

Queen's University
30th Annual Anesthesiology Research Day

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Queen's Anesthesiology Postgraduate Medical Secretary:

Mrs Kim Asselstine

****The Royal College of Physicians & Surgeons of Canada, Region 3 Advisory Committee,
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Queen's University 30th Annual Anesthesiology Research Day

SCIENTIFIC PROGRAMME

0830 – 0840 Opening Remarks – Dr. Joel Parlow

0840 – 0845 Research Day Introduction – Dr. Elizabeth Van Den Kerkhof

0845 – 0930 **Dr. Dean Tripp** PhD, Associate Professor, Department of Psychology, Urology & Anesthesiology, Queen's University
"An Emerging Biopsychosocial Model of a Male Chronic Pelvic Pain Syndrome"

0930 – 1030 Oral presentations (see list below)

1030 – 1100 Poster presentations (see list below) and nutrition break

1100 – 1200 Oral presentations (see list below)

1200 – 1300 * LUNCH (provided) * St. Laurent Room, 5th floor

1300 – 1415 Oral presentations (see list below)

1415 – 1445 Poster presentations (see list below) and nutrition break

1445 – 1515 Oral presentations (see list below)

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

The Judges will be:

Dr. Karen Brown, Professor, Department of Anesthesiology, McGill University

Dr. Eric Dumont, Assistant Professor, Department of Anesthesiology, Queen's University

Dr. Louie Wang, Assistant Professor, Department of Anesthesiology and Pharmacology & Toxicology, Queen's University

1515 **Dr. Karen Brown**, Professor, Department of Anesthesiology, McGill University, Speaker of the Royal College of Physicians & Surgeons of Canada, Region 3 Advisory Committee
"Opioid Sensitivity and OSA in Children"

Followed by a Wine and Cheese Reception *Awards Presentation *

Order of Oral Presentations

- 0930 Dr. Devin Sydor, PGY-4, Queen's Anesthesiology**
"A randomized controlled trial comparing two doses of spinal bupivacaine for total knee arthroplasty and the impact on recovery time" (research update/data presentation)
- 0945 Dr. Chantelle Peter, PGY-3, Queen's Anesthesiology**
"Retrospective Chart Review: Post-operative Respiratory Events in Patients with Obstructive Sleep Apnea Monitored by Overnight Remote Oximetry" (research update/data presentation)
- 1000 Dr. Tracy Cupido, PGY-2, Queen's Anesthesiology**
"Trigger Point Injection Study (TPIS)" (research proposal)
- 1015 Anne Sutherland, MSc Candidate, Queen's Pharmacology & Toxicology**
"DOR enhanced antinociception in chronic pain states is consistent with M/DOR oligomer formation" (research update/data presentation)
- 1030 Poster Presentations & Nutrition Break**
- 1100 Dr. Samia Ali, PGY-4, Queen's Anesthesiology**
"The impact of anesthetic induction drugs on the intraoperative electroencephalogram" (research update/data presentation)
- 1115 Alex Mattioli, MSc Candidate, Queen's Pharmacology & Toxicology**
"Attenuation of morphine-induced astrocyte activation and tolerance development by ultra-low dose naltrexone" (research update/data presentation)
- 1130 Dr. Jason Denis Cyr, PGY-2, Queen's Anesthesiology**
"The impact of stress on the management of medical crises in a simulated environment" (research proposal)
- 1145 Dr. Andrew Lee, PGY-3, Queen's Anesthesiology**
"The effects of intraperitoneal ketorolac on postoperative pain following laparoscopic cholecystectomy" (research update/data presentation)
- 1200 Lunch**
- 1300 Dr. Stacy Ridi, PGY-3, Queen's Anesthesiology**
"The CaRMs Game: What factors influence Anesthesia applicant's rank list?" (research update/data presentation)
- 1315 Dr. Drew McLaren, PGY-2, Queen's Anesthesiology**
"Canadian Anesthesia Workforce Assessment 2009" (research proposal)

- 1330 Dr. Angela Hogan, PGY-4, Queen's Anesthesiology**
"Postoperative Analgesia after Total Knee Replacement: Comparing the analgesic efficacy of the lumbar paravertebral block and the femoral "3-in-1" nerve block" (research update/data presentation)
- 1345 Dr. Tammy Henderson, PGY-4, Queen's Anesthesiology**
"An In Vitro Study Of MRI-Related Heating At 3.0 Tesla Of An Epidural Catheter" (research update/data presentation)
- 1400 Mr. Sanjho Sriandarajah, MD Candidate 3rd year, Queen's Medicine**
"The Measurement Of Movement-Evoked Pain In Postoperative Analgesic Trials" (research update/data presentation)
- 1415 Poster Presentations & Nutrition Break**
- 1445 Dr. Jason McVicar, PGY-2, Queen's Anesthesiology**
"Pediatric Risk Factors for Anxiety at the Induction of Anesthesia" (research proposal)
- 1500 Dr. Jeremi Mountjoy, PGY-3, Queen's Anesthesiology**
"Effects of patient controlled analgesia pump feedback on post-operative pain: can enhanced pump-feedback improve pain control" (research update/data presentation)

Poster Presentations

Ellis J, Cahill CM. **Attenuation of morphine-induced increases in the expression of CGRP and the development of tolerance by ultra-low dose atipamezole**

Grenier P, Cahill CM. **The Role of Glial Activation on δ -Opioid Receptor Trafficking in Neuropathic Pain**

Krawczyk M, Sharma R, Schizkoske A, Dumont E. **Altered excitatory synaptic transmission in cocaine-addicted rats**

Lecour S, Cahill CM. **Spinal administration of a delta opioid receptor agonist may attenuate neuropathic pain via modifying glial activation**

Magnussen C, Sutherland KA, Olmstead MC, Cahill CM. **Conditioned place preference predicts drug effectiveness in alleviating neuropathic pain**

Ong EW, Cahill CM. **Opioid receptor heteromer trafficking**

Philbrook M, Nakatsu K, Cahill CM. **Targeting hemo-oxygenase enzymes as a novel strategy for treating neuropathic pain**

Walker S, VanDenKerkhof EG. **Waiting for Care: Symptoms and Healthcare Utilization of Women Waiting for Gynaecological Surgery**

Zhang KM, Tripp DA, Hsieh AY. **Observer pain estimation accuracy and empathy in cultural concordant and discordant dyads**

Critical Appraisals

Gerlach R., PGY1
Queen's Anesthesiology

Incidence and predictors of difficult and impossible mask ventilation

Grant B., PGY1
Queen's Anesthesiology

Randomized, controlled clinical trial of point-of-care limited ultrasonography assistance of central venous cannulation: The Third Sonography Outcomes Assessment Program (SOAP-3) Trial

Langdon M., PGY1
Queen's Anesthesiology

Effect of propofol and sevoflurane on coughing in smokers and non-smokers awakening from general anesthesia at the end of a cervical spine surgery

Mahaffey R., PGY1
Queen's Anesthesiology

Haloperidol Versus Ondansetron for Prophylaxis of Postoperative Nausea and Vomiting

PRESENTATION ABSTRACTS

Sydor D, Engen D, VanDenKerkhof EG, Orr E, Dumerton Shore D, Jaeger M.

A randomized controlled trial comparing two doses of spinal bupivacaine for total knee arthroplasty and the impact on recovery time

Introduction: Prolonged recovery times in post anesthesia care unit (PACU) lead to delays and potential cancellations of subsequent operative cases. At our institution discharge from PACU requires spinal regression to a level of T8 or below, and postoperative regional blockade is performed after regression to T12. The purpose of this study was to assess the effect of reducing the dose of spinal isobaric bupivacaine for unilateral total knee arthroplasty on recovery time.

Methods: In this triple-blinded randomized controlled trial patients admitted for unilateral total knee arthroplasty for osteoarthritis were assigned to receive a lower dose (9mg) or a higher dose (13mg) of spinal isobaric bupivacaine with the same dose of fentanyl and morphine. The primary endpoint was time from arrival to PACU to sensory regression to T12. Secondary endpoints were sensory dermatome on arrival to PACU, time of spinal injection until regression to T12, conversion to general anesthesia (GA), use of vasopressors, supplemental intraoperative analgesia, and duration of surgery. Data analysis included t-test, chi square, Mann Whitney U, relative risk and Cox proportional hazards modeling.

Results: 140 patients were randomized to each of two groups (55 males and 85 females). Mean age was 70 years and mean BMI was 31. Demographic characteristics were not different between groups. Time from arrival in PACU to T12 was 0:57h (sd=0:51) in the lower dose group and 1:37h (sd=0:58) in the higher dose group (Mann Whitney U=1460, $p<.01$). Fifty percent of patients in the lower dose group had achieved sensory regression to T8 upon arrival to PACU compared to 31% of the higher dose group (RR=1.6, 95% CI 1.1, 2.4). Mean time from injection to T12 was 2:42h (sd=0:45) vs. 3:17h (sd=0:49) ($t=4.2$, $p<.01$). Surgery time (1:20h vs. 1:20h) and time from spinal injection to incision (0:12h vs. 0:13h) were not different between groups. Three patients in the lower dose group and 2 in the higher dose group required conversion to GA. When patients who were converted to GA were excluded from the analysis the time to T12 was 2:44h vs. 3:19h. Patients in the higher dose group were more likely to require vasopressors (26% vs. 10%, RR=2.6 (95% CI 1.1, 5.8), while patients in the lower dose group were more likely to require supplemental intraoperative analgesia (13% vs. 2.9%, RR=4.5 (95% CI 1.0, 20.1). After controlling for vasopressor use, analgesic use, and conversion to GA, time to T12 remained significantly higher for the higher dose group (RR=2.1 (95% CI 1.5, 3.1; $p<.01$).

Discussion: This study demonstrated that lowering the dose of spinal isobaric bupivacaine for unilateral total knee arthroplasty reduced immediate postoperative recovery time by 40 minutes leading to earlier achievement of discharge criteria and the performance of postoperative regional blockade.

Peter C. Turner T, Froese A.

Retrospective Chart Review: Post-operative Respiratory Events in Patients with Obstructive Sleep Apnea Monitored by Overnight Remote Oximetry

The purpose of this research is to explore the relationship between post-operative oxygen desaturations captured by remote oximetry in patients with Obstructive Sleep Apnea Syndrome (OSAS) and the possible association of these events with: perioperative CPAP use/treatment, surgical procedure, type of anesthetic and post-operative analgesia, and extraneous oxygen use.

