$). There was a significant increase in case cancellations ($p<0.05$) in Orthopedics, Vascular Surgery, Neurosurgery, Gynecology, and Plastic Surgery, and a significant decrease ($p<0.05$) in Oral Surgery. Overall, case cancellations increased from 8.8% to 10.7% ($p<0.0001$).

Discussion: Our results found that the flat OR schedule maintained elective surgical volume, had a variable effect on wait times and resulted in an overall increase in case cancellations. Case cancellations could be due to the reduction in surgical beds, hospital renovations, and ineffective resource allocation. Further investigation will be required to understand the variable effect on wait times, the impact on emergency cases, and overall cost effectiveness.

Faculty time distribution across Canadian academic medical centres

Serena Shum, PGY2
Supervisors: Drs. Dale Engen, Rob Tanzola, and Mike McMullen

Background

Accurate quantification of faculty time distribution amongst various activities is vital for the development of many policies concerning academic physicians. These include budget planning, reimbursement analysis, resource allocation, workforce assessment, productivity measurements and promotion evaluations. Unfortunately, there are currently no accepted measures of various activities performed by academic physicians. Previous research has typically divided faculty workload into four components: (1) clinical activity, (2) teaching activity, (3) research activity, and (4) administrative activity.[1,2] Most of the limited literature on the measurement of physician workload focuses on a specific specialty in one academic centre.[2,3,4] Furthermore, few studies[1,2,4] look at how this workload is proportioned amongst these four different activities as most focus on quantifying only one aspect.

Objectives

The objective for this study is twofold. The first is to develop a validated online survey tool for self-reported estimates of the time academic physicians spend performing various activities. Following survey validation, we will distribute the survey to all Canadian academic physicians. In doing so, we hope to compare self-reported estimates of the time academic physicians spend performing various activities between a) different medical specialties; and b) different institutions across the country.

Study Design

This study is comprised of three phases: 1) Survey validation; 2) Local survey; and 3) Nationwide survey. For the first and current phase of this study, we will focus on survey development and validation within our home institution. More specifically, face and content validity will be assessed using a sample of 10-12 local attending physicians who have been with Queen's University for at least 5 years. Subsequently, using the validated tool, we will employ a prospective, cross-sectional study to quantify time distribution amongst academic physicians at Queen's University. Finally, we will distribute the survey to all Canadian academic physicians.

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Electronic Anesthesia Records: Impact Upon Legibility, Accessibility, and Accuracy

Vanessa Sweet, PGY3
Supervisor: Dr. David Goldstein

Background

Pre-Anesthesia clinics are a critical means by which Anesthesiologists can have a positive impact with on perioperative resource utilization. These clinics enable us to optimize patients for surgery and anesthesia and communicate the findings on history, physical exam, and results of investigations to our colleagues who will care for these patients on the day of surgery.

Central to this effort is the effective collection and dissemination of patient information. . This information is collected by and shared with a number of individuals, and is central to perioperative decision-making. In order to manage this information effectively, it ought to be done in a system that allows the information to be *accessible*, *accurate*, and of *value* to the end user. It also needs to be able to be documented and used in an *efficient* manner.

Currently, our information management system in the Pre-anesthesia clinic at HDH is a hybrid model of electronic and paper based. This has inherent issues with respect to the legibility of the records, redundancy in information collection, as well as incomplete and inaccurate documentation. Furthermore, it does not lend itself well to rapid communication or data review for operational research and education.

Purpose

The purpose of our study is two-fold:

1. To complete a Quality Assurance chart review to assess records completed in the pre-anesthesia clinic for legibility, accuracy, and completeness.
2. To implement an electronic anesthetic record within the pre-anesthesia clinic at HDH and study its effect on legibility, availability, and accuracy of the information contained within the record.

Hypotheses

We hypothesize that:

1. The current paper-based anesthetic records are sometimes illegible, incomplete, and contain outdated or inaccurate information.
2. Implementation of an electronic anesthetic record will improve chart legibility, completeness and accuracy.

Methods

Our study will be completed in two phases. The first is a Quality Assurance chart review to assess our paper-based anesthetic records completed in the HDH pre-anesthesia clinic for legibility, completeness, and accuracy. This will consist of a review of 50 anesthetic records and will provide us with information regarding the current state of our records, thereby allowing us to closely define our metrics and complete necessary power calculations for phase two.

Phase two of the study will be the implementation of an electronic version of the anesthetic record within the HDH pre-anesthesia clinic. Clinics will be randomized to either the current paper-based record or the new electronic record. All records (paper and electronic) will then be assessed for accessibility, legibility, accuracy, and completeness. Clinic and OR anesthesiologists will be surveyed regarding perceived clinic workflow and efficiency as well as the overall value and ease of use of the record.

Perioperative Management of Urgent Surgery: A Quality Improvement Initiative

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Dr. Michael McMullen, Assistant Professor, Faculty of Health Sciences/Anesthesiology and Perioperative Medicine
Dr. Dale A. Engen, Assistant Professor, Faculty of Health Sciences/Anesthesiology and Perioperative Medicine
Dr. Robert C. Tanzola, Assistant Professor, Faculty of Health Sciences/Anesthesiology and Perioperative Medicine

Introduction

The perioperative management of patients requiring urgent or emergent surgery is a complex process involving multiple interdisciplinary interactions[1]. Current practice at KGH involves the surgical service triaging patients in a classification system with stated maximum accepted wait times from booking time to OR arrival (A case <2h, B case <8h, C case <24h). This triaging system can be inefficient for numerous reasons. The objective of this project is to review the process of care from initial presentation to definitive treatment in the operating room in order to identify barriers to optimal care.

Methods

Following local ethics approval, all patients who were scheduled for emergency surgery (A or B cases) at KGH from January to March 2013 were identified from the hospital database. A detailed chart review was done for each case to develop an individual perioperative care timeline from time of presentation until the start of the surgical procedure.

Results

A total of 285 patients underwent emergent/urgent surgery during the study and were included in our review. General Surgery was the most highly represented service (41%) amongst all cases. The majority (75%) of cases and in particular 94% of the emergent (A cases) occurred during the on call period (outside of weekdays 07:45-15:30). With respect to local guidelines, 83% of the fully-documented cases were started within the accepted time limits. The average wait times from initial physician assessment to OR arrival was 2:35 ± 2:11 for emergent (A) cases and 14:03 ± 17:25 for urgent (B) cases. However, this data was limited by incomplete booking forms in 29% of cases.

Conclusions

In assessing the timeline of perioperative care, six distinct stages were identified: 1) Arrival at ER 2) Assessment by ER physician 3) Consult to surgical service 4) Booking by surgical service 5) Assessment by anesthesia 6) OR arrival. Each stage has unique requirements that can potentially prolong the time to definitive operative treatment.

Our review suggests that the majority of emergency surgeries are meeting acceptable wait times. However, these conclusions are limited by incomplete data capture in the current OR booking process, especially in A cases. The recent adoption of electronic data collection in the OR will hopefully assist in future quality improvement studies. The data also showed that a majority of urgent cases occur during on call hours. This may be an area to address in future allocation of operating room resources. Future research efforts in this area should include looking for patterns in cause of treatment delay and value-mapping of the various stages of care.

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Frailty Indices As A Predictor Of Postoperative Complications: A Systematic Review

Julie Zalan; Supervisors: Rosemary Wilson and Rachael Seib

Introduction: Over the next 30 years, the Canadian healthcare system will treat an unprecedented number of older adults, many with multiple chronic diseases. Frailty is a state of reduced physiologic reserve associated with increased susceptibility to disability1. It is a global phenotype introducing vulnerability, which limits a person's ability to respond to stressors1. Despite significant frailty, many individuals will be considered for and will ask for highly aggressive care that has uncertain chance of success and may well result in prolonged disability and suffering. Indices exist which incorporate cognition, mobility, function and co-morbidities, to assign a frailty score. Low and high scores correlate with fitness and severe frailty respectively, which effectively estimate important outcomes2, such a survival/mortality, morbidity and institutionalization.

Recent incorporation of this tool in the peri-operative context has shown its predictive value in estimating risk and outcomes postoperatively. Frailty has been identified as an independent risk factor for in-hospital mortality, morbidity including delirium, functional decline, and prolonged ventilation; increased length of stay, as well as discharge to institutional care3,4. The power of this tool in the pre-operative period to predict postoperative outcomes may help patients make informed decisions about their care, to best preserve their quality of life, which may or may not include continuing with surgery. If surgery is decided, additional supports (geriatric multidisciplinary team, intensive care unit, alternate level of care etc.) may be anticipated, and this in turn can help the health care team and policy makers plan resource allocation.

Objective: To describe and compare the predictive value of existing frailty indices for peri-operative morbidity and mortality.

Question: What is the relationship between a frailty score and postoperative outcomes?

Method: We will be using the Joanna Briggs Collaboration (JBI) methodology for systematic review. The search strategy aims to find both published and unpublished studies. A search of EMBASE, MEDLINE, CINAHL and PSYCH INFO will be undertaken followed by an analysis of the text words contained in the title, abstract and hand searching. Studies will be included if they are published in English, employ experimental, observational, or descriptive methods. All surgical specialties will be included, as will all age groups and both sexes. Articles supporting frailty scores where validity data are not provided will be excluded.

