

Queen's University

37th Annual Anesthesiology Research Day

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Scientific Adjudicators:

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MD, FRCPC

Jessica Burjorjee
MD, FRCPC

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SCIENTIFIC PROGRAM OUTLINE

0800 – 0810	Opening Remarks and Introduction of Guest Lecturer – Dr. Joel Parlow
0810 – 0820	Introduction of Research Day Presentations – Dr. Ian Gilron
0820 – 0920	Oral presentations (4)
0920 – 1010	Nutrition break
1010 – 1125	Oral presentations (5)
1125 – 1230	* LUNCH (provided) *
1230 – 1345	Oral presentations (5)
1345 – 1415	Nutrition break
1415 – 1500	Oral presentations (3)

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

The Judges will be:

Dr. Lindsey Patterson, Assistant Professor, Queen's Department of Anesthesiology & Perioperative Medicine

Dr. Jessica Burjorjee, Assistant Professor, Queen's Department of Anesthesiology & Perioperative Medicine

1500 **Dr. Hance Clarke**, Assistant Professor, Department of Anesthesia,
University of Toronto

*** Guest Lecture ***

**"Reducing Post-surgical Pain and Chronic Pain Disability:
The development of a Transitional Pain Service following major surgery"**

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

Oral Presentations (alphabetical order)

(presentation order to be announced) ----- page 1/2

Liban AHMED, PGY3

“Comparison of the efficacy of a novel periarticular analgesic injection to single shot ultrasound guided interscalene brachial plexus blockade as part of a multimodal analgesia regime in patients undergoing arthroscopic shoulder surgery” (update)

Michael BAXTER, B.H.Sc (Hons), MD Candidate Class of 2017

“Effect of antithrombotic agents on surgical timing after hip fracture” (update)

Sophie BRETON, PGY-2

“Hepatitis C virus transmission: Can patients be infected through reuse of anesthetic medication vials accessed with clean needles and syringes?” (proposal)

Mark BROUSSENKO, MD Candidate, Class of 2016

"Dedicated Anesthesia Assistants in Cardiac ORs: A Survey of National Practices" (update)

James CHENG, PGY4

“Periarticular Versus Systemic Ketorolac in Total Knee Arthroplasty Patients: Is there a Difference?” (update)

Jamei ENG, PGY3

“Improving post-operative pain control by increasing the alkalinity of epidural solutions.” (update)

Tanya GRIFFITHS, PGY4

“Prevalence of Thromboembolic Events in Surgical Patients Receiving Epidural Analgesia.” (update)

Yuri KOUMPAN, PGY-2

“Oncologic outcomes in transurethral resection of bladder tumor (TURBT) patients undergoing general anesthesia vs. spinal anesthesia: a retrospective review” (proposal)

Jordan LEITCH, PGY-2

“Randomized Control Trial of Novel Formulation Trigger Point Injections for Relief of Chronic Myofascial Pelvic Pain” (proposal)

Sneha LOHAN, BSc. MD Candidate, Class of 2017

“Current patterns of practice in the management of thoracic epidural analgesia and perioperative coagulopathy in patients undergoing hepatic resection: A Quality Improvement Initiative” (update)

Sarah MAXWELL, PGY-2

“How does maintenance of intra-operative hemodynamic stability with esmolol, labetalol or fentanyl impact recovery during elective outpatient laparoscopic cholecystectomies?” (proposal)

Curtis NICKEL, PGY3

“Perceptions of Yearly Summative Examinations in the Queen's Anesthesia Simulation Program.” (update)

Oral Presentations (alphabetical order)

(presentation order to be announced) ----- page 2/2

Gita RAGHAVAN, PGY4

“Bilateral transverse abdominis plane block with or without magnesium for total abdominal hysterectomy and bilateral salpingo-oophorectomy – a randomized controlled trial.” (update)

Navroop SANDHU, PGY3

“Examining the Influence of Anesthetic Practices on Maternal Outcomes in a Resource Poor Setting (Tanzania).” (update)

Kaitlyn TRESIDDER, BSc, MSc Candidate,

“Chronobiology of pain” (proposal)

Sam WALSH, PGY-2

“Postsurgical Pain After Hospital Discharge: A Systematic Review” (proposal)

Dana ZORATTO, PGY3

“Does magnesium sulfate as a supplement in adductor canal blocks improve pain control after total knee arthroplasty?” (update)

Poster Presentations

Charvi BHATT and Nader Ghasemlou, “Microarray analysis of macrophage subtypes”

Troy CHOW, Amanda MARACLE, Louie Wang* and Nader Ghasemlou*, “Retrospective patient analysis correlates INR levels with adverse surgical outcomes”

Nicole MURRELL (BASc, MENg candidate), Julia PRINCE (BASc, MENg candidate), Joël COUTURE-TREMBLAY (BASc, MENg candidate), T. Bryant, P. Fenton, D. DuMerton-Shore, R. Phelan, D. Petsikas, T. Saha. “Retractor Redesign To Enable Continuous Force Measurements Throughout Mid-sternal Retractions In Cadavers: Implications For Chronic Post-Sternotomy Pain”

Rima SANAALLAH and Nader Ghasemlou, “Tissue damage and mast cell activation in surgical wounds”

David WIERCIGROCH BSc Candidate, Patrick GRENIER MSc, Mary C. Olmstead. “Effect Of Ultra-Low Dose CB1 Antagonist Rimonabant On Chronic Morphine-Induced Tolerance And Gliosis”

Comparison of the efficacy of a periarticular analgesic injection to single shot ultrasound guided interscalene brachial plexus blockade as part of a multimodal analgesia regime in patients undergoing arthroscopic shoulder surgery
Liban Ahmed, PGY2; Supervisor: Dr. John Murdoch

Background: Arthroscopic shoulder surgery can be associated with significant post-operative pain that may be difficult to manage and may delay patient discharge.¹ This pain can be alleviated by the peri-operative performance of a single shot interscalene brachial plexus block. However, this technique remains relatively specialized, and it is not within the skill set of all anesthesiologists. Moreover, the block has significant side effects and complications that may preclude its use in some patients.²⁻³

In knee and hip arthroplasty surgery, analgesia has been significantly improved and simplified with the introduction of the periarticular injection of an analgesic mixture containing a local anesthetic, ketorolac, morphine, and epinephrine.⁴⁻⁸ This mixture is injected in extra-articular tissues, primarily muscular planes around the joint, during the surgery by the surgeon performing the operation. Despite its efficacy in lower limb surgery, there have been no studies examining this periarticular technique for postoperative pain management in upper limb surgery.

Purpose: We propose to study the periarticular instillation of the same mixture used originally in lower limb surgery in shoulder arthroscopic surgery. We will compare the periarticular analgesic injection to a single-shot U/S guided interscalene brachial plexus block as well as standard care in a randomized controlled trial.

Study Design: Inclusion criteria will include ASA 1-3 patients, aged 18-80, having elective shoulder arthroscopic surgery at Hotel Dieu Hospital. Following signed informed consent, participants will be randomized to receive either a (1) pre-operative single shot interscalene brachial plexus regional block, (2) an intra-operative peri-articular injection, or (3) no injection ('standard care'). Participants will receive standardized premedication, a standardized general anesthetic, and standardized intra-operative analgesia and post-operative analgesia. The assessors will be blinded as best as possible as to which modality the participant received.

Outcomes: Postoperative data will be collected by the research nurses in the PACU and in a telephone follow up questionnaire 24 hours after surgery. The primary outcome will be analgesic requirements in the first 24 hours. Secondary outcomes will include pain scores in the first 24 hours, time to first analgesic requirement, opioid-related side effects, time to discharge, adverse events, and overall satisfaction with the analgesia.

Hypothesis: We are hypothesizing that the interscalene block will be more effective than the periarticular injection. We hypothesize that the periarticular injection will be more efficacious than 'standard' care.

References

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3. Hortense A, Perez MV, Amaral JL, et al. Interscalene brachial plexus block. Effects on pulmonary function. *Rev Bras Anesthesiol* 2010;60:130-8.
4. Chaumeron A, Audy D, Drolet P, et al. Periarticular injection in knee arthroplasty improves quadriceps function. *Clin Orthop Relat Res* 2013;471:2284-95.
5. Ng FY, Ng JK, Chiu KY, et al. Multimodal periarticular injection vs continuous femoral nerve block after total knee arthroplasty: a prospective, crossover, randomized clinical trial. *J Arthroplasty* 2012;27:1234-8.
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7. Teng Y, Jiang J, Chen S, et al. Periarticular multimodal drug injection in total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2013.
8. Vendittoli PA, Makinen P, Drolet P, et al. A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study. *J Bone Joint Surg Am* 2006;88:282-9.

Title: Effect of antithrombotic agents on time to surgery after hip fracture

Michael Baxter BHSc, Janet van Vlymen MD FRCPC, Melanie Jaeger MD FRCPC, Wilma Hopman MA

Introduction: Numerous studies have shown that patients with acute hip fractures suffer increased morbidity and mortality if their surgery occurs longer than 48 hours after presentation to the Emergency Department (ED).^{1,2} Managing patients using anticoagulant and antiplatelet medications may result in delays for surgery following hip fractures. However, there is sparse evidence in the literature delineating reasons for surgical delays and outcomes, despite a rising number of our elderly patients taking these medications.³

Methods: Following institutional ethics board approval, a retrospective chart review was conducted on 427 consecutive patients presenting to the ED with suspected hip fracture at Kingston General Hospital between January 2014 and November 2015; of these, 394 had a primary presentation of hip fracture and were managed operatively. Information was collected regarding patient demographics, medications, comorbidities, perioperative investigations and management, operative and anesthetic details, and acute length of stay (LOS). Multivariate linear regression analysis was used to determine the contribution of individual factors to two primary outcomes: time to surgery (TTS) and acute LOS.

Results: Prior to ED presentation, 25% (99/394) of patients were taking warfarin (41/394), a novel oral anticoagulant (NOAC) (20/394) or non-ASA antiplatelet medication (38/394). Mean TTS from ED presentation for all participants was 34.5 hours. Surgery was delayed more than 48 hours in 21% (84/394) of patients, while an additional 20% (80/394) had surgery between 36 and 48 hours. Patients on warfarin and NOACs had a longer TTS compared to those not on an anticoagulant (46.1h and 43.2h vs. 32.5h). Patients taking non-ASA antiplatelet agents did not have a significant increase in TTS. Multivariate analysis revealed a significant association between increased TTS and warfarin use (8.0h longer, 95% CI 1.4-14.6, $p=0.017$). However, the increased TTS did not maintain significance on multivariate analysis for NOACs (7.3h longer, -1.5-16.2, $p=0.077$), likely due to the small numbers. Mean acute LOS for all participants was 8.5 days. The need for a postoperative transfusion was associated with an increased acute LOS on regression analysis. Preoperative warfarin reversal patterns showed uniform usage of an initial Vitamin K dose but variable use of prothrombin complex concentrates, plasma, and additional Vitamin K.