During the last 10 years OSAS has become widely recognized not only by the medical but also lay community, as an important disease with significant implications on the cardiovascular and cerebrovascular systems, not to mention, the daily functional impairment associated with sleep-fragmentation. It is believed that patients with OSAS are at particular risk for worsening of their disease during the perioperative period because of the effect of surgery on sleep architecture and the use of sedatives, hypnotics, and narcotics used during the anesthetic and for post-operative analgesia. Concern for the care of these patients prompted the American Society of Anesthesiologists (ASA) to appoint a task force to review published evidence and poll expert opinion to build consensus for practice guidelines for the perioperative management of patients with OSAS. Many Canadian hospitals, including Kingston General Hospital (KGH), have adopted a version of these 2006 guidelines.

To date there are no published studies evaluating the use of these guidelines and any change in patient morbidity and mortality since their institution. Currently at KGH all patients undergoing post-operative remote oximetry have a comprehensive printed report detailing the frequency and magnitude of oxygen desaturations experienced during their first night after surgery. Although such data is available, no formal evaluation has been made to correlate respiratory events in these patients with the clinical aspects of their surgical and post-surgical care. Last year we proposed a study involving a retrospective chart review, intended as a pilot project to analyze previously collected but not evaluated data from overnight remote oximetry and find relationships between respiratory events and peri-surgical care. The data collected from this pilot project will be presented. We will also present some ideas for a prospective trial to see if perioperative interventions as directed by the ASA guidelines are in fact impacting morbidity and mortality in patients with OSAS.

Cupido T, Henry R, Wilson R, Hope J, Cahill C, VanDenKerkhof EG.
Trigger Point Injection Study

Background: The cost of treating osteoarthritis (OA) in the U.S. increased by 53% from 1996-2004, with the largest proportion of this increase coming from the inflating cost of prescription medications. During the same period, the number of joint replacements has also been on the rise, with knee replacements showing the highest growth. One of the key diagnostic features of OA is pain, without which many patients would not be candidates for surgery.

The pathogenesis of chronic knee pain is not completely understood, but in addition to OA, trigger points have also been implicated as one possible cause. If we can identify and treat trigger points that are causing knee pain we can relieve the suffering of many individuals experiencing chronic pain.

Myofascial trigger points (MTrP) are hyper-irritable areas within taut bands of skeletal muscle or fascia. They are painful on compression and may give rise to characteristic patterns of referred pain, tenderness, autonomic nervous system symptoms and restricted range of motion. Recognition of MTrP has led to various strategies to attempt to relieve pain.

Primary Study Question: What is the feasibility of assessing patients for the presence of a myofascial component to their pain while on the waiting list for primary total knee arthroplasty (TKA) secondary to OA?

Secondary Study Questions: What proportion of patients waiting for TKA have trigger points as a source of their knee pain? What is the effect of myofascial trigger point injections on pain-related interference of activity and range of motion immediately and at one, two, four and eight weeks post-injection in patients on a wait list for TKA? What is the effect of myofascial trigger point injections for pre-operative TKA patients on opioid and non-opioid analgesic usage; satisfaction with pain management; incidence of surgery completion. What is the feasibility of administering the following measures to pre-operative TKA patients who are found to have myofascial trigger points: timed up and go (TUG); short form McGill pain questionnaire (SF-MPQ); brief pain inventory (BPI); centre for epidemiological studies – depression scale (CES-D) and state trait anxiety index (STAI).

Study Design: We will be completing a prospective observational study. Patients will be recruited from a wait list with an indication for TKA secondary to OA. The following baseline data measurement tools will be completed before assessment by a physician: Baseline demographics questionnaire (BDQ); TUG, SF-MPQ, BPI, CES-D and STAI.

Patients will then be evaluated for the presence of trigger points that may be causing knee pain. Those without trigger points will be followed up in 8 weeks time. If trigger points are present, their location will be recorded on a schema of the knee and they will receive trigger point injections by a single practitioner. Data will be collected immediately after injection and during follow-up visits in 1, 2, 4 and 8 weeks after the initial injection. During each follow up visit patients will be re-evaluated and the study intervention will be applied as appropriate. All patients will be discharged after the 8 week follow-up.

Sutherland KA, Devi LA, Cahill CM.

DOR enhanced antinociception in chronic pain states is consistent with M/DOR oligomer formation

In a model of neuropathic (NP) pain induced by peripheral nerve injury, the spinal administration of selective delta opioid receptor (DOR) agonists produces antinociceptive and antiallodynic effects. The increase in DOR functional competence correlate with a change in the sub-cellular location in spinal dorsal horn neurons. In this study we examined whether the DOR molecular species targeted to neuronal plasma membranes in a NP pain model is complexed with mu opioid receptors (MOR). Male Sprague Dawley rats were subjected to peripheral nerve injury via chronic constriction of the common sciatic nerve, or sham surgery. Spinal cords from NP and sham animals were used for co-immunoprecipitation with an antibody that recognizes M/DOR. Examination of the immunoprecipitate by Western blotting with DOR or MOR antibodies revealed a molecular species of high molecular weight (~225 kDa). This is consistent with studies that demonstrate greater antinociception in NP rats when treated with DOR agonists that have a higher affinity for M/DOR. These data may account for altered pharmacology of selective DOR and MOR agonists in NP pain. (CIHR, CRC, CFI, NIDA)

Ali S, Parlow J, Brunet D.

Factors that may precipitate cerebral ischemia during carotid endarterectomy

BACKGROUND: The substantial benefits attained from carotid endarterectomy (CEA) have been well established; however it is well known that this operation carries a significant risk of cerebral ischemia. The use of shunts to maintain cerebral perfusion during the course of this surgery has been in practice for decades, but also carries the risk of complications which include air or plaque embolization, intimal tears and carotid dissection. While some surgeons routinely insert shunts and others do not, the middle ground approach is selective shunting based on monitoring cerebral perfusion. This is the practice at our institution where cerebral perfusion is monitored by the use of intraoperative electroencephalography (EEG). There are several patient (e.g. age, co morbidities, location and laterality of stenosis) as well as anesthesia related factors that may contribute to cerebral ischemia. The aim of this pilot study is to conduct chart reviews to identify factors that may predispose to cerebral ischemia during CEA at our institution.

OBJECTIVE: To determine patient and anesthetic factor(s) that are associated with cerebral ischemia and shunt placement during carotid cross clamping.

METHOD: After obtaining approval from the ethics committee, a retrospective case-control study in the form of a chart review of 80 patients undergoing first time carotid endarterectomy from Jan 2007 to Jan 2009 will be conducted. Based on a previously determined local incidence of cerebral ischemia with cross-clamping, leading to shunt placement of 13%, we expect to find 20-25 cases over 2 years . These cases will be compared to the remaining patients that did not require shunts who will be regarded as controls. Summary EEG data will be reviewed. All instances of ischemic changes will be identified. Changes related to anesthetic drug effect will be documented.

The following variables will be compared between the two groups:

- Demographic characteristics : age/sex
- Pt co-morbidities and medications
- Location and degree of carotid stenosis, bilateral or unilateral.
- Anesthetic agents used for induction and maintenance
- Use of vasopressor agents
- Lowest recorded blood pressure
- The presence or absence of ischemia based on EEG summaries
- New postoperative neurological deficits

Predictors of ischemia will be explored using bi-variate and multivariate logistic regression modeling. Power will be analyzed post hoc to determine sample size adequacy, or need to increase population.

The expected time frame for completion of this study is two months.

IMPLICATIONS: If this pilot study determines correlates of cross-clamp ischemia, a prospective study may be designed to gain further knowledge that may alter clinical practice to reduce this complication.

REFERENCES:

1. Howell S: Carotid Endarterectomy. Br Journal of Anesthesia 2007;99:119-31
2. Bond et al: Routine or Selective Carotid Artery Shunting for Carotid Endarterectomy (and different methods of monitoring in selective shunting). Cochrane Database of Systematic Reviews 2002 (reprinted 2009)
3. Frank et al: Correlation of Continuous Electroencephalograms With Cerebral Blood Flow Measurements During Carotid Endarterectomy. Stroke; 4 , July- August 1973

Mattioli TA, Milne B, Cahill CM.

Attenuation of morphine-induced astrocyte activation and tolerance development by ultra-low dose naltrexone

Ultra-low doses of naltrexone (ULD-N) inhibit the development of spinal morphine antinociceptive tolerance. Chronic morphine administration induces spinal astrogliosis in tolerant animals. Activated astrocytes are characterized by increased production of glial fibrillary acidic protein (GFAP) and increase in cell size. Spinal cord sections from rats administered chronic morphine showed significant increase in GFAP immuno-labelling compared to saline controls ($p < 0.001$). GFAP labelling was attenuated in rats co-administered ULD-N ($p < 0.001$ compared to morphine alone) and did not differ from controls. 3-D images of astrocytes from animals administered chronic morphine had significantly larger volumes compared to saline controls ($p < 0.001$). Co-injection of ULD-N attenuated this increase in volume ($p < 0.001$), but the mean volume differed from saline treated controls ($p < 0.05$). Thus, there is a positive correlation between prevention of tolerance and inhibiting activation of spinal astrocytes by treatment with ULD-N. Further research is required to determine if the ULD effect on modulation of astrocyte function is direct or indirect. *Supported by CIHR, CRC, and CFI.*

Cyr JD, Wang L, Burjorjee J.

The impact of stress on the management of medical crises in a simulated environment

Medical professionals are exposed to significant stressors throughout their career. Over the years, simulator based learning has developed as a tool aimed at better preparing trainees when faced with such situations. In light of the paucity of information within the literature regarding stress levels and their effects on simulator performance, we propose a study aimed at determining performance as it relates to stress levels experienced by candidates during high-fidelity simulation. We hypothesize that in order to reach maximal performance; a certain stress level must be reached. Participants, at similar levels of training, will complete scenarios and have their performance measured while assessing their stress levels with the use of non-invasive monitoring. They will be presented with two scenarios, one of high, the other of lower difficulty. Randomization of which scenarios is presented first will eliminate learning curve bias. Furthermore, participants will complete a short knowledge test and state trade anxiety scale. Once completed, we hope to establish the ideal stress level for optimal performance. This would in turn guide the development of better and more efficient high-fidelity simulator scenarios.

Lee A, Ramsey G, Orr E, Murdoch J.