Articles will be independently reviewed by two independent assessors. Any conflicts of opinion will be independently resolved by a third assessor. Data extraction and analysis will be performed using JBI MASTARI and CReMS software. The protocol for this review will be registered with the JBI Library.

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Time to discharge with ultrasound guided blocks versus general anesthesia in arthroscopic shoulder surgery

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Background: Patients undergoing arthroscopic shoulder surgery traditionally receive general anesthesia (GA). With more recent advancements in ultrasound technology, there is now the option of using ultrasound guided regional nerve blocks in this procedure[1]. Advantages of using ultrasound-guided blocks include faster emergence times, faster induction times and fewer side effects than those associated with GA (eg. nausea, vomiting, confusion). The goal of this study was to compare the time of discharge from the post-anesthetic care unit (PACU) following arthroscopic shoulder surgery in patients who received ultrasound guided blocks and general anesthesia.

Methods: This retrospective observational study looked at the electronic charts of 140 adults (ages 18-90) who had arthroscopic shoulder surgery. This included 86 patients who had GA, 41 patients who had ultrasound guided block and 13 patients who had GA + block. The primary outcome was discharge time from PACU. Secondary outcomes included acute side effects (pain, nausea, vomiting) and post-operative analgesic consumption. Pain was measured using the visual analog scale and analgesic consumption in PACU. The occurrence of nausea and vomiting was reported by nursing staff.

Results: Time to discharge from PACU was significantly less for patients who received ultrasound-guided block compared to GA (80 vs. 120min, P=0.0006). Patients who received a block had less pain when compared to those patients receiving GA on arrival (1.44 vs. 5.42, P=0.00) and discharge (1.10 vs. 2.69, P=0.00) from PACU. There was a 53% reduction in patients who required opioids (Fentanyl) for post-op management of pain. In addition, block patients had an 18% reduction in nausea and 7% reduction in vomiting.

Discussion: There is a significant reduction in the time to discharge with the use of ultrasound-guided blocks when compared to GA in the context of arthroscopic shoulder surgery. The use of blocks improves the flow of patients from the OR to PACU to home. Further studies are needed to compare surgical outcomes between block patients and those receiving GA.

Critical Appraisal

By: **Liban Ahmed**, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication title: "***Local Infiltration Analgesia Versus Intrathecal Morphine for Postoperative Pain Management After Total Knee Arthroplasty: A Randomized Controlled Trial***"

Authors: ***Essving P, Axelsson K, Åberg E, Spännar H, Gupta A, Lundin A.***

Anesth Analg. 2011; 113(4): 926–33

Introduction

Pain following total knee arthroplasty (TKA) is considerable and can adversely affect the patient's post-operative course. In particular, post-operative pain impairs the ability of these patients to mobilize and effectively participate in physical therapy. Moreover, the inadequate management of post-operative pain is associated with impaired wound healing, insomnia, pneumonia, venous thromboembolism, myocardial infarction, cognitive dysfunction, and an overall protracted functional recovery leading to an increased length of hospital stay (1).

There are various modalities available to clinicians for the management of pain following TKA including oral and parenteral medications such as opioids, neuroaxial anesthesia, peripheral nerve blockade, and local infiltration analgesia (LIA). Narcotic medications are associated with significant side effects including pruritus, nausea, vomiting, respiratory depression, urinary retention, and cognitive dysfunction. Therefore, central neuroxial blockade has become commonplace in the management of pain associated with TKA. In particular, spinal anesthesia has achieved prominence with lower extremity orthopedic procedures following numerous trials illustrating the benefit of spinal anesthesia with regards to morbidity and mortality (2, 3). Specifically, intrathecal morphine has become well-established, providing analgesia for at least 24 hours (4). More recently, there has been increased utilization of peripheral nerve blocks such as continuous femoral blocks, and this technique has been demonstrated to provide comparable analgesia to central neuraxial techniques (5). The placement of perineural catheters however demands additional anesthetic time, is technically demanding, and can generate significant motor block of the quadriceps that impairs physical therapy.

LIA at a surgical site is widely utilized for a variety of surgical procedures, and it has been demonstrated to provide effective analgesia (6, 7). Although there are some variations, this technique typically involves the intra-operative infiltration of a long-acting local anesthetic such as ropivacaine, epinephrine, and an NSAID such as ketorolac into the tissue around the surgical field (8). Furthermore, a catheter may be placed for additional postoperative infusions. The modality presents several advantages including the relative technical simplicity compared with other regional anesthesia techniques, the lack of physiological disturbance associated with the procedure, and the opportunity for additional post-operative infusions with an indwelling catheter.

More recently, a few clinical trials have been published demonstrating the efficacy of LIA in TKA (9). However, the majority of these studies have investigated the efficacy of LIA in comparison to placebo rather than with current established modalities. Prior to this trial, only four studies compared LIA with other regional anesthesia techniques, none of which were comparisons with intrathecal morphine. Furthermore, these studies utilized different protocols resulting from differences in the composition and dose of the infusions, the location of the injections, and whether a catheter was employed for continued post-operative infusions. Thus, the results of these trials have been somewhat conflicting. Accordingly, the authors in this study sought to investigate the efficacy of the LIA technique in comparison to intrathecal morphine for post-operative pain management following TKA. The study is particularly important as it is the first evaluating LIA versus intrathecal morphine during TKA. The authors hypothesized that "LIA would provide better postoperative analgesia than intrathecal morphine and thereby reduce IV morphine consumption during the first 48 postoperative hours." Furthermore, the authors sought to investigate whether the LIA technique is associated with a decreased incidence of side-effects, shorter hospital admissions, enhanced post-operative knee function, and enhanced patient-related outcomes.

Methodology

In this prospective, randomized double blinded study, a total of 117 patients booked for TKA secondary to osteoarthritis were evaluated for eligibility. The inclusion criteria included: age 40-85 years and ASA class I–III. Exclusion criteria for this study included: allergy/intolerance to drugs utilized within the study; severe heart, liver, or renal disease; inflammatory

joint disease; chronic pain requiring opioid medication; bleeding disorder, and any other contra-indication to spinal anesthesia.

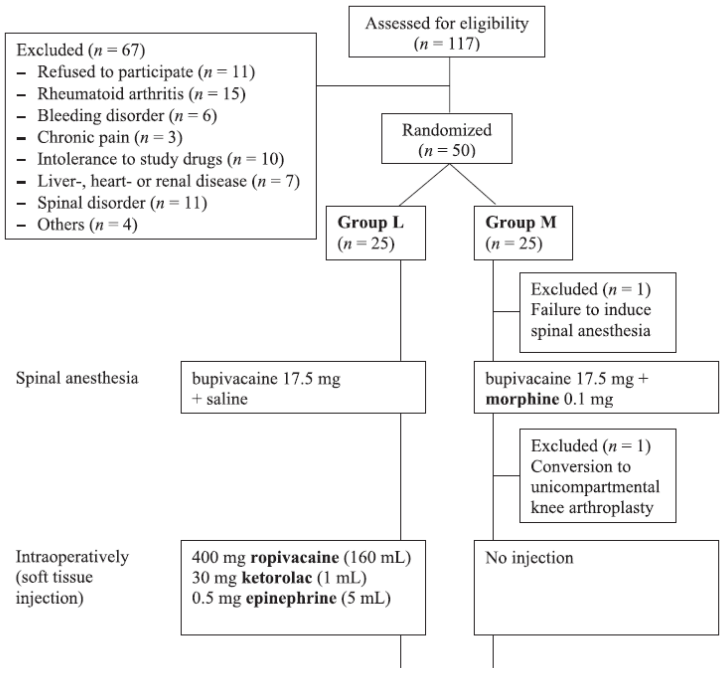
Following evaluation for eligibility, 50 patients were randomized into the two experimental groups: Group L – local infiltration analgesia and Group M – intrathecal morphine. Randomization was performed by the hospital pharmacy by computer-generated randomized numbers with 25 patients in each group. The 50 patients underwent surgery between August 2009 and June 2010 at the Orebro University Hospital. The regional ethics committee in Uppsala, Sweden and the Swedish Medical Products Agency approved the trial, and it was conducted in agreement with the Helsinki declaration and monitored by the Clinical Research Support Unit at Orebro University Hospital.

The patients, all healthcare staff participating directly or indirectly in the trial, and the investigators were blinded to group randomization. However, as the authors note, it was not possible to blind the surgeons to group randomization. In order to eliminate the potential bias this presents, the investigators ensured that the surgeons did not partake in the post-operative care of the patients.

Following randomization, two patients were excluded in Group M. One patient was excluded due to insufficient spinal anesthesia. Another patient was excluded due to conversion to unicompartmental knee arthroplasty.

The authors performed sample-size calculations based upon morphine consumption for the first 48 post-operative hours, which was the primary endpoint. Certainly, the study was appropriately powered (80%) in regards to the primary outcome. However, there was no power analysis provided in regards to the secondary outcomes. Furthermore, the number of patients included in each analysis of the secondary outcomes varied greatly.

Figure 1. Flow chart for the study.
From: Essving P, Axelsson K, Aberg E, Spannar H, Gupta A, Lundin [illegible] morphine for postoperative pain management after total knee arthroplasty: a randomized controlled trial. Anesth Analg 113(4): 926–93.