Discussion: In this retrospective review, patients taking warfarin preoperatively were shown to have increased TTS. Despite recognized guidelines detailing timely INR reversal protocols,⁴ those taking warfarin still experienced significant delays. Interestingly, those patients on NOACs did not wait longer than those on warfarin, even though there is no optimal reversal agent. There is opportunity to improve our management of warfarin reversal to minimize delays in TTS and subsequent increased morbidity and mortality.

References:

1. PLoS One 2012 7: e46175
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3. Clin Geriatr Med 2014 30: 219-227
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Hepatitis C virus transmission : Can patients be infected through reuse of anesthetic medication vials accessed with clean needles and syringes?

S. Breton PGY2 - Staff supervisors : Dr Jaeger and Dr Van Vlymen

Affiliations : Dr Selena Sagan and Dr Prameeth Sheth

Background: Hepatitis C virus (HCV) infections remain a significant cause of morbidity and mortality. Given the current knowledge of blood-borne diseases, it is alarming that patient-to-patient transmission of blood-borne viruses still occurs as a result of unsafe injection practices, poor sanitation procedures, or the use of contaminated medical equipment. In the 1990's increasing health care-associated HCV outbreaks attributed to poor injection practices served as the impetus for health agencies to develop the "One & Only" campaign which advocated '1 syringe + 1 needle + 1 time'. Despite the widespread adoption of these infection-control guidelines, health care-associated HCV outbreaks continue to be frequently reported. Recently, Public Health reported outbreaks of HCV at 4 different endoscopy and colonoscopy clinics in Ontario. Investigations suggested that the most likely source of transmission was from contaminated intravenous medications administered by the anesthesiologist. In most of these cases, there was no evidence that syringes were reused between patients and the anesthesiologists involved adamantly denied this practice.

The practice of sharing medication vials between patients, combined with the inadvertent contamination of an anesthesiologist's workspace may be facilitating these outbreaks. Drug shortages and resources constraints drive the former, and the latter has been well demonstrated. As this contamination is widespread, it is feasible that the rubber diaphragm of a medication vial could become unknowingly contaminated with blood containing a significant viral load when caring for HCV-infected patients. Studies have shown that HCV remains stable on inanimate surfaces and within medications such as fentanyl, midazolam and propofol for days to weeks. If contamination such as this is unrecognized, the risk of transmitting HCV to subsequent patients could be significant, even if a new needle and syringe are used to access the medication.

Hypothesis: When caring for HCV-infected patients, an anesthesiologist may inadvertently and unknowingly contaminate the outside diaphragm of a medication vial with HCV-containing fluids and a sterile needle and syringe puncturing the diaphragm could inoculate the medication inside the vial with virus. This could result in sufficient quantities of infectious virus within the medication to infect subsequent patients receiving the drug with a new sterile needle and syringe. Secondary hypothesis: a single wipe of a 70% isopropyl alcohol swab across the vial top is not sufficient to eradicate the virus.

Methodology: We will be drying a high titer cell culture-derived HCV virus preparation on the outside of the rubber access diaphragm and then puncturing into the medication with a sterile needle. Resultant infectivity of the inoculated media will be determined by focus-forming unit (FFU) and/or 50% tissue culture infective dose (TCID₅₀) assays at various time points post-inoculation. HCV infectivity within vials of propofol, rocuronium, fentanyl and lidocaine will also be determined using these assays.

Significance: HCV infection via our hypothesized mode of transmission has been neither investigated nor demonstrated. Positive study results would have a significant impact on health care as it will highlight the critical importance of appropriate infection control practices as well as identify the necessary cleaning methods of vial access diaphragms to prevent inadvertent transmission of HCV. It has the potential to significantly alter our daily practices concerning medication administration as well as influence pharmaceutical industries to package medication in smaller, single-dose vials.

Title: Dedicated Anesthesia Assistants in Cardiac ORs: A Survey of National Practices

Authors: Saha, T., Allard, R., Arellano, R., Broussenko, M., Diem, T., Engen, D., Tanzola, R. and Pierre Laflamme.

Presenting Author: Mark Broussenko, MSc, MD Candidate Class of 2016

Background: The need for dedicated assistance during complex cases in anesthesia has long been recognized in the literature. The Canadian Anesthesiologists Society (CAS) has issued statements in support of anesthesia care teams; multidisciplinary teams run by anesthesiologists with access to dedicated support personnel, including anesthesia assistants. While access to anesthesia assistants during cardiac anesthesia has been a long-standing CAS recommendation, actual staffing patterns vary significantly nation wide. In order to ascertain the impact of dedicated support staff for complex cases, it is first necessary to identify patterns of access to allied health professionals, as well as both actual and perceived modifications in practice and comfort level amongst cardiac anesthesia providers.

Methods: A fifteen-item inventory was developed to evaluate the types of support staff available at each institution, patterns of practice related to perioperative care delivery and interruptions and perceived impacts on delivery of care, particularly from a patient safety perspective. This survey was distributed to individual cardiac anesthesiologists at all community and academic cardiac centers in Canada. The distribution list was populated using a pre-existing database compiled at the University of Ottawa. Responses were blinded and anonymous, though individuals were asked to identify their primary institutional affiliation. No incentives were offered for participation, and none of the study authors had any conflicts to declare relating to survey distribution or analysis of the data.

Results/Discussion: At the time of this writing, data collection was complete and in the process of being analyzed. Results and conclusions will be presented at the 2016 research day.

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

Dr. James Cheng PGY-4; Staff Investigators: Dr. John Murdoch Dr. Mike McMullen

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

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

Study Design: Prospective, single Center, blinded, randomized-controlled trial

Patient Inclusion Criteria:

- Elective primary unilateral knee arthroplasty under spinal anesthetic
- Age 20-85 years of age
- Able to comprehend and provide informed consent
- ASA: I-III
- Diagnosis of degenerative arthritis

Patient Exclusion Criteria:

- regular opioid use
- bleeding disorder
- psychiatric disease
- previous diagnosis of a chronic pain syndrome
- known allergy to PAI mixture components
- significant liver or renal disease
- severe asthma

Intervention: Patients scheduled for unilateral total knee arthroplasty surgery will receive a spinal anesthetic with standard epi-morph dose +/- short-acting medications for sedation (ie. propofol, midazolam). Intra-operatively, patients will not receive any long-acting opioids or ketamine. Patients will be randomized to either the control group or the intervention group.

1. control group:

- a. PAI mixture of ropivacaine 3mg/kg, ketorolac 30mg, epinephrine 0.3mg diluted with normal saline to 120mL
- b. PAI mixture will be systematically infiltrated into the different knee components as per usual surgical protocol
- c. Patients will also receive an IV injection of 1cc normal saline at the time of PAI injection.

2. Intervention group:

- a. PAI mixture of ropivacaine 3mg/kg, epinephrine 0.3mg diluted with normal saline to 120mL.
- b. PAI mixture will be systematically infiltrated into the different knee components as per usual surgical protocol
- c. Patients will also receive an IV injection of Ketorolac 30mg at the time of PAI injection.

Post-operatively, patients will receive a PCA for post-operative analgesia.

Outcomes: The primary outcome will be post-operative 1-10 numeric pain scores (at rest and with mobilization) in PACU, 4 hours post-op, POD-1, and POD-2. Secondary outcomes will include post-op PCA opioid use, VAS patient satisfaction score, length of hospital stay, and incidence of nausea/vomiting and constipation. A significant difference in the post-operative VAS still be defined as 2.

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Improving post-operative pain control by increasing the alkalinity of epidural solutions. Presented by
Jamei Eng PGY3
Supervisors: Dr. Richard Henry, Dr. John Murdoch

Despite the evolution of various other regional anesthetic techniques, epidurals are still thought to provide exceptional pain control. In patients with significant cardiac or respiratory conditions, epidurals are even more important in postoperative management than PCAs. Despite having a well-trained physician placing the epidural, and positive intraoperative clinical signs, patients are often in PACU complaining of pain. Failure rates for epidurals have reportedly been around 30% for both thoracic and lumbar epidurals. There are numerous reasons for epidural failures, the most common being epidural catheter migration or misplacement of the catheter, resulting in inadequate analgesia.

Current practice with laboring women that have epidurals heading to the OR for a cesarean section consists of administering a bolus of lidocaine in their epidural in order to obtain a rapid onset of surgical block. One of the common adjuncts particularly used in epidurals that had been previously placed includes sodium bicarbonate. In theory, lidocaine enters the epidural space as both its ionized and unionized form. The unionized form allows for migration across the lipid membrane in order to exert its action on the nerve root. The addition of sodium bicarbonate, creates a more alkaline environment, thus increasing the proportion of local anesthetic in its unionized form. By increasing the amount of local anesthetic reaching its target of action, the onset of block is faster, the depth of block is greater, and potentially may even affect the spread of epidural blockade.

Currently, there is no published data available detailing the use of sodium bicarbonate in non-obstetrical surgery. In this study, we hope to determine whether there may be a role of sodium bicarbonate in postoperative epidurals, specifically thoracic epidurals. Preliminary steps include determining the pH of our standard epidural solutions, and determining the pH after the addition of sodium bicarbonate. Secondly, if ethics approval can be obtained, a pilot study will be conducted with 10 randomly chosen patients to receive bicarbonate just prior to arrival to the post anesthetic care unit. Primary outcome measures will include patient pain scores as well as level of sensory block within 24 hours postoperatively. Secondary outcome will look at duration of time until inadequate block.

Prevalence of Thromboembolic Events in Surgical Patients Receiving Epidural Analgesia

Tanya Griffiths, MD, PhD,

Supervisors: Rosemary Wilson RN(EC) PhD, Ryan Mahaffey, Melanie Jaeger

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

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

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

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

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

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

A query of the APMS database from January 2009 – December 2013 was performed to identify all patients undergoing a general surgical procedure with an abdominal incision who had epidurals placed to provide analgesia. Using the CR numbers from the APMS database, patient data was extracted from the hospital database and the subset of patients who had a radiographically diagnosed DVT or PE (ascertained from ICD codes) will have a full chart review performed covering the highest risk 12-week postoperative period. Data analysis is underway and the need for further chart abstraction is being determined.