The effects of intraperitoneal ketorolac on postoperative pain following laparoscopic cholecystectomy

Introduction: Prior studies have shown efficacy for NSAIDs in the management of postoperative pain following laparoscopic surgery. Intraperitoneal instillation of an NSAID (tenoxicam), combined with lidocaine, has been shown to reduce postoperative pain scores following laparoscopic cholecystectomy relative to placebo (1). We hypothesized that intraperitoneal administration of ketorolac (NSAID) alone would be more effective than intravenous ketorolac or placebo in the management of postoperative pain in patients undergoing laparoscopic cholecystectomy.

Methods: Following ethics committee approval, 120 patients ASA Class 1-3 (ages 18-65 years old) undergoing elective laparoscopic cholecystectomy under general anesthesia were recruited. Patients were randomly allocated to one of three groups to receive intraoperatively: 1. 30 mg ketorolac in 250 ml normal saline with IV saline (1 ml) bolus ("Intraperitoneal ketorolac group" or IP); 2. Intraperitoneal 250 ml normal saline with IV ketorolac 30 mg (1 ml) bolus ("IV ketorolac group" or IV); and 3. Intraperitoneal 250 ml normal saline with IV normal saline (1 ml) bolus ("placebo group" or P). All participants received a premedication of oral acetaminophen 975mg and standardized general anesthesia, and all parties were blinded. In the recovery room (PACU) the time to first rescue analgesic (IV fentanyl), amount of rescue analgesic, and visual analogue pain scores (VAS at rest and movement) at specified time points were recorded. Other parameters included nausea and vomiting and the need for rescue antiemetics. Patients were asked to complete a home questionnaire (VAS pain, nausea and vomiting) after 24 hours. The Kruskal-Wallis test was used to test for difference between the three groups. Pairwise comparisons were tested by one-way ANOVA and Wilcoxon-Mann-Whitney analyses.

Results: A total of 120 patients were analyzed (IP=41, IV=39, P=40). Median time to first analgesic was increased from 35 mins. (IQ range 27-49) in the placebo group to 47 mins. (IQ range: 40-75; p=0.003) and to 43 mins. (IQ range: 30-52; p=0.124) for the IV group and IP group, respectively. Median amount of fentanyl in PACU reduced from 0.100 to 0.075 mg for both the IV (p=0.003) and IP groups (p=0.05) versus placebo. There were no significant differences for these parameters between the IP and IV groups. VAS scores at rest were significantly less for the IP and IV groups versus placebo at 30 minutes and 120 minutes. No significant difference between the groups in regards to VAS pain with movement was found at any time point. At 24 hours, there was no significant difference between the groups in regards to pain and nausea scores. No complications attributable to study drug were recorded.

Discussion: This study demonstrates efficacy for the use of intraperitoneal ketorolac over placebo in the management of immediate postoperative pain in patients undergoing laparoscopic cholecystectomy. These results are comparable to intravenous ketorolac.

References: (1) Acta Anaesthesiol. Scand. 2000; 44: 929-33.

VAS (Rest)

Time post-study drug (mins.)	IP	IV	P
30	31.2±19.5*	28.1±21.4*	44.6±21.9
60	28.3±15.0	24.5±17.2*	35.7±19.0
120	19.9±16.7*	19.1±14.7*	29.5±20.3

*p<0.05 relative to placebo

Ridi S, Jaeger M, Patterson L.
The CaRMs Game: Factors Influencing Choice of Residency

To define and explore the major factors influencing a CaRMs applicant's decision to choose one Anesthesia residency program over another. There is currently little to no research on how graduating Canadian medical students rank the various residency programs in their chosen specialty. Although residency programs spend significant resources, both human and monetary, on the CaRMs interview process there is no data available to measure how effective these efforts actually are in attracting top candidates. All 2009 CaRMs applicants interviewing for Queen's Anesthesia Residency Program were asked to complete an online survey assessing factors influencing their choice of residency program. Applicants were initially informed of the survey on their interview day and informed consent was obtained. An initial email with a link to the on-line survey was sent to all interviewees following submission of their rank list. Candidates had 10 days to complete the survey. A reminder email was sent to all applicants who had not completed the survey after 5 days. At this time the survey is still active and data has not yet been analyzed.

McLaren D, Engen D, Tanzola R, VanDenKerkhof E.
Canadian Anesthesia Workforce Assessment 2009

Background: Adequate health care delivery involves planning for the future and ensuring sufficient medical specialists are available to fulfill clinical need. The requirement of anesthesia providers for the Canadian medical system has been estimated in the past but has not been recently revisited. Furthermore, the impact on the number of anesthesia providers required and the role of anesthesia assistants has never been evaluated in detail. Accumulation of such knowledge could be of considerable use in the evolution of anesthesia provider training programs.

Knowledge Gap: The survey based study by Engen *et al* in 2002, quantified the number and adequacy of anesthesia providers across Canada and also predicted same for 2007. Since the publication of this study in 2005, no other studies have further evaluated the need for anesthesia providers in Canada. A new survey would estimate the current nation wide demand and also allow comparison between projected need in 2002 to the deficiency at the present. Also, the impact of similar demand based assessments have yet to be done for anesthesia assistants.

Hypothesis: We predict that this survey will again demonstrate a shortage of anesthesia providers in the Canadian health care system. There has been minimal change in the production numbers from anesthesia training programs across the country in the last five years. For this reason the shortages in anesthesia care may even be deteriorating, and the shortcoming between anesthesia provider need and availability may be worse than predicted in the earlier study. Clarification of the role of anesthesia assistants across the country will likely identify that in many provinces, we expect them to have little impact on the need for anesthesia providers at this time.

Methods: This study will be completed as an online survey sent to every hospital in Canada potentially employing anesthetic services. Similar to the previous survey in 2002, we will ask recipients to quantify the number of anesthesia providers at their institution, judge whether this fills their clinical need and estimate their need in the future. Different from the previous survey, we plan to specifically identify who is completing the survey. Furthermore, we plan to question institutions on their use of anesthesia assistants, the role of these providers, and what impact they have on their anesthesia human resource needs.

Hogan A, Henry R, Saha T.

Postoperative Analgesia After Total Knee Replacement: Comparing the analgesic efficacy of the lumbar paravertebral block and the femoral "3-in-1" nerve block

Abstract: Pain control after total knee arthroplasty (TKA) can be a challenge. Regional anesthesia has been shown to give better pain control than Morphine via intravenous patient-controlled anesthesia (IV PCA) in the early postoperative period. The most optimal method of pain control is however still up for debate. Femoral nerve blocks (FNB) do provide good pain control after TKA, as well as facilitate early ambulation and reduce the length of acute hospitalization as compared to IV PCA Morphine alone. The obturator nerve is not consistently blocked with this technique, and the addition of a sciatic nerve block to the femoral nerve block has not been shown to provide significant improvement in pain control. Lumbar paravertebral nerve blocks (LPNB) have been shown to provide adequate pain control after TKA and significantly reduce early morphine consumption, however no study has yet compared the LPNB with the femoral nerve block (FNB) for analgesic efficacy after TKA. The study we are proposing is a prospective randomized quality control trial of 30-40 patients comparing post-operative pain control using the LPNB at the L2-3/3-4 levels versus the femoral "3 in 1" block, both using 20mL 0.5% Ropivacaine. Study subjects undergoing single TKA will receive a standardized spinal anesthetic for surgery, after which they will be randomized to either the LPNB group or the FNB group, which will be performed in the recovery room after the operation once their spinal has worn off to L2. All patients will receive IV PCA morphine 1.5 mg q 6 minutes for pain control post-operatively, as well as regular Tylenol. Our primary outcome will be total narcotic usage (morphine equivalence consumption) recorded at 4, 8, 12, 24, 48, and 72 hours post-operatively. Secondary outcomes include incidence of nausea and vomiting, and degree of pain as assessed by the Visual analog scale (VAS) scores at rest and with activity at 4, 8, 12, 24, 48, and 72 hours, as well as by the Brief Pain Inventory (BPI) short form which will be administered by telephone 30 days following surgery.

Henderson T. Patterson L.

An In Vitro Study of MRI-Related Heating at 3.0 Tesla of an Epidural Catheter

Background and Objective

Epidural hematoma is a rare but catastrophic complication of epidural anesthesia. Many epidural catheters, including the Flex-tip Plus Epidural Catheter used at our institution, contain a ferromagnetic stainless steel coil. Metal containing epidural catheters are deemed MRI-unsafe due to concerns over heating. If an epidural hematoma is suspected while these catheters are still in situ CT scans must be carried out; an imaging technique which is inferior in diagnostic abilities compared to MRI. We propose to examine the Arrow Flex-tip Plus epidural catheter and ascertain its propensity to cause heating in the MRI at 3.0 TESLA.

Proposed Study Design

Our protocol is based on established methodology used on other metal medical devices that have been tested for MRI safety.

A pilot study has been conducted in which epidural catheters were placed into zucchinis to assess whether the artifact caused by the catheter would preclude utility of MRI with the catheter in place. The pilot study, conducted in July 2007 at Queen's University 3-Tesla MRI, has successfully shown negligible artifact due to the Flex-tip Plus Epidural Catheter.

A Plexiglas phantom will be constructed to approximate the torso of a human subject. This will be filled with a semi-solid gel that is recognized as having the properties which approximate the thermal convectional and dielectric properties of human tissue. This gel has been successfully recreated in Dr Eric Dumont's laboratory. The epidural catheter will be positioned in the gel phantom to approximate both lumbar and thoracic placement, and will be aligned straight and knotted; the latter being an extreme version of coiling within the epidural space.

Temperature will be measured using the Luxtron I652, an MRI- compatible fiber optic thermometer available from Lumasense California. We are awaiting funding to purchase this \$7000 device and complete our protocol.

Future Directions

Our hope is that our investigation will demonstrate in vitro safety of Arrow catheters and inspire a re-examination of the safety label applied to these devices and lead to possible in vivo studies. This will allow for more accurate and expedient detection of pathology by MRI thereby improving patient outcomes.

Srikandarajah S, Gilron I.

The measurement of movement evoked pain in postoperative analgesic trials.

Introduction: Recent research has shown that movement evoked pain (MEP) is often more intense than spontaneous pain (SP), is relatively resistant to opioid therapy and often adversely affects postoperative functional recovery. Despite these facts, measurement of MEP in analgesic clinical trials has not been universal. The purpose of this systematic review is to determine the frequency of MEP measurement in postoperative analgesic trials. Due to the large number of trials overall, we focused this review on abdominal hysterectomy due to the impact of MEP on postoperative recovery in this setting.