The experimental protocol was systematically detailed by the authors enhancing the reproducibility of the study. As seen in Figure 1, all patients underwent spinal anesthesia. In Group M, 0.1 mg of morphine and 17.5 mg of glucose-free bupivicaine was injected intrathecally. In Group L, an equivalent volume of 0.9% normal saline and 17.5 mg of glucose-free bupivacaine was utilized. Pre-operatively, all patients received 2 grams of IV cloxacillin, and this was continued until the intra-articular catheter was removed. The standardized surgical approach including the technique and equipment utilized is detailed within the paper. Intra-operatively, patients received bolus or continuous infusion propofol as needed. Furthermore, intro-operative pain was managed with 25-50 µg boluses of IV fentanyl up to a maximum of 300 µg. In addition, there was a standardized approach to the injections. Patients in Group L received injections of solution containing 400 mg ropivicaine, 30 mg ketorolac, and 0.5 mg epinephrine by the surgeon into all the peri-articular soft tissues injured during surgery. Patients in Group M received no peri-articular injections.

Furthermore, there was a standardized approach to wound closure and the placement of the intra-articular catheter by the surgeon. All catheters contained a bacterial filter with the filter and the catheter filled with 1-2 mL of ropivacaine for bacteriostasis.

Post-operatively, pain was managed via a PCA-morphine pump. The PCA pump was discontinued at 48 hours post-operatively if the VAS pain score at rest was ≤40 mm during a 2-hour period. Subsequently, patients received 100 mg oral tramadol up to 4 times daily in order to achieve a VAS pain score ≤40 mm at rest.

At 21 and 45 hours post-operatively, patients in Group L received an intra-articular injection of 200 mg ropivacaine, 30 mg ketorolac, and 0.1 mg epinephrine via the catheter. Patients in Group M received an equivalent volume of saline. Importantly, the injections

were formulated by the hospital pharmacy in order to ensure blinding. In all patients, the intra-articular catheter was removed at 45 hours postoperatively, and the tip of the catheter was cultured.

Data Collection and Analysis

The primary endpoint for this trial was IV morphine consumption during the first 48 post-operative hours. The secondary endpoints included post-operative pain scores, patient satisfaction with the quality of analgesia, mobilization, time to fulfillment of discharge criteria, hospital length of stay, and patient-assessed health quality via the Oxford Knee Score and EQ-5D during the 3 month follow-up period.

Clinical Outcome	Notes
Pain	A visual analog scale (VAS) utilized. Pain assessments were made at rest and on flexion of the knee to 60 degrees pre-operatively and at 6, 12, 21, 22, 24, 45, and 46 hours post-operatively. Pain when walking was assessed at 24 and 48 hours post-operatively. Following discharge, patients completed a questionnaire regarding pain on days 1, 3, and 14 and after 3 months post-operatively.
Morphine Consumption	PCA-morphine consumption was recorded for the first 48 post-operative hours.
Patient Satisfaction	Patients provided a verbal rating scale of their satisfaction with the quality of analgesia (excellent = 4, good=3, inadequate=2, poor=1) on post-operative days 1, 2, and 7.
Mobilization	Knee flexion and extension were assessed pre-operatively, on day 3, at discharge, as well as 2 weeks and 3 months post-operatively. Ability to climb 8 stairs was assessed at 24 and 48 hours post-operatively. The Time to Up and Go (TUG) test was assessed pre-operatively and post-operatively on days 3, 7, and 14 as well as after 3 months.
Hospital Length of Stay	Following the second intra-articular injection at 45 hours post-operatively, patient fulfillment of discharge criteria was assessed by a physician and physiotherapist blinded to group randomization. This was assessed 3 times daily afterwards. The article details the discharge criteria. Time to fulfillment of discharge criteria was defined as the time from the end of the operation until the patient fulfilled the criteria. Hospital length of stay was recorded (day 0 = the day of operation).
Adverse Events	The incidence of nausea, vomiting, pruritus, and sedation (4 grade scale) were recorded on days 1 and 2 post-operatively. Respiratory rate and arterial oxygen saturation (SaO2) were recorded during the first 24 hours. The investigators defined respiratory depression respiratory rate <10/min alongside a SaO2 <90%. All intra-operative, post-operative, and post-discharge complications and adverse events were registered. Hospital readmission during the 3-month follow-up period was recorded.
Functional Recovery	The Oxford Knee Score was completed pre-operatively and at 2 weeks and 3 months post-operatively. The EuroQol (EQ-5D) questionnaire was completed pre-operatively and at 3 months post-operatively.

For the analysis of the primary endpoint, repeated-measurements ANOVA with Huynh–Feldt corrected P-values was utilized. The mean difference between groups and time points as well as their interaction were investigated. The median VAS pain score for the first 48 post-operative hours was utilized to summarize each patient's set of scores. The difference between the groups was then analyzed using the Mann–Whitney U test. Differences between the groups in regards to the time to fulfillment of discharge criteria, hospital stay, knee function scores, and patient satisfaction with analgesic quality were also analyzed using the Mann–Whitney U test. The Bonferroni–Holm method was used to correct for multiple measures when $P < 0.05$ in the secondary endpoints.

Dichotomous data were analyzed using the X^2 test or Fisher's exact test. $P < 0.05$ was considered to be statistically significant. The confidence intervals around the median were analyzed with the Hodges–Lehmann method using Confidence Interval Analysis (CIA) Software. All other analyses were completed via SPSS software version 15.0 for windows.

Results

The patient demographics in the two study groups were similar. In regards to the primary endpoint, mean morphine consumption during the first 48 post-operative hours was statistically lower in Group L than in Group M. Furthermore, the median VAS pain scores at rest and on flexion for the first 48 post-operative hours were statistically lower in Group L versus Group M. VAS pain scores when walking at 24 and 48 hours post-operatively were also statistically lower in Group L.

Although patient satisfaction was statistically greater in Group L on post-operative day 1, no difference was found in patient satisfaction on days 2 and 7.

With respect to functional recovery, a significantly greater proportion of patients in Group L were able to climb stairs at 24 and 48 hours post-operatively. Despite this, there was no statistical difference between the study groups with regard to knee extension, knee flexion, the TUG test, and patient-related health outcomes – the Oxford Knee Score and the EQ-5D.

The time to fulfillment of discharge criteria was shorter in Group L, with a difference of about 23 hours between the study groups. Accordingly, the length of hospital stay was shorter in Group L.

There was no statistical difference in the incidence of nausea, vomiting, pruritis, or sedation between the study groups. This was an interesting result considering the significantly increased morphine consumption in patients randomized to Group M. Throughout 3-month follow-up period, no patient developed evidence of a deep infection. However, in regards to the cultured catheter tips, 7 catheters were positive for coagulase-negative Staphylococcus. There was no difference in the number of culture-positive catheter tips between the study groups. Furthermore, no clinical signs or symptoms of infection developed among these patients, and no antibiotics were required.

Discussion

On the basis of the results, the authors concluded that "the LIA technique was found to be superior to intrathecal morphine in providing good pain relief and resulted in early mobilization and greater patient satisfaction after TKA. These advantages translated into earlier home readiness and quicker home discharge without increasing any adverse effects". However, the authors correctly assert that this was not associated with differences in knee function outside the immediate post-operative period or in patient-related health outcomes.

This was the first clinical study investigating the efficacy of the LIA technique for TKA in comparison with intrathecal morphine, an already established modality for pain management. As a result, it demonstrates that LIA is a safe and effective for post-operative analgesia for TKA. Furthermore, the authors provide a detailed and clinically relevant protocol for implementing LIA at the knee joint. The lack of consistency in clinical protocols among previous studies investigating LIA with TKA has marred the validity and reproducibility of the evidence provided by the trials.

However, there were various limitations in this study in terms of the clinical protocol and analyses. In regards to the exclusion criteria, they potentially limit the external validity of the results. In particular, a good proportion of patients undergoing TKA have significant liver, heart, and renal disease. Furthermore, many are prescribed opioids chronically for osteoarthritis. As a result, the results attained in this study may not be entirely representative of the true population of individuals undergoing TKA.

As the authors indicated, blinding the orthopedic surgeons to group randomization was not possible. In particular, patients in Group M did not receive any control peri-articular injections intra-operatively. In order to reduce potential bias, the surgeons were removed from post-operative patient care. However, bias can still arise from this aspect of the protocol as surgeons may be more meticulous and particular for patients in one study group. Although unlikely to be a significant issue, the authors fail to comment on this matter. A potential solution for this dilemma was to inject an equivalent volume of normal saline into the peri-articular tissues intra-operatively among patients in Group M. In this scenario, the hospital pharmacy would provide the solution, and the surgeons would be unaware to which group the patient was randomized. The lack of a control intra-operative peri-articular injection among patients in Group M presents further systematic bias. In particular, the mere injection of a solution into a joint space can enhance pain management by the cooling of local tissues and the dilution of inflammatory mediators (10).

Although the current study demonstrated a significant difference between the groups in their requirements for rescue analgesia as well as length of hospital stay, there was no difference in long term knee function or patient-related outcomes. Unfortunately, the authors do not offer much of an explanation regarding this matter beyond: "earlier mobilization and shorter hospital stay do not seem to affect the long-term outcome in any significant way." It is entirely possible that the only benefit of LIA is in the immediate post-operative period with reduced pain scores, morphine consumption, early mobilization, and shorter hospital stays. Certainly, early mobilization and a reduced length of hospital admission are considered to be important endpoints of functional recovery following TKA. However, as noted before, the study was not powered sufficiently to detect a difference in these long-term secondary endpoints.