Oncologic outcomes in transurethral resection of bladder tumor (TURBT) patients undergoing general anesthesia vs. spinal anesthesia

Yuri Koumpan, MD, Glenio Mizubuti, MD, MSc, Melanie Jaeger, MD, FRCPC, Rob Tanzola, MD, FRCPC, Rob Siemens, MD, FRCSC

Background: Despite modern advances in surgical techniques, the main cause of cancer-related deaths is cancer recurrence and metastasis.(1) It is becoming increasingly recognized that the peri-operative period around tumor excision is critical in reducing recurrence, and surgery itself may cause microvascular seeding and dissemination of cancer cells.(2) Various peri-operative factors have been implicated in negatively modulating the immune system to promote cancer cell growth, including surgical inflammation, volatile anesthetics, opioids, hypothermia, and blood transfusions.(3–7) On the other hand, regional anesthesia has been suggested to reduce peri-operative immunosuppression, improve the function of cancer-killing immune cells, and reduce the use of volatile anesthetics and opioids.(3,4,6,8) There have been many studies over the past decade that have attempted to demonstrate a positive effect of regional anesthesia on cancer recurrence and cancer survival with mixed results.(9–15) A recent meta-analysis concluded that regional anesthesia improves overall survival after oncologic surgery, but not cancer recurrence rates.(9) Regarding spinal anesthesia in particular, it has had favorable effects on immunosuppression compared to general anesthesia in human and mice models(16,17); however, a recent retrospective study looking at radical prostatectomy patients failed to demonstrate reduced cancer recurrence with spinal anesthesia alone vs. general anesthesia.(18)

Bladder cancer is the ninth most common cancer in the world, with 430,000 new cases diagnosed in 2012.(19) Most of these are urothelial, 70% of which are non-muscle invasive.(20) These are typically treated with a transurethral resection of the bladder tumor (TURBT). Many of these patients do not die from their disease, but experience frequent recurrences. No studies that we know of have explored a potential impact of spinal anesthesia compared to general anesthesia on cancer recurrence rates or survival in TURBT patients. Given the high rates, we believe that examining the potential role of regional anesthesia on reducing bladder cancer recurrence is important.

Objectives

Our primary objective is to determine if anesthetic type (general anesthesia vs regional) affects cancer recurrence. Our hypothesis is that patients with high grade, non-muscle invasive bladder cancer undergoing TURBTs under spinal anesthesia will have a longer time to first recurrence. Our secondary hypothesis is that those patients who had a spinal anesthetic for their TURBT will have a lower rate of cancer progression, defined as muscle-invasive bladder cancer or requiring cystectomy (secondary outcomes), when compared to those patients who had a general anesthetic.

Methods

We propose to answer our objectives through a retrospective, electronic chart analysis of approximately 560 patients diagnosed with high grade, non-muscle invasive bladder cancer between 2001-2011. We have a database from this time period of all patients undergoing TURBTs for bladder cancer and follow-up data on cancer recurrence incidence and time to first recurrence. We will have to further review this database for information regarding type of anesthetic, but this information is accessible.

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

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Background:

Chronic pelvic pain is a common and disabling condition - it is estimated that 16% of women experience the debilitating functional, emotional, and sexual associated deficits. Practically, this is an extremely costly health care issue, accounting for one of every ten gynecologist visits, and is a frequent indication for surgery, despite little proven benefit.¹ Bedalwy and colleagues postulate that up to 85% of chronic pelvic pain is myofascial in origin, which is comprised of somatic pain (contraction knots or “trigger points”), associated symptoms (dyspareunia, urinary frequency), and co-morbid conditions (endometriosis, recurrent urinary tract infections, interstitial cystitis).²

Trigger points account for the somatic pain experienced by patients, which can be either latent (painful when palpated) or active (unprovoked, spontaneous pain). Trigger points develop due to a failure of voluntary muscle to relax, resulting in a chronic state of contraction and a relative ATP (energy) crisis. Essentially, chronic contraction causes decreased tissue perfusion, which in turn results in a local decrease in energy production and increase in anaerobic cellular respiration. The hydrogen ions (lactic acid) produced during anaerobic metabolism stimulate peripheral nociceptors that cause pain.³ The contraction is further perpetuated by a lack of inhibition of the ryanodine receptors (due to a deficiency of both ATP and magnesium) which results in an increase in the amount of calcium present in the sarcoplasm to facilitate muscle contraction.

Current recommendations for the treatment of myofascial pain and trigger points according to the Society of Obstetricians and Gynecologists includes trigger point injections, physical therapy, and manual therapy. Various formulations have been trialed, including local anesthetics, steroids, and botulinum toxin.⁴ Lidocaine formulations are the most commonly used, despite a paucity of robust research and sound study design demonstrating benefit. As such, there is no clear consensus or guidelines on the most appropriate injection formulation.

Rationale & Hypothesis:

The novel injection formulation utilized in this study targets the pathophysiology of trigger points on a cellular and mechanistic level, and is comprised of magnesium, bicarbonate, dextrose and lidocaine. We hypothesize that women suffering chronic myofascial pelvic pain who receive trigger point injections comprised of this novel formulation will report an average weekly pain score of at least 11mm less on the visual analog pain scale compared to those treated with lidocaine-only trigger point injections.

Study Design & Methods:

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

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Current patterns of practice in the management of thoracic epidural analgesia and perioperative coagulopathy in patients undergoing hepatic resection: A Quality Improvement Initiative

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Introduction:

Epidural analgesia is often the preferred choice for pain management following partial liver resections at our academic center. However, the improved postoperative pain control must be balanced against the risks of bleeding in the setting of an anticipated perioperative coagulopathy. With the potential for significant intraoperative blood loss and associated reduction in the clotting factors, hepatic resections are frequently associated with administration of fresh frozen plasma and vitamin K. In this quality improvement initiative, we sought to retrospectively assess how the use of epidural analgesia, influenced postoperative recovery with a particular emphasis on the perioperative utilization of fresh frozen plasma to correct the postoperative coagulopathy in patients receiving epidural analgesia.

Methods:

Following research ethics board approval, charts of patients who have undergone liver resection surgeries at our institution in the past 5 years were reviewed retrospectively. Several parameters such as patient demographics, use of epidural analgesia, timing of epidural removal, laboratory values (INR, CBC) and the use of FFP and/or vitamin K and any associated complications were recorded. Pain scores (static and dynamic) and the occurrence of side effects were obtained from the electronic database of structured daily assessments performed by our acute pain service on each postoperative day.

Results:

Of the 176 patients reviewed a majority (n=142, 81%) of patients had an epidural catheter. The average time to removal of these epidural catheters was 3.4 ± 1.2 days with a range from 0-7 days. On the day of removal the average INR was 1.25 ± 0.16 and a delay in removal due to coagulopathy was documented in 15 patients. On the day of removal, 18 patients had an INR >1.4 and FFP was effectively administered to 8 patients to reverse the coagulopathy without any noted complications. Vitamin K was administered to 48 patients during the postoperative period. Furthermore, of the 142 epidurals, 25 were converted to PCA pumps due to epidural failure and 44% patients reported being in moderate to severe pain (pain scores greater or equal to 4) upon activity on POD 1.

Discussion:

Following an initial review of dataset, the authors believe that our current practice of using epidural analgesia is safe and has the potential to facilitate postoperative recovery of patients undergoing hepatic resections. However, this preliminary review suggests that there is room for improvement in particular: addressing mechanisms to further reduce the failure rate, and educating all those involved in the postoperative care regarding the unique concerns regarding perioperative coagulation. The changes in postoperative coagulation altered management in a minority of cases (11%) and even fewer involved the utilization of blood products (6%). We intend to conduct further analysis of the database to help determine predictors of the extent of postoperative coagulopathy and options for management that are acceptable to all members of the perioperative team involved in the care of these complex patients.

LABETALOL AND TIME TO DISCHARGE IN LAPAROSCOPIC CHOLECYSTECTOMIES

Sarah Maxwell, Judy Marois, Dale Engen, Rob Tanzola

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

Methods: Local ethics committee approval was obtained and all patients provided written informed consent prior to study enrollment. One hundred and seven ASA class I-II patients undergoing elective ambulatory laparoscopic cholecystectomy at an academic hospital were randomized to one of 3 double blinded groups for management of increased intraoperative HR or MAP over 20% of baseline: 1) IV fentanyl bolus 50 mcg q5 min., 2) IV labetalol bolus 5 mg q5 min. or 3) IV esmolol bolus 0.25 mg/kg followed by a titrated infusion of 5-15 mcg/kg/min. Time from arrival in post-anesthesia care unit (PACU) to readiness for discharge was recorded as the primary outcome. Secondary outcomes included intraoperative and PACU hemodynamics (HR, MAP), total PACU fentanyl requirements, time to first PACU analgesia, the incidence and management of postoperative nausea and vomiting (PONV) and pain scores. Pain was assessed with the Visual Analogue Pain Score (0=no pain, 10=worst pain) and the incidence and treatment of PONV was assessed at 5, 30 and 60 minutes post-arrival in the PACU. Patient satisfaction scores (1= most satisfied, 5=dissatisfied), prescription analgesia requirements, and pain scores were recorded at 24 hours.

Results: The following are preliminary blinded results of the 107 patients enrolled out of the target of 141 (table 1). No treatment was required for intraoperative or PACU hypotension or bradycardia following administration of study drugs. Patient satisfaction at 24 hours was equivalent for each group (1.5/5).

Discussion: The preliminary blinded results demonstrate a safe protocol for the three medication groups. We hope the final results of this study will expand on the potential benefits of beta blockers for managing intraoperative sympathetic stimulation and specifically identify the utility of labetalol. Labetalol may more effectively control intraoperative hypertension given additional activity at alpha adrenergic receptors, is easier to administer since does not require an infusion, and is less expensive than esmolol.