Methods: Medline and Embase databases were searched for relevant key terms. A total of 663 articles were obtained and, of these, 385 were excluded leaving a total of 278 articles for analysis. Articles were then grouped according to whether they measured MEP or not.

Results: Only 35% of included articles specifically listed MEP as an outcome measure. Analysis of data from trials measuring both SP and MEP indicate that MEP within the first 24hrs was, on average, 86% more intense than SP. MEP at 48 and 72hrs was more than 100% greater than SP. Of those studies that did measure MEP, a variety of different pain-evoking maneuvers were used (e.g. coughing, sitting, walking and forced expiration).

Discussion: Our results indicate that MEP is, on average, 86% more intense than SP and persists for a longer time. Despite the functional impact and increased intensity of MEP, only 35% of published trials measured MEP. Thus, we advocate that all postoperative analgesic trials concerned with clinically relevant patient outcomes should systematically assess MEP. Further research is needed in order to determine the most appropriate methods for, and selection of, pain-evoking maneuvers in postoperative analgesic trials.

McVicar J, Ashbury T, Milne B.
Pediatric Risk Factors for Anxiety at the Induction of Anesthesia

Clinical Need & Knowledge Gap:

Pediatric surgery can be a stressful experience for the patient, parent(s) and medical staff. There is evidence to suggest that the conditions in which the child is induced can have significant effects on postoperative outcomes. The current practice of pediatric anesthesia is without an effective clinical tool to predict children who demonstrate adverse behaviors at the induction of anesthesia. As a result many clinicians routinely sedate children to avoid poor outcomes. The consequences of such practice are not insignificant.

Our goal is to develop a clinical tool that will be used in the pre-operative setting to predict which children are likely to demonstrate adverse behaviors at the time of induction of anesthesia so that pharmacologic anxiolysis can be delivered in a directed manner.

Hypothesis: Children at high risk for adverse behaviors at the induction of anesthesia can be identified through the use of demographic, behavioral and situational risk factors.

Study Design: We will review the medical and psychological literature for demographic, behavioral and situational risk factors for adverse behaviors at the time of induction of anesthesia in children. We will develop and administer a yes/no questionnaire to a carefully screened group of elective outpatients aged 4-10 years old and their parents. They will be asked the questionnaire during their preoperative check-in. The choice of anesthetic technique will not be altered in any way. A blinded research nurse will assess for maladaptive behavior at the time of induction of anesthesia using modified Yale Preoperative Anxiety Scale for Pediatrics, a validated tool commonly used in the pediatric anesthesia literature.

Timeline: We have partnered with colleagues from the Queen's Department of Developmental Psychology to help guide us through the psychological literature, assessment tools and questionnaire development and are currently in the process of developing a draft questionnaire.

Mountjoy JR, Murdoch J, Wilson R, Gilron I.

Effects of patient controlled analgesia pump feedback on post-operative pain: can enhanced pump-feedback improve pain control

The post-operative period is characterized by pain, uncertainty and loss of control for many patients. The study was designed to test the hypothesis that increased feedback from a patient-controlled analgesia (PCA) pump will positively affect patients' perception of pain and their satisfaction with their analgesia. This will be a single-centre randomized prospective study of two different settings of the Alaris PCA. Subjects will be chosen among patients undergoing primary hip arthroplasty surgery under spinal anaesthesia. The anaesthetic and co-analgesic treatment will be standardized for patients included in this study. Once enrolled patients will be stratified into two groups: 1) those taking opioid medications chronically, and 2) those not taking opioid medication chronically. They will be randomized to receive opioids via the Alaris PCA pump with feedback provided in one of two ways: 1) the pump beeps every time a request is made, and gives no indication as to whether drug has been delivered or to lockout status, or 2) the pump beeps to indicate drug delivery and uses a coloured light to indicate lock-out status. The effect on the patients' pain will be assessed via a visual analogue score (VAS) scale, their side-effects related to their analgesia and their opioid consumption.

POSTER PRESENTATION ABSTRACTS

Ellis J. Cahill CM.

Attenuation of morphine-induced increases in the expression of CGRP and the development of tolerance by ultra-low dose atipamezole

Chronic administration of morphine has been shown to lead to the development of analgesic tolerance. In morphine tolerant animals, increased expression of calcitonin gene-related peptide (CGRP), a pronociceptive neuropeptide, is observed. Further implicating the involvement of CGRP in tolerance, co-administration of a CGRP antagonist with morphine attenuates the development of morphine tolerance. Ultra-low dose α 2-adrenergic antagonists have also been shown to attenuate morphine-induced analgesic tolerance. The current study investigated the effects of atipamezole, an α 2-adrenergic antagonist, on the expression of CGRP when co-administered with chronic morphine. Male Sprague-Dawley rats were divided into four groups: morphine, morphine & atipamezole, saline and atipamezole alone. All animals received drugs within their respective group via lumbar puncture once daily for seven days. Thermal nociception (tail-flick test) was tested every other day to measure the analgesic effects of the treatments. Behaviour results suggest that ultra-low dose atipamezole does attenuate the development of morphine tolerance ($p < 0.001$). Immunohistochemical labelling for CGRP on perfused spinal cord sections was performed to measure the expression of CGRP. Immunohistochemical results are still in progress.

Grenier P. Cahill CM.

The Role of Glial Activation on δ -Opioid Receptor Trafficking in Neuropathic Pain

Previous studies have reported that activation of glia cells in neuropathic pain states may contribute to the development of tolerance and desensitization to μ opioid receptor agonists like morphine. Activation of glial cells may also contribute to an increase in the trafficking of δ opioid receptors (DOR) to the plasma membrane from intracellular sites, increasing the functional competence of DORs in models of NP pain. The mechanism by which this trafficking occurs is not entirely understood, but it may be influenced by an increase in pro-inflammatory cytokine release following glial activation. The aims of this study are to investigate whether glia inhibition blocks peripheral nerve injury-induced DOR trafficking. Using a chronic constriction injury (CCI) to induce neuropathic pain, propentofylline (a glial inhibitor) or saline vehicle will be administered intrathecally to sham and neuropathic animals. Spinal cord sections will be processed for immunogold electron microscopy to determine sub-cellular localization of DORs. To determine the microglia-specific role in triggering DOR trafficking, minocycline, a microglia inhibitor, or vehicle will be administered before CCI or sham surgeries and daily for 11 days post-surgery. Immunohistochemistry and Western blotting techniques will confirm inhibition of microglial activation. RT-PCR and Western blotting will be used to determine if minocycline altered DOR expression. To determine whether cytokines can trigger DOR trafficking and functional competence, sham or neuropathic rats will receive either saline vehicle or a cytokine cocktail intrathecally, and behavior and other testing will be performed as described for other objectives. It is hoped that this study will provide a better understanding of the mechanism by which DORs are trafficked in neuropathic pain states, which may eventually lead to more effective and consistent treatment of pain.

Krawczyk M, Sharma, R, Schizkoske A, Dumont E.
Altered excitatory transmission in cocaine-addicted rats

Licit and illicit drug abuse largely complicates acute perioperative and chronic pain management. First, acute withdrawal from drugs of abuse perioperatively produces hyperalgesic states that require more aggressive analgesia. Second, most drugs of abuse induce tolerance to opioid analgesia. Third, several analgesics, especially opioids, are amongst the most addictive substances known. We use a rat model of cocaine self-administration to understand the neurobiological basis of drug addiction. In this particular project, we investigated the effect of chronic cocaine use on dopaminergic (DA) modulation of excitatory (mediated by the neurotransmitter glutamate) synaptic transmission in the Bed Nucleus of the Stria Terminalis (BST), a region of the brain critically involved in the addictive properties of all drugs of abuse. In brain slices prepared from drug naïve or rats trained to self-administer a natural reward, sucrose, DA dose-dependently reduced excitatory post-synaptic currents (EPSC) in the BST. The effects of DA involved activation of D1-like and D2-like receptors, the modulation of the enzyme adenylate cyclase, and pre-synaptic activation of GABA_B receptors by GABA acting as a retrograde messenger. In rats that chronically self-administered cocaine IV, the effect of low DA concentration switched from a reduction to an increase in EPSC amplitude. This switch in direction of the effect of DA seemed to result from a change in the respective contribution of D1- and D2-like receptors in the BST. Our results reveal a new locus and mechanism underlying the addictive properties of the psychostimulant cocaine. Our study thus provides important insight into the neurobiology of cocaine addiction that will help in understanding the effects of other drugs of abuse such as opioids. Supported by the Canadian Institutes of Health Research (MOP-79277) and The Canadian Foundation for Innovation.

Lecour S, Cahill CM.

Spinal administration of a delta opioid receptor agonist may attenuate neuropathic pain via modifying glial activation

Neuropathic (NP) pain is a chronic debilitating pain disorder that affects millions of people worldwide. It is now established that neuronal-glial interactions are important in both the development and maintenance of NP pain states. Hence NP pain induces the activation of glial cells and suppression of this activation attenuates pain behaviors. Our laboratory has demonstrated that activation of delta opioid receptors (δ OR) can modulate NP pain. This effect is considered to be primarily via activation of neuronal δ ORs to suppress nociceptive transmission, however, δ ORs are also expressed on glial cells within the central nervous system. To date, the function of δ ORs in such cells has not been investigated. In this current study, we examined the effects of chronic intrathecal administration of the δ OR agonist, [D-Ala²]-deltorphin II (deltorphin II), on mechanical allodynia as well as glial activation in rats following chronic constriction injury (CCI) of the sciatic nerve. CCI rats exhibited mechanical allodynia throughout the 11 days of testing. Anti-allodynic effects were seen acutely following administration on days 4, 7 and 11 following surgery however, chronic administration did not prevent the development of allodynia. To examine the effects of δ OR agonist stimulation on glial cell activation, 3D Reconstruction is currently being used to assess the effects on nerve injury induced microglia and astrocyte activation in the dorsal spinal cord.