Relating to the study protocol, the safety of an indwelling intra-articular catheter can be questioned due to the risk of infection (11). In this study, there were no reported cases of joint infection despite 7 catheters culturing positive for coagulase negative Staphylococcus. However, post-operative joint infections are rare, and the current study was not sufficiently powered to detect such significant adverse outcomes. As the authors correctly note, a number of studies investigating LIA with indwelling intra-articular catheters have not reported any deep tissue infections related to the wound catheter (12-17). Conversely, two previous studies have described cases of deep tissue infections associated with an indwelling intra-articular catheter with an incidence of about 1% (17, 18). The authors of this study however note that deep infection following TKA occurs at about this rate irrespective of an indwelling intra-articular catheter (19). Nevertheless, considering the significant sequelae associated with deep tissue infections, it is imperative to investigate this issue in larger, more sufficiently powered trials. In particular, it appears that one dose of LIA is short-lived and has no advantage versus ITM (20, 21); therefore, an indwelling catheter may be necessary to attain maximal analgesic

benefit. Currently, the evidence appears to suggest that the benefit derived from prolonging pain relief via an indwelling intra-articular catheter outweighs any potentially added risk of deep infection. Certainly, the study protocol outlined in this paper provides various methods to reduce infection rates: the catheters were inserted intra-operatively under sterile conditions, patients were administered antibiotics until the catheter was discontinued, and a bacterial filter was utilized during the intra-articular injections.

Despite being in its infancy, the LIA technique has been adopted widely for numerous surgical procedures (6). This has largely been due to its technical simplicity, the limited additional anesthesia time required, the lack of motor block that can limit rehabilitation, and the opportunity for additional post-operative infusions with an indwelling catheter. However, it will be important to elucidate which components of the LIA technique and at what doses are essential for its analgesic benefits. Previous studies have utilized a wide variety of drugs at varying doses when investigating this modality. As a result, this has significantly hindered the validity of the cumulated research (10). Additionally, more rigorous large-scale comparative studies are needed to further investigate the relative safety and efficacy of this modality.

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Critical Appraisal:

By: **Jamei Eng**, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication title: "***Effect of Perioperative Intravenous Lidocaine Administration on Pain, Opioid Consumption, and Quality of Life after Complex Spine Surgery***"

Authors: ***Farag E, Ghobrial M, Sessler DI, Dalton JE, Liu J, Lee JH, Zaky S, Benzel E, Bingaman W, Kurz A.***

Anesthesiology. 2013 Oct;119(4):932-40.

Introduction:

The role of an anesthesiologist is not only to manage intraoperative care, but pain control particularly in the post anesthetic care unit is also of equal importance. The most common method of pain management includes the use of opioids, which are known to produce further complications such as nausea and vomiting. Depending on the type of surgery that a patient has, the intensity of pain varies. In particular, after spine surgery, the pain most often ranges from moderate to severe. These are some of the reasons why efforts to reduce postoperative pain and the use of opioids, has been an area of interest.

A 2010 review of studies involving the use of IV lidocaine perioperatively in open and laprascopic abdominal surgeries reported that it decreases the amount of pain reported and use of opioids. As a result the time to return normal gastrointestinal motility decreases, which can lead to decreased length of hospital stay (2). There has also been a study that shows decreased persisting pain after breast surgery. (6) Despite these encouraging studies, there have been conflicting reports that found no significant improvement using perioperative IV lidocaine during hysterectomy (3), tonsillectomy, total hip arthroplasty or coronary artery bypass surgery (2).

The recent article written by Dr. E. Farag, et. al. from the Departments of General Anesthesiology and Outcomes Research from Cleveland, Ohio, aims to look at the specific impact of the use of perioperative IV lidocaine on postoperative spine surgery patients. The hypothesis being tested was that IV lidocaine administration during spine surgery decreases pain and/or opioid consumption in the initial 48 hours postoperatively. Secondary outcomes also assessed were major complications, postoperative nausea and vomiting, duration of hospital stay and quality of life. (1) Testing these hypotheses will help to determine whether perioperative IV lidocaine is useful in the consideration of postoperative pain management in spine surgery.

The mechanism behind systemic lidocaine in postoperative pain lies within its anti-inflammatory, analgesic and antihyperalgesic effects (4). Its anti-inflammatory process is mediated via NMDA receptors (1) and by increasing the secretion of cytokine interleukin-1 receptor antagonist, which also has anti-inflammatory properties. (1)

Methodology:

The study design was a double blind randomized control trial. Participants were randomized via a computer-generated number. One group received IV lidocaine 2mg/kg/hr (maximum 200 mg/hr) and the control group receiving saline as placebo. Both groups continued the infusion until discharge from PACU or a maximum of 8 hrs. They studied the local population between the ages of 18 to 75 with an ASA ranging from 1-3 that were undergoing spine surgery with or without instrumentation under general anesthesia. There was no justification provided for this set of patients. Patients that were excluded had contraindications to lidocaine use such as hepatic impairment, renal impairment or seizure disorder requiring medication within 2 years, or if epidural analgesia or anesthesia was also planned. (1)

With regards to the experimental protocol, the design has been set up to answer their question, and has been described well enough such that the study can be reproduced. General anesthesia was induced via propofol or etomidate, maintained by sevoflurane. The study remained ethical as intraoperative management stayed within the standard of care. The paper did not comment on a potential confounder - about which groups patients induced with propofol versus etomidate were randomized to and whether this had an effect within the group that received perioperative lidocaine. Studies have also looked at propofol as having an analgesic property via NMDA receptors, and they may have been more common in the test group or placebo group. (8)

Results:

Initially, 2587 patients were assessed for eligibility, but only 116 participants in the study were included, none were lost to follow up or were removed from the study. The sample size was somewhat small at only 58 in the placebo group and 57 in the test group. Participants were sampled from the population of Cleveland, Ohio, and it should be taken into consideration that the demographics are not likely representative of the general population of Kingston, or the rest of Ontario. The prevalence of pre-existing co-morbidities and characteristics of the sample studied be considered as they can potentially impact the results. The study was well powered having small variance in the pain scores comparing the placebo and test group, but this only confirms a slight difference of 1.1 in the pain score. The total time of lidocaine infusion was shown to have no significant impact on pain scores or opioid consumption. Moreover, pain scores were subjectively scored by the patient, and could easily vary if the study was repeated. No information was provided on how patients were educated with regards to pain scoring. As a result of randomization of a small group, the lidocaine test group had generally lower ASA scores, had spine surgeries on a higher number of vertebral levels and were more likely to also have instrumentation during their operation. Interestingly, on examination of Table 1, the placebo group had a larger proportion of those with chronic opioid use or that smoke. The authors concede that the two groups were not entirely identical, and adjusted the statistical analysis for the ASA scores and level of spine surgery only. (2) The remaining characteristics comparing the two groups were similar in proportion.

Data was collected via verbal pain scores and opioid consumption. Analysis was a joint hypothesis examining superiority and noninferiority via an "intersection-union test".(1) Lidocaine was found to be noninferior and superior with regards to pain, however it was only found to be noninferior to placebo with regards to opioid consumption. Superiority of lidocaine to placebo with regards to opioid use postoperatively was not significant ($p=0.12$) despite the adjusted mean total IV morphine doses being 74 mg for placebo group versus 55 mg for lidocaine, as seen by overlap in the variance of distribution. Interestingly, in Figure 3, both in the pain scores and initial morphine doses in the first four hours showed the greatest difference from the placebo group.

Secondary outcomes were also assessed in this study. In order to assess quality of life, the short form 12 (SF-12) was used which assessed: physical functioning, role functioning physical and emotional, bodily pain, general health, vitality, social functioning, and mental health. (7) Quality of life was significantly higher in the lidocaine group with higher SF-12 physical composite scores at 1 ($p=0.002$) month and 3 months ($p=0.04$). However, it is important to note that baseline quality of life assessments were not conducted. (1) Almost all secondary outcomes such as major complications (ie: pneumonia, respiratory failure, cardiac arrest, etc.), postoperative nausea and vomiting, duration of hospital stay were not found to be significantly different which included readmission, antiemetic use, and fatigue. The authors of the paper did concede that their study was not well powered to examine the secondary outcomes.

Discussion:

The study claimed to be one of the largest looking at the application of IV lidocaine in the perioperative setting. The conclusion was that intravenous lidocaine does decrease pain in spine

surgery patients, which was supported by the results with a small margin of improvement. The authors offer other possible explanations of how the difference may have occurred, suggesting that lidocaine may be operating through other mechanisms of action. The results although statistically significant, do not appear to be clinically relevant. Such a small difference in pain scores could easily change if the study was to be repeated, there is a small number of patients who had chronic pain, which can vary in different populations. There are currently no other published research papers assessing perioperative IV lidocaine specifically in spine surgeries. A study published in 2012 looked at perioperative pregabalin that was shown to be beneficial in reducing pain in spinal surgeries. (5) However, so far, current literature reviews suggest that they have generally only been found to be beneficial in abdominal surgeries.