Table 1: Preliminary blinded results for currently enrolled patients (N=107)

Variable	Group A (n=36)	Group B (n=35)	Group C (n=36)
Time to discharge (min)	132	129	139
Time to PACU discharge readiness (min)	43	46	50
Time to first PACU fentanyl (min)	15	21	17
Total PACU fentanyl (mcg)	77.2	59.3	59.0
Pain scores at rest (#/10)			
PACU arrival (t=0 min.)	2.8	2.1	2.6
t=30 min.	4.4	3.0	3.7
t=60 min.	3.5	3.1	3.2
t=24 hr.	3.1	2.4	3.1
Incidence PONV (%)			
PACU arrival (t=0 min.)	25	37	8
t=30 min.	22	37	14
t=60 min.	22	29	6
PONV treatment (% required)			
Dimenhydrinate	16.7	28.6	2.8
Metoclopramide	38.9	54.3	25.0
Opiate use at 24 hr. follow-up (# patients prescribed [mean # pills taken])			
No medication used (%)	16.7	14.3	5.6
Tylenol#3	3 [3.7]	5 [4.8]	5 [7.2]
Morphine 5 mg tab	1 [3.0]	3 [4.2]	---
Morphine 10 mg tab	---	---	---
Oxycodone 5 mg tab	2 [4.5]	2 [6.0]	1*
Oxycodone 10 mg tab	4 [3.3]	1 [2.0]	2 [6.0]
Percocet	17 [4.4]	17 [5.4]	22 [4.1]
Hydromorphone 1-2 mg tab	---	1 [4.0]	2 [4.5]

* number of pills taken not recorded

Title: Perceptions of Yearly Summative Examinations in the Queen's Anesthesia Simulation Program

Authors: Dr. Curtis Nickel, Dr. M. McMullen

Introduction and Rationale: There has been a significant increase in the usage of simulation based education and assessment methods throughout many professional domains in the past ten to fifteen years. As this has progressed, there has been a renewed exploration of high fidelity simulation as a high-stakes summative assessment method.

Research surrounding simulation as an educational and assessment tool has mirrored its increased usage. There are many potential benefits to using simulation beyond more traditional assessment methods. Research has shown that simulation provides the ability to assess higher levels of competency in Miller's pyramid of competence, specifically the "does" or "Shows How" levels in the behavioural categories. As well, it can assess non-medical knowledge and identify gaps in safe anesthesia practice. Finally, simulation provides an excellent opportunity to assess rare or complicated scenarios in a safe environment.

The practice of anesthesia education and certification is currently undergoing a significant change. The move towards Competency Based Medical Education will drive forward many new and old assessment methods and it is likely that simulation will begin to play a large role in the assessment of residents. In Canada and at Queen's University specifically, the introduction of the CanNASC program for PGY 4-5 has already begun to do this. However, using simulation as a high-stakes summative assessment goes against much of the traditional model of simulation education that focuses on formative assessment and the ability to make mistakes without concern for your academic standing. As these changes evolve, many programs are without a defined simulation assessment tool or evaluation, Queen's included.

Study Objective: Investigate the fundamental perceptions of major stakeholders (program administrators in postgraduate medical education, faculty facilitators in medical simulation, and anesthesia residents) surrounding the adoption of a simulation curriculum that incorporates yearly summative or examinations.

Methodology: The study will be completed using a qualitative and mixed method methodology. Purposive sampling will identify the appropriate stakeholders and an initial survey will assist in grouping individuals and identifying initial themes. Semi-standardized interviews will then occur and be analyzed for predominate themes. This study will be multi-site with the involvement of one to two other major anesthesia programs and simulation centres.

Outcomes: This project will assist in the elucidation of important benefits and barriers to using simulation as a summative assessment. It will also help to identify fundamental aspects desired in simulation assessment, which will inform the development of a simulation assessment tool. Finally, it will assist in the discussion around simulation education and assessment in our residency program and potentially help develop a collaborative simulation research laboratory at Queen's University.

Bilateral transversus abdominis plane block with or without magnesium for total abdominal hysterectomy and bilateral salpingo-oophorectomy – a randomized controlled trial

Gita Raghavan, Mike McMullen, Glenio B. Mizubuti, John Murdoch, Vidur Shyam,
Richard Thomas, Anthony M.H. Ho

Background: Transversus abdominis plane (TAP) block is a frequently performed regional block for abdominal surgery with an incision between the sixth thoracic and first lumbar vertebrae. Local anesthetic is injected with ultrasound guidance between the internal oblique and transversus abdominis muscle. Previous studies suggest that TAP blocks are superior to intravenous morphine in abdominal surgery without neuraxial anesthesia.¹ TAP blocks are often performed post-operatively in women who have undergone total abdominal hysterectomy +/- bilateral salpingo-oophorectomy (TAH+/-BSO) to provide effective analgesia and minimize the systemic side effects of intravenous opioids.

Rationale/Hypothesis: Several adjuncts have been trialed with local anesthetics in TAP blocks to further improve the quality and duration of analgesia. Magnesium is an N-methyl-D-aspartate antagonist that has been shown to reduce peripheral nerve excitability and enhance the effects of local anesthetic in reducing nerve excitability in A β fibres.² Previous clinical studies suggest an improvement in the quality of analgesia when magnesium is added as an adjunct to neuraxial, femoral, and brachial plexus blocks. We hypothesize that adding a moderate amount of magnesium sulfate to the local anesthetic used in TAP blocks will result in improved quality and duration of analgesia in patients undergoing TAH+/-BSO.

Outcomes: The primary outcome will be cumulative opioid consumption at 2, 4, 6, 8, 12, 18 and 24 hours post-TAP block. Secondary outcomes will be assessed at the same time points and include pain scores at rest and with coughing (measured with the visual analog scale), nausea and vomiting, and pruritus. Overall patient satisfaction and any potential side effects will be noted 24-hours post-TAP block.

Study Design: Following informed consent, patients will be randomized to receive bilateral TAP blocks with 20 mL bupivacaine 0.25% and 1 mL normal saline per side (Group A), or bilateral TAP blocks with 20 mL bupivacaine 0.25% and 1 mL magnesium sulfate (MgSO₄) 50% solution per side (Group B). On arrival to the post-anesthesia care unit, patients will receive rescue analgesia (hydromorphone 0.1-0.3 mg IV prn), and started on a patient-controlled analgesia pump (hydromorphone 0.3 mg q6mins prn).

Update: This double-blinded, randomized control trial has been approved by the Queen's University and Affiliated Teaching Hospitals' Research Ethics Board. Funding has been obtained through the Queen's University Establishment Fund. Data collection is ongoing with 12 patients recruited thus far. We anticipate data collection completion in 15 months.

¹Siddiqui MR et al. A meta-analysis on the clinical effectiveness of transversus abdominis plane block. *J Clin Anesth* 2011; 7-14.

²Vastani et al. Sensitivities of rat primary sensory afferent nerves to magnesium: implications for differential nerve blocks. *Eur J Anaesthesiol* 2013; 21-28.

NAME: Navroop Sandhu, MD

TITLE: Examining the Influence of Anaesthetic Practices on Maternal Outcomes in a Resource Poor Setting (Tanzania)

SUPERVISORS: Dr. Susan Haley and Dr. Jennifer Carpenter (Department of Global Health)

Approximately 800 women worldwide die from complications related to pregnancy and childbirth every day [1]. A staggering 62% of these deaths occur in sub-Saharan Africa. This highlights the alarming disparity that exists between the developed and developing world in terms of maternal mortality rates (MMRs), 16/100,000 compared to 230/100,000, respectively. Attempts have been made to lessen this inequality, most recently through the focus on improving maternal health outcomes as part of the Millennium Development Goals created at the Millennium Summit of the United Nations in 2000 [2]. Specifically, the fifth MDG targeted a decrease in MMR of 75% by 2015 compared to 1990 levels. Unfortunately, the MDGs have not been achieved, and the MMR globally has been reduced by less than 50% since the institution of the MDGs [1].

The vast majority of global maternal deaths can be attributed to hemorrhage, sepsis, and hypertensive disorders of pregnancy [3]. A lack of proper anesthetic care has been ascribed as one of the limiting factors in providing life-saving interventions that could prevent maternal deaths in these resource-poor settings [4]. Proper anesthetic care can help in managing rapidly emergent situations, like blood pressure and fluid control, control of a difficult airway, management of hemorrhage, and identification of septic patients, to name a few. In the developed world there has been a push towards anesthetics being delivered by specially trained non-physician providers in places such as the United States, the Netherlands, and Sweden. Comparatively, in parts of the developing world, trained physicians or nurses are seldom available thereby decreasing the likelihood that these vital services would be provided by an adequately trained professional.

Coincidentally the global rate of caesarean sections (CS) has also increased dramatically over the last few decades [5]. Indeed, the rate of CS is rising in the developing world [6] and has been considered to be an indicator of improved emergency obstetrical care in sub-Saharan Africa [5]. Several studies, however, have shown that this is not the case, and highlight an increase in unnecessary operative deliveries and poor obstetrical care in hospitals [5-8].

Tanzania is no exception to this and accounts for 3% of global maternal deaths [1]. Litorp *et al.* [9] examined CS rates, indications, and maternal and perinatal outcomes from 2000-2011 at a large teaching hospital in Tanzania. The rate of operative deliveries was found to have increased from 19% in 2000-2002 to 49% in 2010-2011, but an improvement in maternal outcomes was not seen. In fact, overall maternal mortality was found to increase during the course of the study from 463/100,000 live births in 2000-2002 to 650/100,000 in 2009-2011. Moreover, an evidence based audit conducted at two rural hospitals in Tanzania found that 26% of all operative deliveries occurred due to inappropriate indications, and an additional 38% of cases had no clear indication [10].

For my research project, I am interested in investigating how current anaesthetic practices in Tanzania may contribute to maternal outcomes and the rise in CS rates. I plan on conducting a feasibility study to determine if I can find a link between anesthetic practices, CS rates, and maternal outcomes from hospital records. I will be examining admission data, anesthetic records, operative records, and discharge data over one year's time to determine if a large-scale retrospective chart review can be done. I want to extract the following data from the records: (1) the indication for CS, (2) anesthetic technique, (3) the level of training of the practitioner, (4) anesthetic drugs used, (5) details of the management of difficult situations, (6) the anesthetic monitoring used, (7) fluid management, and (8) maternal mortality rate. I plan on looking at the role a lack of labour analgesia plays in moving to CS, why one type of anaesthetic is used over others, and the average length of hospital stay as the secondary outcomes of my study.

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The Chronobiology of Pain

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Neuropathic pain is a chronic condition defined by the International Association for the Study of Pain (IASP) as “pain caused by a lesion or disease of the nervous system”¹. Neuropathic pain conditions are estimated to affect as much as 8% of the population. More often than not, neuropathic pain is referred to parts of the body that otherwise appear normal, thus making it a hard condition to treat. Currently, the main treatment options available for neuropathic pain involve suppression of neuronal activity. One method includes the use of opioids, which, when used properly, are only effective at reducing pain by 20-30%². The issue with opioid use as a treatment, however, is not only the large number of adverse side effects (including nausea, constipation, and respiratory depression), but also the high risk of addiction and subsequently, overdose. Thus, it is evident that new therapeutic options are required for the treatment of neuropathic pain.