Magnussen C, Sutherland KA, Olmstead MC, Cahill CM. Conditioned place preference predicts drug effectiveness in alleviating neuropathic pain

Neuropathic pain is chronic pain condition characterized by burning, shooting and/or paroxysmal, spontaneous pain and is often associated with the occurrence of hyperalgesia and allodynia. Various animal models exhibit face validity in mimicking clinical features of neuropathic pain as they display behaviours indicative of allodynia and hyperalgesia. Pharmacological preclinical studies investigating potential analgesic effects of drugs to treat neuropathic pain rely primarily on threshold behavioral assays, however, to date, drugs that show effectiveness in such assays have failed to alleviate pain in clinical studies. In this study, peripheral nerve injury (PNI) via chronic constriction of the common sciatic nerve was used to induce neuropathic pain and a conditioned place preference (CPP) paradigm was used to determine drug effectiveness. Two chamber boxes with identical grid wire floors with a neutral compartment for initial introduction to the apparatus was used to induce CPP in sham and PNI rats. Six days post surgery sham and PNI rats were conditioned with spinal administration of deltorphin II, a DOR agonist (30ug/ 15ul) to one compartment and vehicle (saline, 15ul) to the opposite compartment; each animal serving as its own control. Spinal administration of the DOR agonist significantly induced CPP in the neuropathic rats, but sham animals showed no sign of preference for the drug compartment. Rodents learn to associate the rewarding effects of drugs with the environment in which they are encountered and, subsequently, will display a CPP for that environment. Because deltorphin only exhibited CPP in neuropathic but not sham animals, we suggest that the reward was alleviation of pain rather than due to activation of reward pathways associated with addiction. These data suggest that DOR agonists can produce analgesia without the stimulation of reward centers and provide validation for an alternative non-threshold testing paradigm for assessment of pharmacotherapy effectiveness in alleviating neuropathic pain.

Ong EW, Cahill CM.
Opioid Receptor Heteromer Trafficking

This study examines the trafficking of delta opioid receptors (DORs) to neuronal plasma membranes. Such trafficking occurs, in vivo, under conditions of chronic neuropathic pain and chronic mu opioid receptor (MOR) activation and is associated with increased DOR functional competence. We studied the trafficking of DORs, in vitro, using primary cultures of dorsal root ganglia in order to determine whether the trafficked DORs were in the form of DOR monomers or associated with MORs as MOR/DOR heteromers. Chronic morphine treatment was used to trigger trafficking of DORs. Immunofluorescent labelling of MORs and DORs suggests increased colocalisation at the cell surface following chronic morphine treatment. Such increases appear to occur predominately in smaller neurons. MOR/DOR heteromers were immunoprecipitated using a specific antibody (Gift of Dr. L. Devi). Immunoblotting with antibodies specific to MOR or DOR revealed a molecular species of high molecular weight. These findings support the presence of MOR/DOR heteromers and their increased formation following chronic MOR activation.

Philbrook M, Nakatsu K, Cahill CM.

Targeting heme-oxygenase enzymes as a novel strategy for treating neuropathic pain

Heme oxygenase (HO) is a catalytic enzyme converting heme into free iron, biliverdin, and the second messenger carbon monoxide. HO exists in two isoforms: the inducible HO-1 and constitutive HO-2. Previous studies demonstrated that non-selective inhibition of HO activity attenuated neuropathic pain behaviours in animal models of peripheral nerve injury. The lack of an isoform selective inhibitor has prevented characterization of HO-1 or HO-2 in neuropathic pain. In the present study, the selective role of HO-1 and HO-2 in neuropathic pain will be investigated using recently available selective inhibitor in animal models of neuropathic pain. Neuropathic pain will be induced by constriction of the Sprague Dawley rat common sciatic nerve (n=12) using 4 chromic sutures. Sham animals receiving the equivalent muscle injury without nerve constriction (n=12) will serve as control with baseline nociceptive behavior. Half of the neuropathic (n=6) and sham animals (n=6) will be administered treatment with selective inhibitors, whereas the other half will receive saline vehicle. Nociception will be assessed blind to treatment using von frey filaments, as well as several other modalities of nociception. Post-perfusion spinal cord HO activity will be measured using a carbon monoxide release assay to determine the degree of inhibition in treatment animals versus saline. Additionally, HO expression post injury will be quantified using immunohistochemistry and western blotting.

Collectively, this research proposal will demonstrate changes in both expression and function of HO-1 and HO-2 in a model of neuropathic pain.

Walker S, VanDenKerkhof EG.

Waiting for Care: Symptoms and Healthcare Utilization of Women Waiting for Gynaecological Surgery

Background: Waiting for surgery occurs for many elective procedures. Little is known about waiting for gynaecological surgery and the symptoms experienced. There is a requirement for research to better understand psychological and physical symptoms in this group of women.

Objective: To what degree is pain a part of the waiting experience? The level of pain intensity, interference and frequency of healthcare utilization due to pain are examined in addition to psychological characteristics of women waiting for gynaecological surgery.

Method: The data was collected for a larger study and comprised of 429 women from the South Eastern Ontario region. The women were asked about anxiety using the trait anxiety inventory (STAI), depression with the centre for epidemiologic studies depression scale (CES-D), somatization from the seven symptoms screening test (SSST) and feelings of catastrophizing when experiencing pain, (using two questions from the coping strategies questionnaire). The pain experience was assessed using the Brief Pain Inventory (BPI). Women also reported on their healthcare utilization for pain over the past 12 months. The surgical priority score given to each patient and length of wait were obtained from hospital waiting data.

Results: 18% of women had a high anxiety score, 37% indicated depression, 47% experienced 2 or more symptoms of somatization and 70% of women either sometimes or always felt a degree of catastrophizing with their pain. Of the women that experienced pain in the last week, 81% believed their pain was due to their primary condition. Pain intensity was moderate to severe for 31% of women and the level of pain interference was moderate to severe in 32%. Regarding healthcare utilization, out of 429 participants, 179 did not visit a healthcare practitioner for pain over the past year, but 250 women carried-out a total of 1417 healthcare visits and 3 or more visits were carried out by 41% of participants. During the previous year 22% of women missed more than 30 days of work, school or other regular activities because of pain, 35% of women felt pain interference with physical or daily activities, including socializing. Pain medication provided less than or only 30% relief for 26% of women and 19% felt they needed more pain medication than was prescribed. Waiting time was within the Priority 4 Level of 26 weeks or less for 96% of the women.

Conclusion: A substantial number of visits to healthcare practitioners occur because of pain and also pain causes considerable interference with daily activities, causing women to miss work and or social activities. As research is in progress, bivariate analysis will be carried out to see if any psychological or physical variables are associated with healthcare utilization for pain. Improved understanding of the impact of unpleasant symptoms on the waiting experience will be gained. Primary care practitioners can then direct care towards areas of need.

Zhang KM, Tripp DA, Hsieh AY.

Observer pain estimation accuracy and empathy in cultural concordant and discordant dyads

Objectives The present study will investigate potential differences in pain estimation accuracy of Chinese and European Canadians when observing others' pain. The experimental design has two objectives: 1) to test whether a match in culture between the observer of the pain experience and the pain sufferer will predict higher observer pain estimation accuracy and 2) to investigate whether pain estimation accuracy is affected by the observer's empathy levels.

Methods This study will recruit 50 Chinese and 50 European Canadian students from Queen's University. Participants will either receive \$5 cash or 0.5 bonus credit if they are enrolled in Psychology 100. Participants will view short video clips of individuals in pain and are asked to estimate the level of pain experienced. Two empathy questionnaires, the David Empathic Concern Scale and Empathic Feeling and Expression Scale, will also be administered.

Proposed Analysis of Results Three sets of 2x2 Mixed model analysis of variance (ANOVA) will be conducted to assess our first hypothesis of whether a match in observer-pain sufferer ethnicity is associated with higher pain estimation accuracy. Each ANOVA set will have one of the three indices of accuracy (difference score, covariation, and within-sender difference score) as the dependent variable. All three 2x2 Mixed model ANOVAS will have the same within-group independent variable (observer ethnicity: Chinese/European Canadian) and between-group independent variable (video subject ethnicity: Chinese/European Canadian). The second hypothesis of whether observer empathy influences pain estimation accuracy in cultural discordant conditions will be examined by using three 2x2 Mixed model ANCOVA for each of the dependent variables suggested above. The sum of the DECS scores and the EFES scores will be the covariate variable.

Discussion Clinical implication of the results will be discussed.

CRITICAL APPRAISAL ESSAYS

Rebecca Gerlach
PGY-1 Anesthesiology

“Incidence and predictors of difficult and impossible mask ventilation”

The paper *Incidence and predictors of difficult and impossible mask ventilation* was published in *Anesthesiology* in 2006 by Kheterpal *et al.*¹ of the University of Michigan medical school in Ann Arbor, Michigan. It addresses the question, what are predictive factors for difficult and impossible mask ventilation (DMV and IMV)? It also reports the final airway outcome in incidences of IMV. There are few papers studying the topic of mask ventilation as a primary endpoint. This study uses a four grade system for describing ease of mask ventilation as established by Han *et al.* (2004)², with grade 3 and 4 being DMV and IMV respectively. It builds on the results of Langeron *et al.* (2000)³ which used a three grade scale for DMV in 1,502 recorded cases and identified several independent predictors, namely age >55, BMI >26, beard, lack of teeth and history of snoring. Langeron *et al.* anecdotally recorded one instance of IMV. Being able to more accurately predict incidences of DMV and IMV may improve the safety of delivering general anesthesia, as mask ventilation is fundamental to airway management.

This study was prospective and observational. All adult patients undergoing general anesthesia at the University of Michigan medical school over a 24 month period were included. The sample size and study duration were set by estimating that they would need approximately 20,000 cases of MV to record 1,000 cases of DMV and 20 cases of IMV, based on the work by Langeron *et al.* and Han *et al.* The study was approved by the institutional review board and patient informed consent was not required, as no personally identifying data was used and clinical management was not altered.

In 24 months, 61,252 anesthetic cases were performed in adult patients. MV was attempted in 22,660 cases, which were included in the study. The only exclusions from this data were 2 cases where IMV was recorded due to existing patent tracheotomy site.

At the University of Michigan hospital, registered nurse anesthetists may make attempts at MV and intubation, which is different from the practice at Kingston General Hospital. Anesthesiology residents are involved at both

centers.