From reading this paper, there does seem to be some role of perioperative lidocaine in reducing postoperative pain. Despite the lack of statistical significance, there was a larger difference noted in the postoperative opioid use. Also, in reference to the study by Grigoras et. al., they suggested that the decreased persistant pain after breast surgery may be due to prevention of hyperalgesia, perhaps explaining the improved quality of life in the lidocaine test group from Farag's study. (6) In order to further investigate this phenomenon, a larger study should be conducted. However, independently, I do not believe at this time that this study is sufficient enough to change my clinical practice in the setting of spinal surgery. The difference noted was small, and hardly any of the secondary outcomes were a significant improvement over the placebo group and the quality of life assessment was missing a baseline measurement. The other concern I have is that the maximum infusion was 200 mg/hr and continued for up to 8 hours postoperatively. According to UpToDate, the 300 mg dose for systemic lidocaine should not be exceeded or repeated within 2 hours. I would be concerned about the potential for toxicity if such large infusions were necessary in order to reduce pain. While completing this paper I was humored by the ease that a p value could suggest that a 1.1 difference was statistically significant finding. I also have a greater appreciation for reading through the paper in order to determine its clinical significance and that this can also be achieved without relying on excessive statistical analysis. Regardless, I do hope to improve my skills at critical analysis of statistics in the future.

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Critical Appraisal Article

By: **Curtis Nickel**, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication title: "***Treatment with neuromuscular blocking agents and the risk of in-hospital mortality among mechanically ventilated patients with severe sepsis.***"

Authors: ***Steingrub JS, Lagu T, Rothberg MB, Nathanson BH, Raghunathan K, Lindenauer PK.***

Crit Care Med. 2014 Jan;42(1):90-6.

Sepsis is an incredibly significant problem in today's healthcare system. It kills one in four and is increasing in incidence1. The Surviving Sepsis Guidelines by Dellinger et al1 reinforces the importance of early intervention having a significant influence on outcomes. Neuromuscular blockers are used widely in critically ill patients to facilitate intubation and assist with mechanical ventilation. However, the systematic use of neuromuscular blockers in the critically ill patients has yet to be formalized. Recent trials have investigated their use in patients admitted to the ICU with ARDS and have found increased survival if used within the first 48hrs of onset of ARDS2,3. However, patients suffering from ARDS are only a small subset of those admitted to critical care units.

The study produced by Steingrub et al4 entitled "Treatment With Neuromuscular Blocking Agents and the Risk of In-Hospital Mortality Among Mechanically Ventilated Patients With Severe Sepsis" and examined in this essay attempts to extend this new knowledge to a more general population of mechanically ventilated patients with severe sepsis. As such, Steingrub et al specifically examine the "association between receiving a neuromuscular blocking agent and in-hospital mortality in patients with severe sepsis and a respiratory source of infection who were treated with mechanical ventilation"(p. 91). This is an important extension of the current line of research, as it comprises a large percentage of patients in critical care units.

Methodology

Steingrub et al used an observational retrospective cohort study design for their research. This provides benefit in that it shows the temporal relationship between the exposure of neuromuscular blockers and mortality compared to a case-control study. It also allowed Steingrub et al to examine more than one outcome. This is an appropriate initial study design in a relatively new area of research. It is relatively easy to complete and inexpensive and assists in establishing new knowledge that can then be tested in a larger randomized control trial. While a retrospective study design is appropriate, it does have inherent biases with the possibility of misclassification, and loss to follow-up. As well, the validity of the results can be at risk due to confounding variables. The authors attempted to address these issues in their statistical analysis including regression, propensity matching, stratification, as well as instrumental variable analysis.

The patient population included adults with a diagnosis of sepsis based on billing codes who were admitted to an ICU, placed on a ventilator, underwent blood culture and were treated with antibiotics within the first two hospital days. Only patients with severe sepsis as evidenced by respiratory failure, and a respiratory source were included. The author's justification for this was that pneumonia was a common source of ARDS and the majority of previous research with neuromuscular blockers was in patients with ARDS making this population an appropriate extension of previous knowledge. Patients who died in the first 48 hours were excluded in order to avoid immortal time bias, as were those transferred to or from another facility due to the inability to determine onset or follow-up of their illness.

This patient population and exclusions is an excellent extension of the previous research. The justification for respiratory sources is adequate; however, it does limit the generalizability of the results as many patients present to the ICU with other sources of infection. In terms of follow-up and minimizing loss to follow-up the exclusion of those patients transferred to other sites is also appropriate.

Experimental Protocol

Data was mined from a large voluntary database that comprised standard discharge files as well as a log of all charges (medications, tests, interventions) provided to the patients. This provided them with detailed clinical information such as types of drugs used, co-morbidities, types of infection, and supportive therapies used. The cohort of patients treated with neuromuscular blockers was determined through the examination of the

pharmacy charge file and patients were included if they received one of seven neuromuscular blockers on at least one day during the first two days of admission. Succinylcholine was excluded as it is most often used only for induction.

This cohort was then matched to a patient not treated with a neuromuscular blocking agent using a Greedy Match algorithm. Patients who were matched had similar propensity for treatment based on a logistic regression analysis taking into account patient, hospital characteristics, and all other treatments and diagnostic tests.

The primary outcome of interest in this article was in-hospital morality. Numerous secondary outcomes were examined including the number of days on mechanical ventilation, and length of stay in both the ICU and hospital. Finally, they examined secondary diagnoses such as barotrauma.

The experimental protocol utilized in this article is excellent. It is appropriately designed to answer the author's hypothesis and is easily reproducible. The authors follow previously validated methods and explain their data source. Their primary endpoint is mortality, which is in line with their hypothesis. They also identify important secondary endpoints and examine them.

However, one major issue with the protocol is the source of data. It relies on detailed billing codes and as a result there is no chart review. This detracts from the understanding of the clinical reasoning associated with the use of certain medications or interventions. It also does not allow the author or reader to understand the exact protocols used to treat the patient. The authors do recognize this limitation and state it in the article.

Statistical Analysis

A detailed description of the statistical analysis employed by the authors is given within the article. The statistical analysis focused on minimizing selection and confounder bias, while still attempting to answer the hypothesis. In order to minimize selection bias beyond the propensity-matched cohort, a balance assessment was completed to ensure no there was no statistical different in the covariates between groups.

Multiple analyses were completed in order to minimize the effect of cofounder bias. Stratified analyses assessing for heterogeneity were employed in order to ascertain the importance of specific known confounders such as organ supportive therapies, age, and vasopressor usage. Two separate sensitivity analyses were completed; the first limiting the sample to patients receiving two consecutive days of neuromuscular blocker or dosages compatible with continuous infusion. The second examined how an unknown confounder might influence the effect estimate of neuromuscular blocker therapy. This unknown cofounder was given a specific mortality risk and estimated prevalence in untreated patients and effect was then quantified. Finally, an instrumental variable analysis was completed to address concerns regarding residual unmeasured confounding.

The statistical analysis employed in the article was very appropriate and well delineated. It was based on validated methods and assisted greatly in decreasing the inherent biases associated with a retrospective cohort study.

Results and Discussion

The study enrolled a total of 7, 864 patients after all inclusion and exclusion criteria were met from an original sample of over 70, 000. Treated patients tended to be younger, male, and more likely to receive vasopressors and other organ supportive therapies. A full covariate balance was achieved with 97% of treated patients being matched to a non-treated patient with similar propensity.

The authors found that the in-hospital mortality rate was 31.7% for treated patients vs. 36.1% in the matched controls, a risk ratio of 0.88, which was statistically significant. Length of stay in ICU and hospital did not differ significantly between the two groups. Treated patients had lower mortality in all strata and while the difference was not statistically significant, it did show a mortality benefit.

The effect of the first sensitivity analysis suggested an increased risk of mortality associated with neuromuscular blocking agents, (RR 1.10) but was statistically insignificant. The second sensitivity analysis determined that an unknown confounder associated with a 50% increased risk of mortality would only need to be in 10% of untreated patients to render the previously observed association insignificant. Finally, the instrumental analysis showed an estimated reduction in mortality similar to that from the matched analysis.

Based on these results, the authors concluded that the early use of a neuromuscular blocker in mechanically ventilated patients with severe sepsis from a respiratory source were less likely to die. It would appear from the results, that this conclusion is appropriate. There is a

statistically significant reduction in mortality, which is a very strong endpoint. This would be clinically significant in a population that has a high mortality rate already.

The authors did an excellent job of attempting to address bias and employed robust statistical analyses to their data. While each subgroup did not show a statistically significant benefit, it did show a mortality benefit that would likely be clinically significant. This correlates well with published research in ARDS that has recently shown a mortality benefit with use of neuromuscular blockers. Interestingly, the size of the benefit is much smaller in this study. The authors explain this through differing levels of severity of illness, with the current study having less severely ill patients. It may also be due to the inability to obtain information surrounding dosing and administration of the drugs and mechanical ventilation protocols.

A possibly important results occurs from the first sensitivity analysis, in that it found that the use of neuromuscular blockade for 2 consecutive days or at doses consistent with infusion were associated with increased risk of mortality. This was not a statistically significant result, but it does correlate with results found in the International Study of Mechanical Ventilation5. The authors don't follow-up on this due to the lack of statistical significance and state that the likely difference in mortality seen between the studies is due to the inclusion of only respiratory infections in the current study. It is important to consider that the use of neuromuscular blockers may only help in patients with significantly altered respiratory physiology due to ARDS or a respiratory source of infection and that this study cannot be generalized to the general ICU sepsis population.

Finally, the authors' felt their results were robust and could stand up to potential bias due to the various statistical methods they employed. I would tend to agree with their conclusion as they attempted to address a large number of confounders with their statistical techniques. However, as stated in the article their result is relatively sensitive to residual confounding as seen in the second sensitivity analysis. This does make it potentially more difficult to extrapolate these results to other patients were these confounding factors may be present.