Studies in humans have demonstrated that patients with chronic neuropathic pain often exhibit circadian fluctuations in pain intensity, with patients reporting significantly higher levels of pain in the evening than during the day³. Interestingly, this circadian pattern is one that persists even with treatment. There have been relatively few animal studies regarding the circadian variation of pain, but those that have been done have demonstrated that mice also display a circadian pattern in their sensitivity to mechanical and thermal stimuli. This circadian pattern is one that complements that observed in humans. However, the mechanisms through which this circadian pattern of pain is regulated have received little attention.

It is now understood that the nervous and immune systems are extensively linked, and it has also been demonstrated that certain cells and factors of the immune system display a circadian pattern in either their activation, recruitment, or levels of expression⁴. Furthermore, circadian rhythms have been linked to the function of the immune system as well, and have been shown to alter the activity of macrophages, NK cells, neutrophils, B cells, T cells, as well as the expression of cytokines including IL-6 and TNF- α . There has been no study to date linking the circadian response in neuropathic pain to the circadian immune response. Therefore, we hypothesize that one of the underlying mechanisms behind the circadian variation of neuropathic pain lies in the circadian pattern of immune cells and their secreted factors. Using a number of standard behavioural sensitivity assays as well as cellular and molecular techniques, we will be identifying various immune cells and factors and investigating their contribution to the circadian variation of neuropathic pain.

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Postoperative pain in patients post hospital discharge: A systematic review

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

Clinical Need: Postoperative pain is an issue that many anesthesiologists face on a daily basis. We have made major advances in our attempts to treat this pain in hospital; however, patients continue to have pain well after we discharge them from our care(1). A 2013 survey in the United States found that of a random sample of 300 patients 74% experienced moderate to major pain after being discharged from hospital(2). This result echoes the results of a Canadian study finding that pain was experienced by 68% of inpatient and 49% of outpatient surgery patients(3). Poorly controlled postoperative pain has a major impact on quality of life during the recovery process and time needed to return to work. In addition, many patients seek unplanned medical attention for pain control, which places additional strain on health care resources. A multicenter RCT studying pain in 171 patients post total knee replacement found that 60% had to seek additional medical attention from a primary care provider and 3 patients returned to hospital for pain management(4). Acute pain may also contribute to the development of chronic pain, and the latter places a significant burden on healthcare and society today. A recent expert review by Katz and Seltzer identifies moderate to severe acute pain as a major risk factor for the development of chronic postsurgical pain(5).

Currents gaps in knowledge: Pain after hospital discharge is more difficult to study than in inpatients as the subjects are now dispersed causing collecting data difficult and more labor intensive. There is a growing body of studies about postoperative pain after hospital discharge. However, many of these studies have small sample sizes and deal with different populations. There is currently no systematic review of these studies in the pain literature. A large systematic review would be helpful in tracking what, if any, improvement has been made over time and identifying areas of need for future research. It would also help to quantify the scope of the problem and the impact on both individuals and their societies as a whole.

Study design: The study design would focus on developing a search strategy and inclusion exclusion criteria to capture as many relevant articles as possible while keeping the number of articles to review manageable. Possible outcome measures in our population could be severity and duration of postoperative pain, delayed time to return to work or emergency room visits and readmission due to pain and development of chronic post surgical pain. No research ethics or funding would be required.

Potential pitfalls: Developing a search strategy that is broad enough to capture all relevant studies while still keeping the number of results manageable will be a major challenge. Based on an initial survey of the literature the wide variety of study types and heterogeneity of outcome measures will likely make a classic systematic review difficult.

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Does magnesium sulfate as a supplement in adductor canal blocks improve pain control after total knee arthroplasty?

Resident: Dana Zoratto, PGY3 Supervisor: Dr. Shyam

Background and Rationale

Total knee arthroplasties (TKA) are widely recognized as effective treatments for degenerative joint disease. The number and prevalence of TKAs have increased significantly over the last quarter century with over 57,000 performed in Canada in 2012-2013 alone. One of the many challenges of TKAs is balancing postoperative analgesia with safe early ambulation to facilitate efficient hospital discharges. Multimodal approaches have been instituted including periarticular injections of local anesthetic, patient-controlled intravenous narcotics, and various regional techniques. Various medications have also been investigated including the addition of magnesium to both systemic and regional techniques to improve both duration and efficacy of analgesia. This research looks specifically at whether the addition of magnesium sulfate to an adductor canal block will increase the duration of a sensory block to the operative knee while maintaining normal quadriceps strength in patients undergoing TKAs. We hypothesize that patients who receive the magnesium sulfate will have prolonged analgesia with better ambulation and thus shorter hospital lengths of stay.

Study design

This study is designed as a single-centred, double-blinded, randomized controlled-trial with three groups of 40 participants each to compare (1) current standard of care (spinal anesthetic with epimorph, periarticular injection and patient-controlled analgesia), to a group receiving (2) standard of care plus an adductor canal block with only local anesthetic, and (3) to a group receiving standard of care plus an adductor canal block with both local anesthetic and magnesium sulfate.

Outcome Measures

Primary outcome: time to first analgesic request (first use of PCA pump after surgery)

Secondary outcomes: (1) cumulative PCA morphine-equivalent consumption in the first 24-hours postoperatively; (2) VAS pain scores post adductor canal block within the first 24 hours at different intervals; (3) hospital length of stay; (4) side-effects (nausea, respiratory depression, pruritus, falls, etc); and (5) gross assessment of strength on post-operative day 1.

Update

Data collection is currently underway. We have recruited more than half of our participants (65/120). Accommodations have been made for challenges involving participant selection and timing of data collection. Funding has been obtained through both the Senate Advisory Research Committee (SARC) and the Alison B. Froese grant. We anticipate an additional 8 months of data collection to reach our target.

Critical Appraisal

By: **Matthew Bilbily**, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication title: "*Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis.*"

Authors: *D.C. Hammell, L.P. Zhang, F. Ma, S.M. Abshire, S.L. McIlwrath, A.L. Stinchcomb, K.N., Westlund*

Eur J Pain. 2015 Oct 30. doi: 10.1002/ejp.818. [Epub ahead of print]

Introduction

The paper I have chosen to critique caught my interest for several reasons. Firstly, the therapeutic role of cannabinoid compounds with regard to pain reduction and inflammation has not been thoroughly investigated. There is of course some evidence, both anecdotal and in the literature that seem to suggest cannabinoid compounds may be useful as another tool in our analgesic armamentarium in some populations. For example, the literature seems to support some role for cannabinoid compounds for pain reduction in ulcerative colitis, neuropathic pain, and multiple sclerosis among others. Of course there are significant dose dependent psychotropic side effects that limit their use currently.

To me, these observations warrant further investigation, regardless of perceived societal notions. Secondly, the cannabinoid chosen and the mode of drug delivery in this study has important implications with regard to the pharmacokinetics and side effect profile of the compound in question. Lastly, arthritis is a very common disease, with over 50 million Americans between 2007-2009 being diagnosed. This simply made the study relevant and practical.

The question this study is trying to address is: is transdermal cannabidiol effective in reducing inflammation and pain related behaviours in a rat adjuvant-induced mono-arthritis model? I believe this is an important question because the over arching goal of this study is to potentially characterize a new therapeutic modality for the treatment of arthritis and possibly other inflammatory disease processes. The value of this study also stems from some of the reasons previously mentioned including, high prevalence of the disease process, unclear potential and poor current insight into

cannabinoid role in therapy.

Currently, the most effective treatment for rheumatoid arthritis is injectable fusion proteins which sequester the most prominent pro-inflammatory cytokine, TNF α . However, side effects of this treatment include suppression of the immune system. That is to say, there is room for improvement in our current gold standard therapeutic option.

Cannabinoids and cannabinoid receptors have been implicated as potential targets for reducing pain and inflammation. Cannabis Sativa, contains approximately 80 different cannabinoids, however, there are two predominant compounds: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Critically, the former is a psychoactive compound while the latter, which this study investigates, is not.

CBD is a hydrophobic compound with poor oral bioavailability secondary to first pass metabolism. Prior studies have successfully delivered CBD transdermally, thus bypassing portal circulation. The mechanism of action of CBD is unclear at this time, it has a poor affinity for cannabinoid-1 and cannabinoid-2 receptors contrary to THC which has a very high affinity. GPR55 and TRP channel superfamilies have been implicated as potential signalling channels that are inhibited by CBD in in-vitro studies. The hypothesis of this study is: in-vivo transdermal CBD is effective in reducing inflammation and pain related behaviours in a rat adjuvant-induced model of arthritis. Testing this hypothesis would help solve the stated problem because it would clarify the therapeutic role of CBD for this disease process in rats for possible translation to human therapeutic applications.

Methodology

This is a prospective experimental randomized unblinded control study. Fifty-four male Sprague-Dawley rats (260-280g) were randomly subjected to complete Freund's adjuvant (CFA) to induce a mono-arthritis in one knee joint, or assigned as naive controls which did not get

CFA. They did not state how this randomization was achieved. Of the 54 rats in the experiment, they state 21 were assigned as naive controls and 23 received CFA. The authors did not comment on the 10 rats not accounted for. It is possible that this was a typographic

mistake that was meant to state “44 rats”. Exclusion criteria were not outlined.

Rough overview of 7 day experimental course:

Day 1: mono-arthritis induced. Joint circumference and pain related behaviours assessed prior to CFA injection

Primary outcomes measured:

1. Joint circumference as a measure of inflammation: measuring tape around centre of joint with hindlimb in full extension.
2. Behavioural Assays
 1. spontaneous pain rating: limb posture scored daily by scientists blinded to animals treatment.
 2. Hind paw thermal hypersensitivity quantitated as paw withdrawal latency (PWL): technique described in their previous study.
 3. Exploratory activity: total time spent in exploratory activity (active time, distance travelled, total photo beams broken, rearing time) and resting were recorded in a 40x40x40 plexiglass box 45 minutes prior to and end of experiment.
3. Plasma Concentration of transdermally absorbed CBD
4. Spinal cord, dorsal root ganglia, and knee joint synovial fluid capsule membranes were obtained and sectioned for immunohistochemistry analysis. Right and left knee joints were sectioned as to provide internal controls.
 - Spinal cord: stained with Anti-OX-42 and anti-CGRP
 - synovial fluid capsule: stained with hematoxylin and eosin. Also measured thickness of membrane.
 - DRG: measured intensity of TNF alpha staining in the substance gelatinosa

This design is appropriate in testing their hypothesis as they are quantitatively measuring evidence of inflammation in multiple ways, including well established pro-inflammatory marker TNFalpha, joint circumference, and synovial joint membrane thickness. In addition, they are qualitatively and quantitatively assessing pain related behaviours by previously described methods. They are able to relate these findings to their treatment by measuring the CBD plasma concentration.