Data was collected using an electronic perioperative record system with standardized pick-list choices, as well as the option of free text entry if required. Information gathered included a standard airway assessment, physical features present affecting mask fit (beard and dentition), details regarding history of cough, rhinorrhea, COPD, asthma, nightly snoring or OSA, as well as patient age, ASA, BMI and operation characteristics. The two styles of mask used and the electronic system used are described. Initial attempts at MV were made by anesthesiology residents or nurse anesthetists present in the room. The primary endpoint was Grade 3 or 4 MV. Grade 3 and 4 MV were defined as the following respectively: “Difficult ventilation (inadequate, unstable, or requiring two providers) with or without muscle relaxant” and “Unable to mask ventilate with or without muscle relaxant”. The study does not differentiate the stage of resident/fellow attempting MV, nor does it explicitly define if the label of Grade 3 or 4 MV was always made by attending staff, as opposed to resident or nurse anesthetist. Clinical decisions regarding awake fiberoptic intubation were at the discretion of the attending staff, thus avoiding an attempt at MV. Intubation attempts in the cases of IMV were also recorded, with clinical decisions made by attending staff regarding patient positioning, blade used and thyroid pressure. A grade III or IV view on direct laryngoscopy or more than three attempts at intubation by attending staff was defined as difficult intubation (DI). Inability to intubate using direct laryngoscopy despite more than three attempts was defined as impossible intubation. The study did not comment on if/when adjuncts were used for intubation attempts, however did report the outcome of incidences of Grade 4 MV (1/37 cases could not be intubated and required emergent cricothyroidotomy, 10/37 had difficult intubation, and 26 were intubated without difficulty).

The protocol is clinically relevant as it simulates the routine clinical conditions encountered in providing general anesthesia. It includes routinely assessed patient characteristics in an attempt to identify patients at risk for difficult or impossible ventilation before they arrive in the OR.

The data collection methods were largely objective, however the authors comment on the potential for inconsistent application of MV and intubation techniques, as the level of training of the providers can differ significantly, as well as personal practice. Also, the data collection forms

did not include extensive descriptions or diagrams to aid in selection of the most representative choice. This study defined a stricter definition for difficult MV by using the as yet unvalidated four grade scale defined by Han *et al.* Risk factors for grade 3 MV, grade 4 MV, and grade 3 or 4 MV and DI were identified through univariate analysis between patients with or without the outcomes using Pearson chi-squared or Fisher exact test, with a P value less than 0.05 being significant. These variables were then entered into multivariate analysis to identify independent predictors of each outcome. Odds ratios for Grade 3 MV and Grade 3/4 MV plus DI were calculated based on the number of risk factors present, and ROC curves calculated. The paper includes tables documenting data collection characteristics, mask ventilation scale and incidence, univariate predictors of airway outcomes and airway outcome independent predictors.

The group studied in which attempts at mask ventilation were made was somewhat skewed, in that many patients in whom difficult ventilation or intubation was a concern underwent awake fiberoptic intubation at the discretion of the provider. These patients had higher rates of risk factors for grade 3 MV than the studied population. Therefore, the conclusions drawn regarding predictive factors for DMV are in a lower-risk population and may not be relatable to the general population as a whole.

One of the main conclusions of the study is that the mandibular protrusion test is an essential element of the preoperative assessment, as limited or severely limited protrusion may be associated with Grade 3/4 MV. This was a previously unverified association, and though the ability to prognath is included in the practice guidelines for airway assessment in difficult airways by the ASA⁴, the authors comment that their institution had not routinely performed the test prior to this study. The most potentially concerning of clinical scenarios, Grade 3 or 4 MV and difficult intubation, was associated with five independent risk factors, namely limited jaw protrusion, thick/obese neck anatomy, sleep apnea, snoring, and BMI>30. The study was unable to confirm lack of teeth or age >57 as an independent predictor, as reported by Langeron *et al.* The overwhelming majority of these patients could still be intubated and the incidence of Grade 4 MV was rare at 0.16%, while the incidence of Grade 3 MV was 1.4%.

The study confirmed the observations by Langeron *et al.* that increased BMI, beard, history of snoring and advanced age are independent predictors of Grade 3 MV, as well as identifying Mallampati III or IV and severely limited jaw

protrusion as independent predictors. Presence of a beard is the only easily modifiable risk factor. The presence of 3 or more predictive factors increased the baseline incidence of Grade 3 MV by 20 times and may be an appropriate cutoff to raise concern. When 3 or more factors are present, the provider should consider having an assistant in the room and prepare for a rescue method of ventilation, as well as advise the patient to shave their beard. The incidence of clinically significant DMV was lower than reported by Langeron *et al.* (1.4% vs. 5%) due to the inclusion of Grade 2 MV, where MV is not 'easy' but does not pose clinical concern.

This series of 37 instances of IMV represents the largest group of patients ever reported on. Unfortunately, only two predictors were identified, that of a history of snoring and thyromental distance of less than 6cm. It is unclear if this is simply due to an inadequate sample size or to underlying fundamental differences in etiology of Grade 3 and 4 MV.

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Brian Grant
PGY-1 Anesthesiology

“Randomized, controlled clinical trial of point-of-care limited ultrasonography assistance of central venous cannulation: The Third Sonography Outcomes Assessment Program (SOAP-3) Trial”

General

I will be reviewing an article from 2005 in the Critical Care Medicine Journal, Vol.33, No. 8, titled, “*Randomized, controlled clinical trial of point-of-care limited ultrasonography assistance of central venous cannulation: The Third Sonography Outcomes Assessment Program (SOAP-3) Trial.*” As Anesthetists, we commonly find ourselves inserting central lines in many environments, be it the Operating Room, the ICU or Emergency Department. Often it is a very controlled environment. At times it may be slightly chaotic such as in a resuscitation. In any event, it is a procedure with definite risks to the patient. Therefore, it should be done with utmost caution and performed using whatever tools are available to minimize these risks. With patient safety at the forefront of medicine and in an increasingly litigious environment, it impresses upon us to decrease the risks to both patients and ourselves whenever possible. This article attempts to show us a manner in which we can reduce these risks.

The article was written by Truman et al. from the Department of Emergency Medicine at the New York Methodist Hospital, New York, NY; The Department of Emergency Medicine, University of California-Davis Medical Center, Davis, CA; and the Department of Medicine, Weill Medical College of Cornell University, New York, NY.

Introduction

The paper states that in 2001, “an agency for healthcare research and quality evidence report listed ultrasound assistance of central cannula placement as one of the “Top 11 Highly Proven” patient safety practices that are not routinely used in patient care and it recommends all central cannula placements be guided by real-time, dynamic ultrasound.” However, it “dismissed as unhelpful the use of static ultrasound assistance – a quick-look visualization before the procedure to evaluate the best approach and mark the skin over the vein...” The authors felt that the use of static ultrasound had been too quickly dismissed based on limited data and wanted to see if static ultrasound was in fact useful.

Over the last number of years there has been an increase in literature that shows the

superiority of dynamic ultrasound over traditional landmark techniques when it comes to overall and first attempt success. This has been found by Keenan (1), Randolph et al. (2) and later confirmed in a meta-analysis by Hind et al. (3). However, the authors claim that the two studies used by the 2001 Agency for Healthcare Research and Quality Evidence Report, that dismisses use of static ultrasound were flawed. They felt that Mansfield et al. (4) was flawed because it was “performed in a high-volume center with very high pre-existing success rates” and “...included only subclavian central cannulas, which are the least amenable to ultrasound assistance.” Nadig et al. (5), they felt was flawed, because it “had no control group.” No study had previously compared both static and dynamic ultrasound with the use of a landmark group as a control.

This trial had primary and secondary hypotheses. The primary hypothesis, “that the ultrasound assistance of central cannula placement, both static and dynamic, would be superior to the landmark approach for cannulation success.” And the secondary hypothesis, “that ultrasound assistance, both static and dynamic, would be superior with regard to first-attempt success rate, number of sticks, time to cannulation, and complication rate.”

By directly comparing static ultrasound guidance with landmark technique, and comparing this with how dynamic ultrasound compares with landmark, the authors would be able to definitively comment on the usefulness of static ultrasound for central venous cannulation.

Methodology

This was a randomized, controlled clinical trial. It was experimental but not blinded due to the nature of the experiment.

The study was conducted on humans, the majority of which were from the Emergency Department and the Medical Intensive Care Unit. The controls were those patients randomized to the historical standard of central line placement by landmark technique. They estimated a sample size of 210 patients randomized to 3 groups would provide a power of 80% to detect a 25% difference in success rates at a test level of 0.05. The study fell slightly short of their goal and only enrolled 201 patients. However, I feel that the sample size was large enough to accurately assess their hypotheses. No specific description of the patients’ medical condition was given in the study, however, they indicated that any patient with an indication for central cannula placement, as determined by the attending physician, was included. Based on this we can assume when practicing in the

Emergency Department and ICU settings, the patient characteristics in the study would likely be similar to our own. However, this study did not include any elective/emergent Operating Room cases, which represents a large proportion of the lines we put in.

I feel the study was ethically sound. All three methods being studied are approved methods of central venous cannulation with very low risks associated with each. I do not feel that any specific group was put in a compromising situation by being entered into one of the three groups. In addition, these were procedures that were performed for a specific medical indication and no patients were subjected to any unnecessary procedures.

The exclusion criteria were any contraindications to internal jugular central cannula placement or inability to obtain or refusal of consent.

I feel the experiment protocol was properly designed to test the hypothesis. The study design was detailed sufficiently to allow reproducibility. The Methodology appears to be validated. The Likert scale measuring the clinician's overall preprocedure impression of difficulty was developed and validated in a previous article. As well, the statistical methods used have been validated such as R software, logistic and linear regression. The equipment used was detailed. They used an iLook25 SonoSite ultrasound machine with a 7.5-Mhz linear-array probe. Randomization was performed using a random number table. Enrolment forms were sealed in coded opaque envelopes. After consent was obtained and immediately before the procedure, a study investigator at the bedside opened the enrolment packet, which indicated the group to which the patient had been randomized.

The primary endpoint was based on the sample size needed of 210 patients.

As the study was performed in a clinical setting, I feel the protocol was clinically relevant.

Data Collection was performed by the investigator. They recorded the sonographer, operator, patient demographic data, vital signs, comorbidity, indication for central cannula, and anatomy score. In the ultrasound groups, vein diameter was also recorded. Following the procedure, the investigator recorded cannulation success, first-attempt success, number of attempts, time to cannulation, and complications.

Statistical analysis appeared appropriate. Data analyses were performed on an intention-to-treat basis. All enrolled patients were included in the analyses. Results were controlled for pretest difficulty assessment and were reported as odds

improvement over Landmark technique for both Dynamic and Static Ultrasound.

Results

The 3 groups were compared based on age, gender, ethnicity (as determined by investigator), preprocedure vital signs, comorbidity, indications for central cannulation, history of central cannulation, and anatomy score. The differences between the groups were negligible and were not considered significant. No group-to-group variability was noted.