Summary

Overall, the authors completed an excellent observational study examining the use of neuromuscular blockers in patients with severe sepsis due to a respiratory source and who where mechanically ventilated. They found a statistically significant mortality benefit in the early use of the medications. The statistical analysis performed was appropriate and assisted in minimizing the bias associated with this study design. However, the results are still sensitive to confounding bias and don't entirely correlate with previously published results.
I am encouraged by the results and conclusions drawn by the authors, but feel that caution needs to be exercised in interpreting the data due to the stated limitations and sensitivity to confounding factors. It may be that the majority of neuromuscular blocker use was for intubation, as the clinical reasoning behind the drug use was not available. If this were the case, the first sensitivity analysis showing an increased mortality in patients receiving 2 consecutive days or dosages consistent with infusion would be very important clinically.

I believe that while these results are promising, further experimental studies that control for confounding factors need to be established before this is put into widespread use.

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CRITICAL APPRAISAL ESSAY

By: **Navroop Sandhu**, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication title: "***Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction***"

Authors: ***Radtke, F.M., Frank, M., Lender, J., Kruger, S., Wernecke, K.D., and Spies, C.D.***

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INTRODUCTION

The Canadian population is steadily aging, with the proportion of those aged 65 or over rising from 7.6% in the 1960s to 15.3% in 20131. Aging itself is associated with a loss of global functional reserve, polypharmacy, and an increased susceptibility to many disease states 2. Thus, it is not surprising that the incidence of neurobehavioural complications associated with intraoperative care, mainly postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are also increased in this patient population3,4. Moreover, with 37% of all inpatient procedures in the US (as of 2010) being performed on those aged 65 and above, this will continue to be a significant burden to the health care system in the future5.

POD can be characterized by periods of lucidity after surgery, however, the clinical features of delirium become apparent most frequently between postoperative days 1 and 36. The incidence of POD reported in the literature ranges from 9% in patients over the age of 50 undergoing elective non-cardiac surgery7, to 18% in patients over the age of 65 undergoing emergency surgery4, and as high as 87% in elderly ICU patients8. POD is associated with increase costs to the health care system9, lengthier hospital stays10, and increased risk of morbidity and mortality11. Aside from age, other risk factors for POD include type and severity of surgery, medications, comorbid disease, baseline cognitive dysfunction, and metabolic disturbances12,13.

POCD, comparatively, is typically diagnosed based on neuropsychological tests, assessing memory and attention, and is characterized by a decline in cognitive function temporally related to surgery13. The incidence of POCD has been reported to be as high as 25% at 1-week postoperatively and 10% at 3-months3. No clear association between POD and POCD has been elucidated as of yet.

Given the toll these complications take on not only the health care system but the patient as well, it stands to reason that trying to prevent such neurobehavioural disorders would lead to better patient outcomes after surgery. Using bispectral index (BIS) monitoring, which estimates the depth of anaesthesia as a single value derived from Fourier transform analysis of electroencephalographic (EEG) data14, Radtke et al. 15 set out to determine if tailoring anaesthetic delivery based on neuromonitoring could reduce the incidence of delirium in postoperative patients.

METHODOLOGY

The study itself is a dual-centered, double-blinded, randomized, prospective, parallel group trial. It was specifically aimed at assessing the affect that monitoring the depth of anaesthesia has on the incidence of POD. Approximately 13, 605 patients were initially screened for eligibility and of those 1277 patients were enrolled over the course of 15-months. Patients were initially stratified according to the American Society of Anaesthesiologists' Physical Status (ASA PS) scale (I or II vs. III or IV) and then subsequently randomized into the two study groups, BIS monitoring versus routine care with blinded-BIS monitoring. Patients were allocated to appropriate operating rooms through an operating theatre coordinator, who was not involved in any other aspects of the study save for selecting the anaesthetists. In terms of intraoperative monitoring, each patient had bilateral BIS electrodes applied to his or her forehead as per the manufacturer's recommendations prior to the induction of anaesthesia. In the BIS-blinded group, however, only the signal quality indicator was visible. Data was collected at 1-minute intervals and electronically recorded in both groups.

The study population was blinded as to whether or not BIS-monitoring was used to tailor the delivery of anaesthetic but for obvious reason the operating room staff was not. To keep things consistent, anaesthetists remained in the same arm of the study throughout. Additionally, the group carrying out the POD and POCD testing were unaware of "treatment" allocation.

Patients included in the study were at least 60 years old, and underwent elective surgery expected to last a minimum of 60 minutes under general anaesthesia.

Surgical interventions included most elective surgical procedures (Table 1). The following exclusion criteria were employed: Mini-Mental State Examination (MMSE) score of < 24, patients with a history of neurological deficits, participation of the patient in a pharmaceutical study, patients not undergoing general anaesthesia, and patients who did not speak the local language (as verbal responses were needed for all tests) or who were unable to provide written informed consent. These exclusion criteria were appropriate, as baseline issues with cognition or language would have confounded the results of the POD and POCD testing.

I feel that the clinical conditions in this study are similar to my own practice. The majority of the cases I see are elective and the patient population in Kingston tends to be slightly older and thus at a higher risk of POD. The study, itself, is ethically sound and was granted ethics approval by the institutional review board.

The experiment is adequately designed to test the hypothesis. Patients received pre-, intra-, and postoperative treatment as outlined in the institutional standard operating procedures16 (SOP) and anaesthesia and analgesia were provided as outlined by Mei et al.17. The dosing of various drugs was in accordance with standard regimens but up to the discretion of each anaesthetist. The methodology has been validated and is detailed enough to be reproducible. Additionally, the protocol is clinically relevant as it is in keeping with current Canadian practice.

While reviewing the experimental protocol, however, I have identified a few problems. One of the first things that caught my eye was the fact that the investigators noted the use of sedative premedication. Specifically, midazolam at a dose of 0.1 mg/kg was allowed according to the institutional SOP. However, no mention was made in the paper in regards to how many patients in each group received midazolam or the doses actually given to patients. I question the use of midazolam in this study, as the same research group previously established that sedative premedication significantly increases the risk of emergence delirium18. Other studies have shown a dose-dependent relationship between midazolam and POD, with each mg of midazolam increasing the risk by as much as 7-8%19,20. Moreover, given the correlation between episodes of intraoperative hypotension and the incidence of POD19,21, it would have been nice if the author's specified what degree of hypotension was tolerated in the study, how it was treated, and the frequency of such events in each group. Furthermore, the study itself is underpowered. A sample size of 1450 (n=725 per group) would be required to reach a statistical power of 80% as desired by the investigators. The trial was stopped prematurely due to funding limitations.

The primary endpoint of this study was the assessment of POD with POCD and 3-month mortality being secondary endpoints.

Delirium screening was conducted twice daily (in the morning and at night) by trained medical personnel under the instruction and supervision of a psychiatrist and delirium experts from postoperative days 1-7. POD was assessed and diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders IV. The authors assumed that the expected incidence of POD was 15% and that anaesthesia with additional BIS monitoring was expected to reduce the incidence of early delirium to 10% (33%) in order to be considered relevant clinically.

POCD, on the other hand, was evaluated through a battery of neurophysiological tests that included: a motor screening test, two tests of visual memory (spatial and pattern recognition memory), one test of attention (choice reaction time), one test of colour word inference, and one test of visual verbal learning. Testing was done on the evening before surgery, and on postoperative days 7 and 90 (or as soon as possible thereafter). All tests were carried out at the same time of day. The reliable change index (RCI) was used to establish the definition of POCD, which is defined as the change in a patient's score divided by the standard error of the difference test(s) being used22. For this assessment, an age- and MMSE-matched control group consisting of 93 testers aged 60 and older not undergoing surgery were used. POCD was defined in the following way: an RCI score of <-1.96 on ≥ 2 tests, a combined Z score was <-1.96, or both.

Statistical analysis involved the computation of descriptive statistics for all study variables. Continuous variables were expressed as the arithmetic mean standard deviation with 95% confidence intervals, while discrete variables were expressed as frequencies with percentages23. Regression coefficients and odds ratios with 95% confidence intervals were computed using logistic regression analysis. Differences between groups were assessed using the Mann-Whitney U-test for continuous variables and the x2 test for categorical data. Statistical significance was set at a two-tailed P-value of <0.05. Multiple logistic regression with delirium as an endpoint was carried out using the following variables: age, duration of surgery, MMSE score, ASA PS, delirium, %BIS <20, and BIS open vs. blinded. For the sake of consistency the same features were used in the calculation of 3-month mortality.

RESULTS

The groups are fairly well balanced as outlined in Table 1. The duration of surgery in the BIS-guided group was shorter (Table 2) but this was not found to be a statistically significant difference (P=0.055). Additionally, the years of training of the anaesthesiologist's in each arm of the study was similar (4.03 yr vs. 4.14, P=0.427).

A total of 1277 patients were randomized, 638 were assigned to the BIS-guided anaesthesia group and 639 to the BIS-blinded anaesthesia group. Of those in the BIS-guided "treatment" arm of the study, 45 were excluded from the initial study and 18 lost to follow-up. Comparatively, in the BIS-blinded group, 39 were excluded from the initial study and 20 lost to follow-up. Thus, only 575 patients in the BIS-guided group and 580 in the BIS-blinded group were actually included in the analysis. A total of 141 patients in the BIS-blinded group were "unblinded" during the course of their procedures. The investigators performed a modified intention-to-treat (ITT) analysis including these "unblinded" patients but excluded those that were lost to follow-up and those that did not participate in the study after randomization.