Their protocol is sufficiently detailed to be reproducible. The drugs, equipment, gel preparation & application, time courses, and measurement of outcomes were all explicitly outlined. The author's could of been more clear with regard to number of rats in each group, for example by using a simple flow chart.

and daily beginning on day 3.

Day 3-7: daily application of gel with desired CBD concentration onto shaved portion of a rats back. Joint circumference and pain-related behaviours assessed 4 hours after gel application.

Day 7: Rats killed, blood samples collected, and tissues sectioned & immunostained

Means were used to present most of the data. For the analysis of joint circumference and behavioural results, the naive and naive rats treated with CBD were combined for comparison to CFA + vehicle, CFA + low dose (0.62 & 3.1mg/day), and CFA + high dose (6.2 and 63.2mg/day). This seemed appropriate since you would not expect any difference in the primary outcomes if CFA was not given.

The protocol is clinically relevant given the gel used as the drug vehicle would likely not need any major changes if applied to human subjects. The primary outcomes involving tissue sectioning and immunostaining are less clinically relevant given the ethical differences between animal and human subjects.

Results

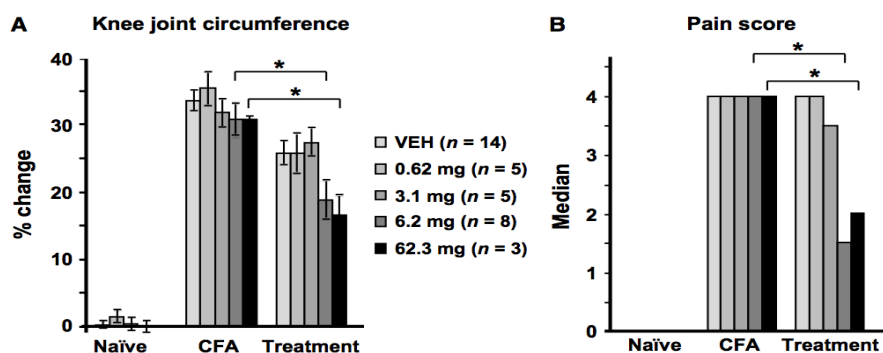
The groups in this study were of the same species, similar weight, and exposed to the same environment including food availability, light exposure, experimental protocol procedures. Thus i believe the groups are comparable. The age of the male rats was not mentioned. If the ages are significantly variable it may potentially introduce some physiologic differences between groups. That said, I do not believe age is a major contributing factor in this study.

Selected Results

Table 1 Plasma concentrations (\pm SD) of CBD in rats with and without complete Freud's adjuvant (CFA) induction after 4 days treatment with transdermal CBD gel.

Dose applied	Dose per unit area	CFA+CBD group (ng/mL)	All CBD treated (ng/mL)
0.6 mg/day	0.18 mg/cm ²	4.3 \pm 2.6	3.8 \pm 1.4
3.1 mg/day	0.18 mg/cm ²	18.8 \pm 2.8	17.5 \pm 4.4
6.2 mg/day	0.18 mg/cm ²	34.6 \pm 11.0	33.3 \pm 9.7
62.3 mg/day	1.8 mg/cm ²	1470.1 \pm 260.7	1626.9 \pm 379.0

Table 1: Plasma concentrations at end of experiment. The highest CBD dose does not show linear pharamokinetics with regard to plasma concentrations as you see in the first 3 dosages.



Graph A) The percent change in joint circumference among the different treatment arms. I am not sure why the total n here is 35 when they state 54 rats total were used, with 21 naive controls and 23 CFA exposed rats.

Graph B) pain scores were reported as medians.

Discussion

The authors conclude that the outcomes obtained in this study indicate that topical application of CBD gel is an effective treatment for reduction in inflammation and pain related behaviours associated with the rodent adjuvant induced mono-arthritis model.

The results as previously mentioned do support this conclusion. Notably, the findings in support of their conclusion were only seen for the high dose CBD treatment groups (6.2mg/day & 62.3mg/day). I thought it was quite useful to see the difference in results between the low dose and high dose groups because it provides a reference for therapeutic dosing. I do wonder if the lower dose groups would show more improvement in the primary outcomes if the experiment had gone on for a longer duration. I suppose this would depend on if steady state was achieved.

The authors suggest these findings are partly the result of CBD mediated inhibition of GPR55's pronociceptive signalling. In addition, they reference previous works that describe CBD agonistic effects on TRPA1 and TRPV1, two widely co-expressed ion channels that are important for neurogenic inflammation, edema formation, and inflammation induced mechanical and thermal hypersensitivity. They reference studies that show CBD results in desensitized responses following noxious stimulation with capsaicin or mustard oil (the respective agonists of TRPA1 and TRPV1).

Notably, the CBD plasma concentrations for rats dosed with 0.6, 3.1, and 6.2mg/day displayed excellent linear correlation. However the 62.3mg/day group did not fit this linear pharmacokinetic profile. Dosing was increased by massaging the total amount of CBD gel into a larger

skin area on the back while gel concentration (1%) remained identical. However, a 10% gel was required for the highest CBD treatment group since skin area could not be appropriately increased. The 10% concentration may have resulted in an increased absorption rate compared to the 1% formulations. They attribute the lack of increased response to the highest CBD concentration may be due to maximally activated CBD effects or capacity limited absorption and metabolism.

In regards to the gel application protocol, they did not apply the gel to the knee because the rats would have the opportunity for oral ingestion of the gel. They suspect that if they did apply it to the knee, it would increase local CBD concentrations, increasing effectiveness and decreasing systemic involvement.

Although they have shown statistical significance in the reduction of inflammation and pain related behaviours between the high dose CBD groups versus the remaining groups, the sample size is quite low. However, it is important to keep in mind that previous studies support the proposed mechanism and results of this study.

Overall, I thought this experiment was well thought out and had some interesting findings. Reading this paper I learned about some of the advantages and disadvantages of working with animal models. For example the ability to use invasive techniques is obviously useful, which might be impossible to do with human subjects. At the same time, important outcomes like pain must be inferred, which can introduce inaccuracies. I hope that future experiments will investigate the role of non-psychoactive CBD applied as a transdermal patch on human subjects with rheumatoid arthritis.

Critical Appraisal:

By: Johnathan Godbout, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication Title: "Is Infusion of Subhypnotic Propofol as Effective as Dexamethasone in Prevention of Postoperative Nausea and Vomiting Related to Laparoscopic Cholecystectomy? A Randomized Controlled Trial."

Authors: Mine Celik, Aysenur Dostbil, Mehmet Aksoy, Ilker Ince, Ali Ahiskalioglu, Mehmet Comez, and Ali Fuat Erdem
Biomed Res Int. 2015;2015:349806. doi:10.1155/2015/349806.

Introduction

The common and distressful side effect that is postoperative nausea and/or vomiting (PONV) has fuelled extensive research to determine the most effective and well-tolerated treatments and methods of prevention. As is the basis of all medical management, clinicians and researchers strive to find agents and combinations with the best therapeutic effect, minimal side effects, and the best safety profile. The aim of the study was to compare different modalities to help prevent PONV. Though there is no mention as to the authors' specific reason(s) to explore the differences between these 2 treatments, one would assume they might be trying to minimize cost, offer the safest treatment possible, optimize therapy, or increase convenience. It is up to the reader to decide why such research may be relevant. PONV is a very well known problem related to inhalational anesthetics and surgery, particularly laparoscopic surgery.(1,2) There have been

correlations made between many different factors (such as age, sex, type of surgery, duration, drugs used, etc.) and incidence/severity of

PONV.(3) There is a myriad of medications covering different mechanisms of action that we have at our disposal to prevent and treat PONV, but it unfortunately remains a common problem.

The study stipulates that a subhypnotic infusion of propofol may be as effective as single dose dexamethasone in preventing PONV after lap. cholecystectomy in ASA I/II patients. As previously stated, answering the above hypothesis can help establish safer and/or more effective means for preventing PONV. It also offers another modality to prevent this complication in the event that certain prophylactic treatments may be contraindicated or unavailable.

Methodology

This is an experimental, prospective, randomized, double-blinded, placebo-controlled study. The demographic is generally healthy adults (ASA I and II) that are undergoing elective lap. cholecystectomy. The study compares 3 groups of patients receiving either: 1) dexamethasone 8 mg (isotonic saline given as a control for the other groups) 1 minute prior to induction (group D); 2) – "Group P" – a propofol infusion of 1 mg/kg/hr during the operation (a suspension of 10% intralipid was given as a control for the other groups); or 3) both saline and an intralipid suspension with no active anti-emetic (Group C). Patients were randomized to 1 of the 3 groups with the use of blind envelopes. After undergoing surgery and being transferred to the post anesthetic care unit, all patients were observed for 24 hours by another anesthetist. The incidence of nausea, vomiting, and antiemetic requirement was recorded during three assessment periods, 0–6 h, 6–12 h, and 12–24 h after recovery from anesthesia using a four-point ordinal scale for PONV (0 = none, 1 = nausea, 2 = nausea with request for antiemetic, and 3 = vomiting).

The study states that "There was no statistically significant difference among the 3 groups in terms of age, body weight and height, ASA classification, duration of anesthesia or surgery, smoking status and total fentanyl consumption". The mean age is approximately 50 years old +/- approximately 12 years. The control used is experimental. The sample size was calculated by power analysis based on an assumed total incidence of PONV of 70% in the placebo group, a 35% reduction of PONV in either treatment groups, an alpha error set at 0.05, and a power of 0.8. Each group required 31 participants. Therefore, the authors enrolled "40 patients per group to allow drop out.

Statistical analysis was performed using the program of SPSS20. One-way ANOVA was used to compare the differences of numeric data among the groups. Chi-squared test was used for categorical data. Level of significance was set at $P < 0.05$.

All patients involved in the study gave signed informed consent. The Institutional Review Board also approved

the study. Its design does not go against any basic standards of care in any treatment group. The medications provided to all 3 groups are also commonly used in this setting and have satisfactory safety profiles. Also, regardless of the group, patients were not withheld rescue antiemetic or analgesic medication postoperatively. Based on the information provided, all patients seem to have received appropriate care.

Exclusion criteria were pregnancy, use of antiemetic drug 24 hours before lap. cholecystectomy, a history of nausea and vomiting in previous operations, susceptibility to nausea and vomiting, menstruation, emergency operation, severe diabetes mellitus, and conversion from lap. cholecystectomy to laparotomy. The article does not offer details as to why certain criteria excluded patients. One can assume that this is done to ensure similarity within the 3 groups without introducing too many confounding factors. It would also be unreasonable to withhold prophylactic antiemetic from someone with a history of PONV or is prone to nausea for whatever reason.