No data/subjects were eliminated. However, 34 patients receiving central cannulation during this time period were eligible but not enrolled due to unavailability of an investigator (10) or investigators not called (24).

All results, both primary and secondary outcomes are laid out well in two tables.

Discussion

The main conclusions of the study were, 1) Ultrasound assistance is superior to the landmark technique, 2) Dynamic outperformed static ultrasound but may require more training and personnel, 3) All central cannulations should be conducted with ultrasound assistance, and 4) The 2001 Agency for Healthcare Research and Quality Evidence Report on patient safety dismissing static assistance was incorrect.

I would agree with the authors that the results support their conclusions. Their primary hypothesis which stated, "That the ultrasound assistance of central cannula placement, both static and dynamic, would be superior to the landmark approach for cannulation success" was directly addressed by the results. The authors do not explicitly explain the results, however, one could easily expect this as direct visualization of the vein during cannulation should lead to increased success, less pokes, less complications, etc. The authors suggest that an alternative interpretation of the data might be that "dynamic ultrasound should always be used when available and static ultrasound should be used only when the operator is unable to perform dynamic guidance single-handedly or when a second person is unavailable to facilitate the two-person technique." Alternatively, I would suggest that either static or dynamic approaches could be used as both have the exact same complication rate which is the ultimate concern regarding venous cannulation. Sure, the dynamic approach appears to be slightly faster on average (17 seconds), has a 12% superior first-attempt success rate, as well as a 0.6 difference in mean number of attempts than static ultrasound, however, as mentioned previously,

complication rates remain the same. Therefore, an argument could easily be made, that based on the physicians comfort level and tools available, the static approach would be perfectly acceptable.

All of the results, both primary and secondary outcomes, excluding complication rate were statistically significant. When comparing ultrasound techniques versus landmarking, I feel that the results are definitely clinically significant. However, when comparing static versus dynamic ultrasound, the results are a little less convincing to be applied to every clinical situation.

The results regarding ultrasound assistance versus landmark techniques for central cannula are in agreement with previous studies. The results examining the usefulness of static ultrasound, however, are in conflict with the few studies previously performed. This was in fact the impetus for the study.

This study gives further support behind the mounting evidence in favour of using ultrasound for all central venous cannulations, if at all possible.

Limitations noted by the authors included a selection bias towards “tough sticks” as physicians were more likely to contact the investigators for these types of patients. Ultrasound proponents could not be excluded from the study as they were among the few physicians in the hospital trained to use ultrasound, however, no significant difference in success rates among investigators and noninvestigators was found. The lead author placed about half the central cannulas. He was not blinded to study outcomes and could have inadvertently introduced bias, however, his success rates did not vary significantly from those for the study population at large.

Another limitation, from an anesthesia point of view, would be the fact that most patients were from the Emergency Department or the Medical Intensive Care Unit as opposed to the Operating Room. This selects patients who would be theoretically a little less stable than those coming to the O.R. Although we could generalize the findings of this study to apply to our patient population, there definitely is a difference. I think another key limitation is the small sample size when looking at complication rates. The small sample size did not properly differentiate the dynamic and static complication rates. It would be interesting to study a much larger population and see if there is any significant difference in complication rates between the dynamic and static groups.

I feel that very few questions are left unanswered following this third study by the Sonography Outcomes Assessment Program. The

data has consistently shown the superiority of using Ultrasound for central cannula placement versus the traditional landmarking technique. This study now proves the validity of using the “quick-look” technique. I think the final question remaining would be comparing dynamic with static ultrasound in a very large trial to fully assess complication rates. Most of the studies have shown dynamic ultrasound to be superior in reference to mean number of attempts, time to cannulation, first attempt success, but have not shown it to be overly superior in regards to complication rates. Many physicians feel it to be very cumbersome performing the dynamic approach and often assistance is not available. I think if a study were performed showing no difference in complication rates between the two groups, then we would be left with the ideal situation of the staff physician deciding on the method of ultrasound based on their own comfort level.

Applicability of the Paper

Throughout my Anesthesia training and over the course of my career, I will no doubt insert countless central lines. I will be training in a time when, based on these studies, all central lines will be placed under ultrasound guidance. This leaves me in a bit of a precarious position as I will get little experience putting lines in with the traditional landmark technique. And no doubt in the future, I will find myself in a situation without the availability of an ultrasound machine. However, this is no excuse to abandon a clearly superior technique for the very few occasions when ultrasound is unavailable. Having read this paper, I have a duty to my patients to insert them under ultrasound guidance whenever possible.

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“Effect of propofol and sevoflurane on coughing in smokers and non-smokers awakening from general anesthesia at the end of a cervical spine surgery”

Introduction

Critical appraisal of medical literature is the focused evaluation of proposed evidence by systematically investigating the validity of the study, soundness of the results, and relevance to clinical practice. It is the objective assessment of study design and process, including evaluation of its strengths and weaknesses and should be incorporated by all health professionals.

When reading published research it is important to understand that not all investigations are created equal, i.e., published information may not always be reliable or relevant, and we need to be careful that we do not make assumptions regarding the conclusions. Hence, to ensure clinical appropriateness, there needs to be a systematic method of evaluating printed research. Such a framework will be applied here to assess the clinical effectiveness of the prospective randomized double-blind study by Hans et. al. in the September 2008 volume of the British Journal of Anaesthesia.

To critically appraise this research we will be exploring three broad questions: 1. Are the results valid? 2. What are the actual results? and 3. Can these results be applied to day to day clinical practice? These three questions will help determine the reliability and relevance of the proposed conclusions and ultimately help us decide if this new information will ultimately be beneficial to our patients.

Are the Results Valid?

When assessing the validity of a study the initial question to ask is whether or not the study clearly addresses a focused issue. Is there a clear question proposed which requires a specific answer for which no previous answer exists under the same circumstances. The authors in our study clearly state in the title the aim of their research, including the populations of focus. They want to know specifically the effect of propofol versus sevoflurane on coughing in smokers and non-smokers while awakening from a very specific type of cervical surgery where they feel a reduction in cough would be clinically important. They give a clear description of how these interventions will be

implemented and compared, including specific drug concentrations and times of administration and completion, as well as a specific description of how outcomes were measured, thus allowing for reproducibility of the methods by another researcher if necessary. Description of any equipment used was also provided.

Further to the main question of focus, other study aims were also well delineated. Secondary outcomes were to determine the severity and moment of occurrence of the coughing episodes during emergence from anesthesia, as well as the influence of residual concentrations of anesthetic agents on the incidence of coughing. The authors do well in reporting on these listed outcomes only.

Inclusion and exclusion criteria for study subjects are also stated appropriately. Any ASA I or II patients undergoing cervical spine surgery via the anterior approach were potential participants. Those excluded from the study were those whom confounding variables were deemed likely - patients with a history of recent respiratory infection, asthma, COPD or coughing, those with signs of a difficult intubation, pregnancy and alcohol or drug abuse. The goals of the research are established from the beginning and they are sure not to deviate from this question throughout the paper.

Another key component of assessing study validity is randomization. Randomization is essential to ensure the elimination of bias during patient allocation. If subjects are not adequately randomized, the quality of the study should be questioned. The authors of the study in question claim it to be a randomized prospective study by describing the allocation process. Based on the chronological order of admission for surgery patients were randomly and equally placed into one of the two groups (propofol or sevoflurane) using a computer-generated randomization list. This appears to adequately meet the randomization requirement and thus helps to eliminate bias.

When further assessing validity, it is also important to be sure that all study participants are properly accounted for. It is common for participants to not complete a study for various reasons. All participants were adequately accounted for in the present study, with no loss of enrollment. It is also essential that the study question be adequately reviewed via an appropriate up to date literature search. On brief review of the listed references the authors appear to have provided adequate up-to-date, relevant and

supportive literature as a foundation for their proposed investigation.

Finally, when evaluating validity, it is essential to characterize some properties of the participants and researchers themselves: Were the participants and researchers 'blinded' to the treatment? Were the two groups being investigated similar? And were the two groups treated equally? Furthermore, it is important that ethical issues are considered.

Blinding is a means of ensuring that participants and researchers are unaware of which treatment group they are in, and thus preventing bias. In this study, it may be more important that the researchers are blinded when assessing coughs on emergence since the participants will unlikely be able to influence their coughing outcome on emergence from anesthesia regardless of whether or not they knew what treatment they were getting. In this study both the patients and researchers were blind to the treatments given. Coughing was assessed by a second anesthesiologist who entered the room following cessation of the anesthetic agents. Due diligence was performed to ensure monitors, syringes and other identifying material were hidden from the anesthesiologist doing the cough assessment.

The participants in both groups had similar pretreatment characteristics, including age, weight, height, gender, ASA classification and smoking status. An attempt was also made to treat both groups equally except for the type of anesthetic used. Each participant was pre-medicated with alprazolam + atropine at the same time prior to surgery, the same monitors were applied to all, including monitoring for depth of anesthesia, and extubation criteria were pre-established and adhered to closely. Coughing assessment was also performed equally on both groups at predetermined times. It is unsure if the same anesthesiologist did all of the intubations, but it is noted that they were performed by a senior anesthesiologist, thus helping to eliminate traumatic inductions and variations in intubation technique. It is also unclear if whether or not the same anesthesiologist evaluated the severity of the coughing on emergence of each participant. This may have some variation between observers. One difference is noted as well, in that the propofol group did not receive any sevoflurane, but the sevoflurane group did receive an induction dose of propofol. This should not be confounding however, given the length of the case prior to emergence and the relatively low effect of propofol at this time.

Ethical approval was noted to be obtained from the Institutional Ethics Review Board and informed consent received from each participant prior to enrollment.

Based upon acceptable answers to the above questions, the study appears valid and it is thus worthwhile continuing with evaluating the results.

What are the Results?

When considering the results of a study printed in medical literature, it is imperative to first determine if the results are valid before looking at the details. We have, in the above section, determined that the results of the study by Hans et. al. are likely valid and thus we can look a little closer at the claims made. It must be determined if there is an adequate description of the data collection methods used, whether or not the methods of analysis are appropriate and whether or not the key findings are significant.