As indicated in Table 2, a total of 191 patients (18.8% of the study population) were found to have POD, 95 patients in the BIS-guided group (16.7%, 95% CI: 13.9–20.0) compared to 124 patients in the BIS-blinded group (21.4%; 95% CI: 18.3-24.9%) and this was found to be a statistically significant difference (P=0.036). Radtke et al. 15 also performed a per protocol (PP) analysis, including all "unblinded" patients in the BIS-guided group. The results of this analysis, however, showed a non-significant association between the two study groups and POD (P=0.052; 4.7%, 95% CI, 0-9.5%).

Delirium was found to be associated with a longer hospital stay, a higher incidence of POCD on the 7th postoperative day, and an increased mortality at 3-months (P=0.015; OR=2.05, CI=1.15-3.65). The study results also showed that ASA PS and delirium were independent risk factors for mortality after adjusting for duration of surgery (Figure 3). POCD, as shown in Table 2, was increased in the BIS-blinded group on postoperative day 7 (90 (23.8%) vs. 70 (18.1%), P=0.062). A similar trend was seen on the 90th postoperative day (28 (10.3%) vs. 21 (8.0%); P=0.372). However, neither result was found to be statistically significant.

DISCUSSION

The main conclusion of the study was that the use of BIS-monitoring to titrate the delivery of anaesthetic versus routine anaesthetic care reduces the incidence of POD in the elderly. This is supported by the results of univariate analysis (p=0.036, Table 2). The study authors make multiple mentions of conducting an ITT analysis but do not actually perform a true ITT analysis. None of the patients that failed to complete the full study were included, although, these patients can be justifiably excluded due a lack of clinical data. Also of note, is the fact that, the PP analysis did not show a significant difference between the two groups in terms of the incidence of POD. This definitely reflects a limitation of the study in that not all patients were able to adhere to the study protocol to which they were randomized. Additionally, the incidence of POD in the "unblinded" population was 19.9% (28/141), which is actually in-between the two study groups (16.7% and 21.4%). It can be argued that a PP analysis is more reflective of true treatment differences24. However, in the case of a "superiority trial", the ITT analysis is considered primary and PP analysis merely supportive25. I wonder if the fact that the study is underpowered (another limitation) accounts for the differences in the two analyses.

Another interesting finding of the study is the fact that mean BIS values (both absolute and relative) only differed significantly in the lower < 20 range between the two groups (Table 2). The author's attributed this to each anaesthetist either not following instructions regarding the use of the monitor or due to an inability to obtain the desired range (40-60) in the clinical setting. However, the average burst suppression ratio (the % of suppression during burst suppression pattern) and occurrence of BIS values < 20 (both relative and absolute) were increased in the BIS-blinded group and this was found to be statistically significant (Table 2). Burst suppression is a pattern on EEG characterized by alternating periods of high-voltage electrical activity and no electrical activity, and is found in patients with inactivated brain states (e.g., general anaesthesia)26. According to Bruhn et al.27 there appears to be a linear correlation between BIS values < 30 and the burst suppression ratio, and thus the author's infer that BIS monitoring aided in avoiding low BIS values and that this may have accounted for a lower incidence of POD.

The investigators also state that univariate analysis showed a correlation between POD and BIS values in terms of absolute numbers and in relation to surgical duration (%), "significantly more often"15. However, the statistics associated with this assessment are never stated in the paper. Multivariate analysis (Figure 2) does show a statistical correlation between the percentage average BIS < 20 and POD (P=0.006, OR=1.027). MMSE score, age, and duration of surgery also seem to be correlated with POD in multivariate

analysis (Figure 2) but this was not established in univariate analysis. The fact that each variable is only significant in multivariate analysis would seem to indicate that each is only significant in the context of the others. Other known risk factors associated with delirium (i.e., low MMSE score, higher age, ASA PS, duration of surgery, prolonged fluid fasting, and surgical specialty)28 did not differ between the two study groups. Moreover, despite an association between delirium and the length of hospital stay, a higher incidence of POCD and an increased incidence of mortality (P=0.015), when one compares the two study groups in Table 2, no statistically significant difference in mortality (P=1.000), postoperative length of stay (P=0.818), or the incidence of POCD (P=0.062) is seen. Likewise, no statistical correlation was elucidated between BIS monitoring and a decreased incidence of POCD on postoperative day 7 or 90 in this study. I wonder if this had something to do with the subjectivity of the battery of neurophysiological testing employed.

Are the results clinically significant? Radtke et al.15 established that they required a 33% decrease in the incidence of POD in the BIS-guided group to consider it significant clinically. If one compares the frequency of POD in the two groups, a mean of 16.7% in the BIS-guided group compared to 21.4% in the BIS-blinded group, the incidence was only actually reduced by ~22%. Thus, by the investigators own caveat the results are likely not too relevant clinically. Furthermore, while % BIS < 20, duration of surgery, MMSE, and age were found to statistically significant when comparing patients with and without POD (Figure 2), none seem to be very clinically significant based on odds ratios. The same can be said of the results obtained in the multivariate analysis of 3-month mortality (Figure 3). This is likely due insufficient sample size.

The fact that sedative premedication was given to patients with no information regarding the mean or range of doses administered and no mention was made in regards to the degree of hypotension tolerated in the study is problematic. Moreover, many experts question the reliability of BIS monitoring to give information regarding anaesthetic depth29. The full details of the algorithm are unknown, the calculation is not based on any physiological model of brain function, and it is insensitive to certain anaesthetic agents (e.g., nitrous oxide and ketamine).

The most interesting revelation of this study was the result of post hoc analysis showing that episodes of deep anaesthesia (BIS < 20) were independently predictive for POD (P=0.006, OR 1.027). This is something that is worth exploring, specifically if the same correlation can be found in a sufficiently powered study.

This paper is one of the first looking at using a measure of anaesthetic depth as a means to try to prevent POD. I did not come across any studies showing a clear correlation between BIS-guidance and an influence on POD, POCD, or mortality. Ultimately, there does appear to be a correlation between extreme low BIS values and the incidence of delirium, thus this study could have some interesting implications in more high-risk surgical patients. However, the results I feel are not generalizable to all patients undergoing elective surgery aged 65 and above.

APPLICABILITY OF THE STUDY

By reading this paper and reviewing the literature on POD and POCD, I have not only learned a great deal about factors precipitating these complications but it has also made me even more aware of how my anaesthetic choices can influence a patient's postoperative course.

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Critical Appraisal Essay

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Publication: "***Residual neuromuscular blockade affects postoperative pulmonary function***."

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Introduction

Critical appraisal is an important skill for anesthesiologists to develop. There is a constant influx of new literature being presented as well as innovative drugs, technologies and techniques that all promise to remedy the gaps in current practice. Whether the study is a cohort study, case study or randomized control trial, all information should be reviewed for its scientific rigour and impact on current practice.
In 2012, Kumar et al. published a prospective randomized cohort study on the effects of various neuromuscular blocking agents on pulmonary function tests. Prior to the study it was known that residual neuromuscular blockade was associated with postoperative respiratory complications and they hypothesized that these complications would be found on pulmonary function tests in the immediate postoperative period. In this essay, the abovementioned study will be critically appraised using the tools provided from Queen's Department of Anesthesiology website.

Critical Appraisal

Residual neuromuscular blockade (RNMB) is recognized to be associated with respiratory complications postoperatively; however, this study is unique in quantifying the effect of RNMB on pulmonary function in the immediate postoperative phase. The title provides a simple, clear description of the purpose and outcome of the paper. It does not mention the study design nor is does it specify which parameters of the pulmonary function tests were affected with RNMB. The abstract provides an informative and balanced summary of the background, methods, results and primary conclusion. The authors of this paper are all from Manipal Hospital, a tertiary care centre and teaching hospital, in Bangalore India. The hospital has been accredited with the AAHRPP (Association for Accreditation for Human Research Protection Program) certifications. In addition, this article received ethics approval through the institutional review board (Hospital Ethics Committee for Human Research) and has been selected for a Continuing Medical Education (CME) Program.

The short introduction of the paper briefly describes the importance of recognizing RNMB as a contributor to complications in the post-anesthesia care unit (PACU). It also addresses patient and surgical factors that lead to postoperative respiratory complications including pain, incision site, obesity, etc. From a brief literature review, there have been a number of studies that have looked at the incidence of RNMB in the PACU using a TOF <0.9. Despite the increased awareness and use of reversal agents, the literature suggests that patients continue to arrive in the PACU with RNMB (Naguib et al. 2000, Murphy et al. 2010). The literature further recognizes RNMB as a contributor to respiratory compromise in the post-anesthetic setting.

Other studies have been designed to look at mild degrees of residual block on pharyngeal and respiratory muscle function using manometry and videoradiography. As recently as February 2014, Cedborg et al. (2014) published an article describing the effect of partial neuromuscular blockade on pharyngeal function of breathing and swallowing in the elderly population. The study found an increased incidence of pharyngeal dysfunction with impaired ability to protect the airway at TOF of 0.7-0.8; however, was unable to demonstrate a link between coordination of breathing and swallowing and the degree of neuromuscular blockade.