The experimental protocol effectively tests the hypothesis. At the same time, the authors evaluated

Results

A total of 120 patients were enrolled in the study and divided evenly into 3 groups, with no dropouts or data being eliminated. During the first 0–6 h post-op, total incidence of PONV was 65%, 30% and 30% in groups C, P, and D respectively. In that same order, for 6–12 h post-op, the incidence of PONV was 52.5%, 25% and 20%. For 12–24h, the results were 45%, 20% and 10% respectively. In group D, PONV was significantly lower than in group C at 0–6h ($P = 0.007$), 6–12h ($P = 0.06$), and 12–24h ($P = 0.02$). Also, patients in group P had significantly less PONV than those of group C at 0–6h ($P = 0.07$), 6–12h ($P = 0.013$), and 12–24 h ($P = 0.039$).

There were no significant differences between the group D and group P with regards to PONV. In terms of rescue

the rescue antiemetic requirements as well as the analgesic requirements postoperatively. All demographic details, drugs & their doses, anesthesia times and important surgery details were provided. This study can easily be reproduced.

The study's protocol mirrors appropriate clinical practice. Intra-operative opioids and muscle relaxant are provided with inhalational anesthetic to all patients. They also receive tramadol, acetaminophen, reversal of muscle relaxant and local anesthesia around the incisions prior to extubation. As stated above, the primary outcome observed was the incidence of PONV. The secondary outcome observed was both the use of rescue antiemetics with IV metoclopramide and the need for post-op analgesia with IV diclofenac sodium.

Induction of anesthesia with thiopental in Canada is no longer seen nowadays as it has largely been replaced with propofol, and no manufacturers remain in North America. Diclofenac sodium is also rarely used perioperatively in Kingston, in my experience. Otherwise, the procedures and conditions described in the study largely resemble our clinical practice here.

antiemetic requirement, patients in group D and group P had significantly less rescue antiemetic requirements than those of group C for 0–6 h and 6–12 h. There were no significant differences among the groups in 12–24 h. For 6–12 h, patients in group D had significantly lower antiemetic drug requirement than those of group P ($P = 0.01$). Finally, the difference between group D and group C for analgesic requirements the first 24 hours post-op was significant ($P = 0.04$). All of the above data was adequately provided in the form of a table. Another table compared the demographics and operative characteristics between the groups, which shows that the groups were very similar:

TABLE 1: Demographic and operative characteristics of patients.

	Group D (<i>n</i> = 40)	Group P (<i>n</i> = 40)	Group C (<i>n</i> = 40)
Age (years)	49.6 ± 11.7	50.07 ± 12.1	49.9 ± 12.6
Weight (kg)	74.5 ± 13.3	74.2 ± 12.9	73.9 ± 13.5
Height (cm)	169 ± 9.7	168.1 ± 10.5	168.7 ± 10.1
Sex (M/F)	23/17	24/16	25/15
ASA (I/II)	27/13	29/11	28/12
Smokers (<i>n</i>)	11	10	12
Duration of surgery (min.)	78.5 ± 14.2	77 ± 13.9	80.2 ± 14.4
Duration of anesthesia (min.)	101.8 ± 9.5	99.9 ± 10.5	98.7 ± 11.6
Fentanyl administered (μg)	173.1 ± 55.2	169.3 ± 55.8	170.6 ± 53.9
Awakening time (min.)	5.9 ± 1.24	6.2 ± 1.21	6.1 ± 1.2

Values are *n* or mean ± standard deviation. ASA: American Society of Anesthesiologists classification.

Discussion

This study concludes that infusion of propofol 1mg/kg/h during the operation was as effective as dexamethasone in preventing PONV. Unsurprisingly, PONV in both treatment groups was significantly reduced when compared with control group. Furthermore, dexamethasone effectively reduced the rescue analgesic requirement, while subhypnotic propofol infusion did not. The results of the study support this conclusion. However, there was a significant difference between rescue antiemetic requirement between groups P and D for the 6-12h period, suggesting that dexamethasone may prevent

more severe forms of PONV or be more effective when compared to a propofol infusion. The authors did not elaborate on this during their discussion.

Though the results address the stated hypothesis of the study, it was not made clear why exactly they decided to investigate the matter to begin with. Though the results are statistically relevant, they may not be clinically relevant with regards to PONV, as they only show equivalence between 2 readily available treatments. Another shortfall of this study is that although they were able to reach statistical significance, there weren't many subjects in the study, making results seem less impressive. To illustrate this, 2/40 patients in group P requiring post-op analgesia vs. 8/40 in group C was statistically significant, whereas 3/40 in group P was not. Their statement that dexamethasone reduces analgesia requirements whereas propofol does not on the basis of 1 less patient asking for pain medication seems questionable. Also, pain and nausea and their severity are rather subjective, which makes studying these effects difficult (even when using a visual analog scale). I would have appreciated if certain factors were included in the

study, such as degree of pain, blood pressure, heart rate, etc. when patients were nauseated to gain further insight about other factors possibly contributing to PONV.

This study was one of the first to evaluate an intraoperative propofol infusion as prophylaxis of PONV. Another study in children concluded that a propofol infusion combined with dexamethasone was more effective than dexamethasone alone in the prevention of PONV.(4) Both studies' results were in-line, though the present study did not evaluate a multimodal

approach as the other did. Both studies also demonstrated no prolonged awakening time after the propofol infusion. This was a problem (specifically the delay for room turnover) seen in certain other studies evaluating single-dose subhypnotic propofol prior to extubation, although no increase in length of stay in the post-anesthetic care unit was observed.(5) This

study therefore describes another standalone effective method to help prevent PONV, without any documented major complications. This method can be performed while the patient is under general anesthesia and therefore does not carry the same side effects as having a subhypnotic propofol infusion in awake patients (burning at IV site, sedation).(6, 7) In future work, it would be useful to study subhypnotic propofol infusion in different populations (ASA>II, patients with a history of PONV, etc.) alone and in conjunction with other antiemetics as part of a multimodal approach. It would also be useful to examine the difference in costs and side effects to establish which treatments or combinations of treatments are worthwhile. I believe this study could have been more thorough in that perspective.

From reading this paper, it seems that propofol, when given as a low-dose infusion intra-operatively, can be an effective method to prevent PONV after lap. cholecystectomy (in this patient population). Knowing this, I hope to see other studies expanding the concept to different populations undergoing different surgeries, and combining propofol infusion with other antiemetics that

are commonly used in my area. If, for instance, infusion of subhypnotic propofol combined with ondansetron and/or dexamethasone was reliably shown to be more effective than those agents alone in patients with previous PONV, then I will strongly consider adding it to the intraoperative management of these patients.

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Critical Appraisal:

By: Farah Pabani, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication Title: "*Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer.*"

Authors: Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, Liberman AS, Stein B, Charlebois P, Feldman LS, Carli F.

Anesthesiology. 2014 Nov;121(5):937-47.

Optimizing both prehabilitation and rehabilitation is an important area of research aimed at understanding how we can decrease the risk of postoperative mortality and complications, while improving postoperative physiological and functional capacity. The title of the selected paper¹ by Gillis et al is straightforward and immediately tells the reader that the purpose of the investigation is to compare prehabilitation to rehabilitation through a randomized control trial in a specific patient population. The results appropriately reflect this title and purpose. The authors consist of an interprofessional team from McGill University in Montreal, Canada and include a registered dietician, psychologist, kinesiologist and mix of notable clinician scientists in anesthesia and surgery who study perioperative care.

INTRODUCTION

The problem addressed in this paper is the need to improve the existing rate of postoperative complications and the current status of physiological and functional recovery following colorectal surgery. The post surgical period is associated with a 20 to 40% reduction in functional capacity even without complications, especially in elderly individuals with comorbidities. The

METHODS

The study was a sophisticated single-blind parallel-arm superiority randomized controlled trial. The patients were not blind to the intervention, but those collecting data were not aware of group allocation. The study was carried out at a single university-affiliated centre in Montreal with human adult patients scheduled for curative resection of non-metastatic colorectal cancer. This is the relevant population in which the problem of postoperative recovery lies and thus, fitting for this investigation. In many ways, the patient population of the study is similar to the population one might encounter in Kingston in the categories of age, gender, TNM staging, type of resection and adjuvant and neoadjuvant therapies. However, less than half of the population in both the prehabilitation and rehabilitation

traditional methods of rehabilitation in the postoperative period are met with challenges like patient fatigue, weakness and anxiety. Poor preoperative physical performance also increases the risk of mortality and number of postoperative complications and prolongs functional recovery. Thus, the preoperative period may be a more appropriate and beneficial time to intervene. A prior observational study has suggested that preoperative exercise, diet-counselling including protein supplementation and anxiety-reduction strategies accelerated postoperative recovery.² The authors hypothesized that prehabilitation would exhibit a clinically meaningful increase in functional walking capacity before surgery and that this improvement would translate to earlier recovery of functional exercise capacity postoperatively. This hypothesis is tested through comparing the efficacy of a trimodal prehabilitation program including exercise, nutrition guidance and counselling to reduce anxiety, to the efficacy of the same program implemented in the postoperative period alone. Testing this hypothesis demonstrates whether or not prehabilitation is a potential solution to improving preoperative physical performance and physiological and functional recovery following surgery.

groups suffered from comorbid ischemic heart disease, hypertension or diabetes, which seem to be quite prevalent among the patient population in Kingston. Furthermore, the authors introduce the paper by emphasizing that postoperative functional recovery is especially challenging in the elderly with comorbidities which is not entirely reflected in the study population. This was a prospective parallel-arm study, so both groups were experimental rather than historical. The sample size calculations were based on a two-sample comparison of mean changes in the primary outcome – 6 min walk test (6MWT) at 8 weeks – compared to baseline. The average difference in the 6MWT at 8 weeks in the rehabilitation group versus the prehabilitation group, compared to baseline was assumed

from two previous studies carried out by the same team of investigators.^{2,3} A sample size of 80 in total was required to detect the assumed differences between groups with a power of 80% and alpha of 0.05.