First, there is adequate description of the data collection methods. Severity of coughing was measured using a four-level scale that was adapted from a previous study, and was again described here. The descriptions were clearly defined and appear to provide adequate information for assessment. Data for coughing episodes were specifically recorded at predefined intervals. Emergence time was described, and estimated residual anesthetic levels were measured at a specific time during emergence. Thus there is very little ambiguity in how the data were gathered and could easily be reproduced. I do not feel that there was another variable that should have been measured - the outcome was coughing secondary to the use of two anesthetic agents, and this is exactly what was recorded. Whether or not there is a more effective and objective way to measure cough (eg. pressure measurements) is unclear.

Secondly, a reasonable attempt was made at explaining the data analysis and statistical tools used. Sample size rationale was given based on previously recorded global incidence of coughing, and requirements were met (34) based upon the rationalization given. Data were expressed in appropriate terms, i.e., mean + standard deviation and percentages. Comparison of data was done using appropriate statistical tools, with variables described and appropriate p-value levels to demonstrate true differences. Strengths of relationships between variables were also elucidated using a sophisticated multinomial equation to determine the potential cough-reducing effect of any remifentanyl remaining at the time of emergence, since this may have been a

confounding factor if not analyzed appropriately.

Finally, the findings in this study directly answer the primary research question - that using propofol reduces the incidence of cough on emergence from anesthesia as compared to sevoflurane. The secondary aims are also addressed, including the finding that smokers in general have a higher incidence of cough as compared to non-smokers regardless of what anesthetic is used, and that the decrease in incidence of cough may be proportional to the level of residual anesthesia at the time of extubation, except in smokers receiving sevoflurane. The researchers were also able to determine the level of severity of cough at various times during the emergence process.

Are the Results Applicable?

It is essential that the results of any given study be applicable to day-to-day clinical practice. A good study will provide results that are transferrable to the population at large and improve individual patient outcomes and standard of care. For this to be the case the study participants need to have similar characteristics as patients that will be encountered by practitioners in similar fields. Furthermore, the practitioner implementing the results must be able to reproduce the study environment and have the skills and ability to effectively deliver the intervention, including the necessary supplies and equipment.

I feel that the results of this study by Hans et. al. are applicable and easily transferrable. There is no special equipment or skills required preventing easy implementation. The participant population does not appear to be different than the norm, although it remains to be seen how this technique could be employed in ASA III and above patients. The results may also be extrapolated into other types of surgeries where coughing could be detrimental to post-operative outcomes.

There appears to be clearly demonstrated differences between the use of propofol and sevoflurane and the incidence of coughing during emergence from anesthesia. Practical information related to the timing of severe cough during emergence and the level of residual anesthetic which may be required to prevent cough is also valuable. Other considerations for the use of these agents may have to be considered however, including cost of total intravenous anesthesia. On the other hand the benefits of preventing cough in certain surgical situations, may lead to the prevention of long term post-operative sequelae

which would be more costly in the long run. There is also further evidence for the cessation of smoking prior to surgery, and the use of IV anesthesia in smokers.

Overall, I feel this is a well designed study, based upon the framework used for critical appraisal of medical literature. A simple question was asked, a study designed, and results gathered and formulated into a conclusion which may be incorporated easily into clinical practice and ultimately improve patient care.

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***“Haloperidol Versus Ondansetron for
Prophylaxis of Postoperative Nausea and
Vomiting”***

The study *Haloperidol Versus Ondansetron for Prophylaxis of Postoperative Nausea and Vomiting* was published in the May 2008 edition of *Anesthesia and Analgesia* by Rosow *et al.* The research was based out of work done in the Department of Anesthesia and Critical Care at Massachusetts General Hospital, Department of Anesthesiology at the Yale University School of Medicine and Boston University School of Medicine. The study was directly comparing both the efficacy and side effect profile of Haloperidol versus Ondansetron as an anti-emetic for the treatment of post-operative nausea and vomiting (PONV). A large meta-analysis published in 2004 reviewed 23 studies (15 published and 8 unpublished) dating from 1962 – 1988, investigating the efficacy of haloperidol as an anti-emetic. This analysis found that at dosing of 0.25mg, haloperidol was not effective as an anti-emetic but at dosing of 1-4 mg statistical efficacy was obtained (Buttner *et al.*, 2004). There has been extensive research into the role and efficacy of dopaminergic antagonists and 5-HT₃ as anti-emetics (including side effects), but this was the first large study directly comparing Haloperidol to one of the 5-HT₃ antagonists. The hypothesis was that there would be no statistically significant difference between 1mg IV Haloperidol and 4mg IV Ondansetron when being used as a prophylaxis for PONV. The investigators also hypothesized that at the doses being used for the study, the risk of side effects would be extremely low.

This study was a third party blinded randomized control study, comparing parallel groups of 1mg IV Haloperidol versus 4mg Ondansetron. The patient group being investigated were scheduled for elective surgical procedures receiving either a general or combined general-epidural anesthetic, and were 18yrs or older and ASA I-III. The anesthesiologist was not blinded to the group assignment. No other prophylactic anti-emetic drug was used and propofol infusions were not used. Evaluation of the efficacy of the anti-emetic was performed by a blinded nurse in the PACU. The sample size in this study was 244 patients (n=119 haloperidol, n=125 Ondansetron) and based on the anticipated responder rate of 70% for the Ondansetron group, a power analysis concluded that the sample size was adequate.

The breakdown of surgical patients had nearly a 50-50 split between abdominal/pelvic procedures versus superficial/extremity, which would be a similar distribution to what is seen at Kingston General Hospital. The average duration of surgery was 195.5 minutes for the Haloperidol group and 196.9 for the Ondansetron group, which is likely longer than the average anesthesia time for Kingston General Hospital. Ondansetron is a widely used anti-emetic at Kingston General Hospital – making it a relevant control group.

There were a number of patients excluded from the study. Exclusion criteria included: severe documented PONV, cardiac arrhythmias, prior adverse reaction to Haloperidol/Ondansetron, current use of dexamethasone or dopamine antagonists, or a history of Parkinson’s disease or seizures. Excluding patients with prior severe PONV is ethically sound as multiple drug therapy should be used in these patients. The other exclusion criteria are all logical based on the guidelines for the use of dopamine antagonists. The study specifically attempted to include the widest patient base – so there were no other restrictions based on anesthesia, surgical or post-operative care. Of note, the anesthetic technique, use of nitrous, and the quantity of narcotic administered, were not mentioned in the paper.

The study protocol utilized a blinded PACU nurse to assess nausea using an 11-point verbal scale (0 = no nausea, 10 = worst possible nausea), in addition to patient demographics, risk factors, pain, sedation, dysphoria, delirium, dystonia, akathisia, and both pre and post-operative ECGs were used to investigate QTc prolongation. The primary endpoint was an Efficacy Analysis comparing nausea, emesis/retching, rescue anti-emetic drugs needed, highest nausea score and mean time to rescue drug. In addition a Safety (side effect) Analysis looking at QTc prolongation, sedation and time to discharge from PACU was performed. Data was collected up to the point of discharge from the PACU – so only early onset PONV was being examined by this study. The protocol utilized standardized ‘clinical supplies’ for the Ondansetron with no mention of a particular source, and the haloperidol was prepared by the hospital pharmacy with stock from Ben Venue Laboratories. There was no mention in the paper as how the patients were randomized to either the Ondansetron or Haloperidol groups, which was rather surprising. Adequate details of the statistical analysis were provided in the paper. The protocol was designed to test the hypothesis and was sufficiently detailed for easy reproducibility. A substantial shortcoming of the protocol is that there was no mention as to a standardized time for

administration of the anti-emetic. The haloperidol was given 87.8 ± 68.6 minutes before arrival in PACU compared to 56.6 ± 38.7 ($p = 0.02$). Not only is the difference statistically significant between the anti-emetics, but the variation within each anti-emetic group is substantial. Had the protocol standardized the time the anti-emetic was given it would make for a more reproducible study. The authors also mentioned that a lack of standardized anesthetic technique was a limitation in the protocol and would make reproducing the results more difficult.

The two groups had no statistically significant difference in their demographic data. As already mentioned – the only statistically significant difference between the two groups is the time the anti-emetic was administered prior to arrival in the PACU. There was no mention as to how many patients were eliminated from the study based on the elimination criteria. A point to note is that only 156 sedation scores were available due to an error in data entry. The results of the study are well presented in the paper using three tables: Clinical Characteristics of the Study Population, Efficacy Analysis, and Safety Analysis. No figures were used and there was likely no need as the tables provided a good representation of the data.

The main conclusion reached by the study is that 1mg IV Haloperidol has a similar efficacy and safety profile as 4mg IV Ondansetron. The study found no statistically significant difference between the Haloperidol and Ondansetron groups using any of the efficacy or safety (side effect) end points that were being evaluated. The study adequately answered the hypothesis and did not clog the paper with unnecessary information or statistics. The conclusions reached by the authors are supported by the published results in this paper and there is no obvious alternative interpretation of the data. The results of this study coincide with the results of a smaller study comparing Haloperidol to Ondansetron for gynecological procedures (Aouad *et al.*, 2007), though the efficacy of both anti-emetic drugs was greater in this study. The authors speculate that the patient criteria of this study may have excluded patients with more severe PONV when compared to the Aouad *et al.* study. An interesting addition to this study would have been to have a placebo group, as done in the Aouad *et al.* study. The results from this study clearly add to the existing literature as the sample size was larger, males were included, and a broader scope of surgical procedures were considered. The lack of standardized anesthetic technique make transferring the results from this study to routine practice more difficult.

Despite the results of this study there is still substantial work that could be done investigating the use of Haloperidol as an anti-emetic. This study investigated using both Ondansetron and Haloperidol as single agents. It would be interesting to see the results of a third group – investigating both the efficacy and safety of using the two drugs in combination. This study only investigated the use of 1mg IV Haloperidol whereas Buttner *et al.*'s meta-analysis noted the use of up to 4mg IV Haloperidol with increasing efficacy at higher doses. Finally comparing Haloperidol and Ondansetron using a more standardized or documented anesthetic approach would make it easier to transfer the results to routine practice.

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Queen's University Department of Anesthesiology Publication List 2008

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Full Papers:

1. Karkouti K, Beattie WS., **Arellano R.**, Aye T., Bussieres JS., Callum JL., Cheng D., Heinrich L., Kent B., Lee TW., MacAdams C., Mazer CD., Muirhead B., Rochon AG., Rubens FD., Sawchuk C., Wang S., Waters T., Wong BL., Yau TM. Comprehensive Canadian review of the off-label use of recombinant activated factor VII in cardiac surgery. *Circulation*. 118(4):331-8, 2008
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