Kumar et al. hypothesized that RNMB would cause a reduction in pulmonary function in the first hour postoperatively. The background information they provided suggested they expected the RNMB to result in a restrictive respiratory pattern (Eikermann et al. 2003) and thus opted to specifically look at forced vital capacity (FVC) and peak expiratory flow rate (PEF). They further designed the experiment to include different neuromuscular blocking agents, but did not hypothesize how the outcomes would vary between the different agents. By testing this hypothesis, the study helps quantify the physiological decrease in pulmonary function caused by residual neuromuscular blocking agents in the first hour postoperatively.

METHODS

As aforementioned, the study was designed as a prospective randomized cohort study with 150 human participants. The 150 participants were randomly assigned to one of three neuromuscular blocking agents, vecuronium, atracurium, or rocuronium, using an Excel randomly generated table that aimed to match age, sex, weight, height, body mass index, and type of surgery. The data were collected over a two year period. Neither the anesthesiologist nor the investigator were blinded to which agent was used. The patients were all given the same reversal agent and the time this occurred was documented. In the PACU, the degree of RNMB was assessed using an acceleration transducer and nerve stimulator as previously described in other studies. The train-of-four (TOF) was documented every five minutes in the PACU. If at the time of the PFTs, it was <0.9 then the patient was categorized as having RNMB present. Pulmonary function tests were performed when the patient felt able and willing to perform the test irrespective of their TOF score. Combining all of the results, only 39 of the 150 patients had PFTs with RNMB present. Thus just over one quarter of the patients had residual neuromuscular blockade at the time of PFTs after reversal and being sent to the recovery room. The authors selected this sample size based on the expected incidence of RNMB based on a previously published meta-analysis as well as the calculation for sample size estimation for proportions. To be safe, they increased the expected number of participants per group from 28 to 50 (an increase of 44%). For each subgroup, the authors were able to comment on whether RNMB altered pulmonary function, but were unable to accurately compare the different groups due to the small sample size.

The inclusion and exclusion criteria were determined to minimize confounders and ensure patient safety. Patients were included if they were healthy adults undergoing elective procedures that were less than 3 hours. Exclusion criteria included specified medical conditions, extremes of age, smoking, certain types of surgery, and obesity, all of which could alter pulmonary function after an anesthetic. All patients selected to participate were exposed to the same methodology, but it was their own response to the residual neuromuscular blockade in the PACU that divided them into RMNB-present or RNMB-absent groups postoperatively. This helped minimize the risk of selection bias. Furthermore, having a quantifiable cut-off helped minimize bias; however, the measurement of TOF using acceleromyography does produce inconsistencies. A study by Baillard et al. (2000) found that TOF ratios measured even at thirty second intervals varied in awake patients. In this study, the time between TOF measurements was five minutes. Continuous recording of acceleromyography may have provided more accurate results, but would have been uncomfortable for participants. Bias was also minimized by anesthesiologists charting during each case and not retrospectively days-months later. The authors did address the concern of the variability of TOF recordings in the PACU in their discussion of the limitations. All patients were included in the analysis.

The primary anesthesiologist was given a predetermined cocktail of induction agents, inhalational anesthetic (to maintain blood pressure within 20% of baseline), and opioids (at a per kilogram dose), with the only controlled variables being the neuromuscular agent selected and any further muscle relaxation. The authors, however, do not comment if further analgesia could be or was provided to patients either in the operating room or in the PACU. Given that we know that opioids decrease respiratory drive, this could be a source of bias or a confounding variable not addressed. The reversal and time to the PACU followed normal operating room procedures and were not altered to meet study design.

The experimental protocol was well designed to test the hypothesis. The study provided enough details to be reproducible including the name, dose and frequency of drug administration, trade names of spirometry and TOF equipment as well as the details of the patients in each group. While PFTs are not normally conducted postoperatively, the study does provide new data on the effects of RNMB on pulmonary function.

Analysis of the data was conducted using standardized model for comparing means and different groups of similar data. Statistical significance was defined as a P value of less than 0.05. To compare the means of the three groups with respect to demographic data and other study variables, ANOVA or chi-squared tests were used as appropriate. Similarly they used paired student t-tests to compare pre- and postoperative PFT parameters. They used the Bonferroni correction to control the number of false positive that would be obtained for multiple comparisons (P = 0.013).

RESULTS

The results demonstrated that the three groups were comparable with respect to demographic data, type of surgery, and pre-operative PFT (P-values >0.05). Similarly the P-values were not significant for differences between the duration of NMB, time to reversal of obtaining a TOF >0.9, time of reversal to

postoperative PFT. There were, however, significant differences between the three groups with respect to TOF ratio on arrival in the PACU, TOF ratio at time of PFT, and whether the patients required top-ups or infusions of neuromuscular blocking drugs during the procedure. The latter is in part a consequence of variability in practice among anesthesiologists and more importantly a variable that furthers the difficulty in comparing the three agents used in this study. The other two groups that needed to be compared were the groups of RNMB-present and RNMB-absent. As above, the groups were statistically significant from a demographics perspective. They did differ in their time from reversal agent administration to PFT. Interestingly, the study found that it was longer in the group with RNMB-absent, likely because of the voluntary nature of PFTs. These patients may not have felt able to participate before the RNMB had faded to a more normal physiological level.
For the comparison of pre- and postoperative PFTs, the authors specifically looked at forced vital capacity (FVC) and peak expiratory flow rate (PEF). They found no statistical difference between the patients with RNMB-present versus absent for either FVC or PEF when comparing postoperative values as a percentage of preoperative values for each neuromuscular blocking agent with the exception of FVC for patients receiving vecuronium. The authors attribute this to the sample size of the study. Because of the relatively small changes, they felt that this study may have been underpowered to look at each agent; however, the investigators were able to report a significant difference for both PEF and FVC between RNMB-present and RNMB-absent when comparing postoperative values as a percentage of pre-operative values (PEF: $P<0.008$; FVC: $P<0.001$) when all patients were combined. The graphical and tabular data ensure that the results are clearly explained in the paper.

DISCUSSION

The discussion was divided into three sections: the incidence of RNMB, the effect of residual paralysis on PFTs, and limitations. In the first section, the authors discuss whether their reported incidence of RNMB was comparable to previous studies where there was no intraoperative TOF monitoring. They reported 57% of patients in this study had a TOF <0.9 when they arrived in the PACU. This was compared to a meta-analysis by Naguib et al. who reported a mean incidence of RNMB of 54.4% in patients who used intermediate acting NMB agents. They further discussed which agent had the lowest RNMB on arrival in PACU; however, this was neither useful nor accurate as the administration of neuromuscular blocking agents was left to the discretion of the anesthesiologist and thus not amenable for direct comparison.
As mentioned in the discussion of the results, the authors found a statistically significant change between the PEF and FVC values preoperatively to postoperatively. They attributed this finding to evidence that general anesthesia depresses pulmonary function for several hours postoperatively (Berg et al. 1997, Mimica et al. 2000). They further described a significant difference between patients with RNMB-present to RNMB-absent when comparing the postoperative value of FVC and PEF as a percent of preoperative value. They attribute this difference to RNMB. Unfortunately, they do not comment on other possible confounders or bias in their discussion. When they looked at the individual agents; however, they were unable to demonstrate a significant difference between RNMB-present and RNMB-absent with the exception of vecuronium on FVC. The investigators attributed to each group being underpowered in terms of sample size despite their efforts to select sample size based on the abovementioned algorithm.
In the discussion of their limitations, they mention three factors which weaken their study. The first is the use of TOF and acceleromyography as it is a discrete measurement and is subject to variability. The second limitation is that they only recorded one set of PFT values and recognized that serial PFTs over an extended time period would have allowed them to track the recovery of PFT values postoperatively. Finally, they mention that the study may have been underpowered to compare three different agents.
The authors do not discuss other potential or unknown confounders of the results. They had a systematic approach to identify and ensure known confounders (such as age, BMI, type of surgery) were evenly distributed among the three neuromuscular blocking agents and again among the RNMB-present and RNMB-absent group. Both of these tables were published in the article showing no significant difference between the groups. Unfortunately, they only briefly mention that general anesthesia is known to reduce pulmonary function. They do not elaborate on which components of general anesthesia are the potential confounders. They did ensure that all patients had roughly the same anesthetic with the only differences being the amount and type of neuromuscular blocking agent. They do not discuss what if any medications were given in the PACU. PFTs are voluntary tests and require patient participation. This in itself can contribute to a difference in patient effort between the two groups. The authors mention that most patients were able to complete the PFT within 30 minutes of their anesthetic, but four required closer to one hour (the time limit they had set). The authors did not mention what the potential reasons for the time variance were or if they could have contributed to changes in the pulmonary function tests.

Conclusion

In conclusion, I believe this study was well done. For a prospective cohort study, it ensured that the groups were statistically similar and that they could control potential confounders during the anesthetic. This study was adequately powered to determine if a relationship exists between RNMB and PFTs; however, it was underpowered to compare the three different neuromuscular blocking agents. The results of this study help us quantify the effects of RNMB on pulmonary function in the first hour postoperatively or while the patient is still in the PACU. It affords us a better understanding of potential respiratory complications post-operatively. In the future, there will be further opportunity to trend PFTs as RNMB wears off. Similarly, with a larger sample size, one may be able to quantify a relationship between RNMB and the degree of change in pulmonary function.

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