Post operative care was dictated by an enhanced recovery after surgery pathway based on the consensus review on best care for patients undergoing colorectal surgery.³ The trimodal intervention of exercise, nutrition guidance and anxiety counselling to both the prehabilitation and rehabilitation arm surpasses the standard of care provided at most institutions where rehabilitation may not be as holistic and rigorous. Nonetheless, neither intervention was known to be better than the other at the time of the investigation and so clinical equipoise is assumed. All patients regardless of group assignment participated in the trimodal rehabilitation program postoperatively. Thus the only difference between groups was the addition of a prehabilitation program, preoperatively. The study was approved by the Research Ethics Board of McGill University Health Centre and procedures were reportedly carried out as per ethical standards of the trial. Consent was obtained in eligible patients enrolled from November 2011 to March 2013 at their initial office visit with their surgeon. Subjects were not eligible if they did not speak English or French, or if they had pre-morbid conditions that contraindicated exercise. There was no specific reason provided for excluding those who were not bilingual. Perhaps this exclusion was made simply to limit any communication barriers in the study between participants and various facilitators.

The protocol is effectively designed to test the specific hypothesis that prehabilitation would exhibit a clinically meaningful increase in functional walking capacity before surgery and that this improvement would translate to earlier recovery of functional exercise capacity post-operatively. The protocol is set up to compare the efficacy of prehabilitation plus rehabilitation to rehabilitation alone. Thus, as stated previously all participants regardless of group assignment participated in the postoperative program and the only variable between groups was the addition of prehabilitation. The trimodal intervention is described in sufficient detail to be reproducible. Each component of the intervention – exercise, nutrition and coping strategies to reduce anxiety – is documented in a comprehensive manner and supported by relevant evidence. For the exercise intervention, the exact forms of exercise, time of training and physiological goals for each patient are outlined

clearly and guided by the American College of Sports Medicine.⁵ For the nutrition intervention, the authors describe the individualized care provided to each patient based on a 3-day food diary documented at the time of enrolment as well as Dietary Reference Intake Values⁶ and Canada's Food Guide.⁷ Specific guidelines for the amount of individual protein intake, including specific supplements used and timing of intake relative to time of exercise are provided based on prior investigations.⁸ Finally, the anxiety reducing techniques are specified and the number of sessions per week documented. These components were guided by a certified kinesiologist, registered dietician and trained psychologist, respectively. Patients were randomly assigned on a 1:1 ratio by computer generated random numbers to receive either the additional prehabilitation intervention or the rehabilitation intervention alone.

The primary outcome was functional walking capacity, as measured by the 6MWT at 8 weeks compared to baseline. The 6MWT has been validated in the colorectal surgical population.⁹ It is used clinically to evaluate an individual's capacity to maintain physical endurance and correlates with maximum oxygen consumption values obtained with other forms of exercise testing.^{10,11} Predicted distances for age and sex were calculated based on standardized formulas.¹² Secondary outcomes included self-reported physical activity as assessed by the Community Health Activities Model Program for Seniors¹³, health-related quality of life as assessed by the SF-36 from the RAND Medical Outcomes Study¹⁴⁻¹⁶, and anxiety and depression as assessed by the Hospital Anxiety and Depression Scale¹⁷. All outcomes were assessed at baseline, before surgery and at 4 and 8 weeks after surgery by a blinded assessor. Continuous data were appropriately compared using the student t test or Mann-Whitney U test depending on distribution, while categorical variables were compared using the chi-square or Fisher exact tests. The secondary outcomes were analyzed using a random-coefficients model with the treatment group and time as fixed effects, and patient identifier as a random effect, in consideration of the longitudinal nature of the data. All analyses were performed with STATA 12 (Stata Corp., College Station, TX) or open-source R v2.13 statistical software. There was missing data for several secondary outcomes, but attempts were made to minimize any resulting bias. Still, the power of the study was not sufficient to detect a statistically significant difference in all secondary outcomes.

RESULTS

The two groups were quite similar across all demographic and prognostic characteristics as well as the

baseline 6MWT and comorbidities. Of the 106 patients approached, 89 were randomized and 12 were excluded as they did not undergo resection, had emergency

surgery, were operated at a different hospital, withdrew consent, or were lost to follow-up. Thus, results were not analyzed by intent to treat and instead by per-protocol analysis. Although this resulted in a smaller sample size, the sample size was already quite small so analyzing individuals who did not receive the intervention would

DISCUSSION

The study concludes that a trimodal preoperative program including exercise, nutritional counselling and anxiety reduction strategies leads to a better functional walking capacity before and after colorectal surgery compared to starting the program postoperatively. The overall changes in the 6MWT compared to baseline showed a statistically significant difference between the two groups ($p=0.032$). There was a clinical and statistically significant difference in the mean change in walking capacity over the preoperative period and at 8 weeks after surgery. Specifically, the prehabilitation group showed a significant improvement from baseline functional capacity in the preoperative period, compared to the rehabilitation group which declined in functional capacity before the surgery. The magnitude of these changes was above the minimal clinically important difference for the 6MWT.¹⁸ This functional data was supported by a statistically significant increase in self-reported physical activity by the prehabilitation group during the weeks before surgery. At 8 weeks after surgery, a much higher proportion of patients in the prehabilitation group were either above or recovered to baseline walking capacity compared with the rehabilitation group. Thus, the results directly address the stated purpose and hypothesis of the study and the conclusions are appropriately limited to only the evidence revealed from the results.

The authors suggest that the 25.2 m increase in walking capacity of the prehabilitation group during the preoperative period offset the 21.8 m decline of the rehabilitation group during this time, providing the prehabilitation group with a physiological buffer that facilitated a faster return to their baseline walking capacity after surgery. They support this interpretation with the statistically significant change in preoperative self-reported physical activity in the prehabilitation group. However, it may also be possible that the prehabilitation group was more well-adjusted to the trimodal program after having already experienced it preoperatively and thus, their mental and physical engagement and motivation in the postoperative program were much greater. The rehabilitation group was asked to initiate the program at a potentially weaker mental and physical state. However, self-reported assessment of motivation to participate in the program preoperatively versus postoperatively was not formally assessed.

arguably dilute the effect of the intervention. An appropriate graph and table is provided showing details of the primary outcome data, while secondary outcome details are adequately reported in table format. Data collected at all four different time points for both primary and secondary outcomes is reported.

Previous studies exploring the impact of preoperative exercise programs have had mixed results. One study demonstrated that preoperative exercise decreases length of hospital stay and pulmonary complications in patients undergoing cardiac and abdominal surgery.¹⁹ However, another systematic review was unable to demonstrate that exercise alone offers a physiological and clinical improvement.²⁰ Prior investigations by the authors have shown that individuals prescribed intense preoperative exercise fared worse than those prescribed moderate preoperative exercise due to poor compliance in the intense group.³ The authors highlight that it also became clear from this prior study that there was a need to understand the various factors that could be contributing to functional deterioration in the preoperative period such as disease progression, catabolic state, poor compliance and psychological stress. It was from this study that the trimodal program was developed. An observational, feasibility pilot study with historical controls who received no intervention showed patients enrolled in a trimodal program had significantly higher compliance and functional walking capacity throughout the perioperative period.² In analyzing this pilot study and the current study, 62 and 84% of the rehabilitation group and prehabilitation group, respectively returned to baseline levels,¹ while only 40% of the historical control group had recovered by 8 weeks without intervention. Unlike previous studies, the results of this study demonstrate clinical and statistically significant improvements in functional capacity – as represented by the 6MWT – from a trimodal prehabilitation program versus rehabilitation alone.

However, there are also many limitations to this study. Due to the trimodal approach, the investigators cannot confirm which element of the program – exercise, nutrition or anxiety counselling – contributes most to recovery, or whether there is a synergist effect from all three. The nutritional guidance and psychologically supportive activities of the rehabilitation group were not monitored. Thus, it is possible that these individuals may have engaged in diet changes or psychological support independent of the investigation. The authors reported a moderate amount of missing data that may have biased the results of the secondary outcomes. Although the sample size may have been adequate to detect a difference in some of the secondary outcome categories with sufficient power, future studies may benefit from

increasing the sample size and broadening the detection to pick up differences in all secondary outcomes. With respect to the study population, both groups had relatively high baseline 6MWT (65% of predicted), so conclusions from the study are limited to individuals with this baseline level of functional capacity. Little can be said about individuals starting at poorer baseline function. Similarly, as discussed previously, the population included relatively healthy individuals with few comorbidities which is not representative of the population for whom functional recovery is the greatest challenge.

Many unanswered questions remain. Further investigations may be dedicated to exploring the impact

of prehabilitation on individuals with poorer baseline functional capacity. Another future study may compare multiple groups receiving a single prehabilitation intervention to determine the impact of each individual component of the trimodal program. The benefits of prehabilitation also have the potential to impact postoperative functional capacity in other surgical fields. A pilot RCT has demonstrated promising impacts of prehabilitation in cardiovascular surgery and follow up investigations are in progress.²¹ Patients are also being recruited for prehabilitation studies in other surgical fields where the impact of prehabilitation remains in question. Finally, there remains work to be done to investigate the benefits of prehabilitation in older elderly populations with multiple comorbidities.

APPLICABILITY OF THE PAPER

An important idea to take from this paper is the value of the 6MWT. As the authors report, it is a validated form of assessment of functional capacity as it incorporates various components of physical activity such as balance, speed, muscle force and endurance. It is simple, requires no equipment and lacks a ceiling effect. However, it is only a snapshot in time. The writers highlight that the increased walking capacity and physical activity were not associated with improved health related quality of life. The 6MWT measures functional capacity and not general health. Six weeks after colorectal surgery, the clinical correlation between the 6MWT and physical subscales of the SF-36 while statistically significant, is poor to moderate.⁸ The impact of the intervention on activities of daily living, return to employment or leisure activities outside of the Community Healthy Activities Model Program for Seniors was not investigated. The authors appropriately acknowledge these limitations.

Although this study has demonstrated the efficacy of the trimodal prehabilitation program, it has yet to translate into clinical effectiveness and efficiency. Implementing

changes in clinical practice demand consideration of both feasibility and patient compliance. The trimodal intervention clearly demands significant clinical time, including thorough education and guidance as well as regular check ins to ensure patient adherence. It also demands significant human resources including a multidisciplinary team of professionals offering unique services. How much would the intervention cost in return for the clinical benefit? Would patients be as adherent if they were not participating in a formal study? To what patient populations would the intervention actually be accessible in the future? The answers to these questions will play a role in determining the clinical value of this intervention in the future. Therefore, the results of this study are unlikely to immediately alter clinical practice. It would be fair to continue to encourage patients to engage in moderate exercise, a balanced healthy diet and seek out psychological support, but there is much work to be done in the field before standard trimodal prehabilitation guidelines are produced. Nonetheless, this is certainly an exciting area of research that brings true preventative medicine to perioperative care.

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Introductory PGY-1 Critical Appraisal Essay

By: **Danika Vautour**, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication title: *"Comparison of small dose Ketamine and Dexmedetomidine infusion for postoperative analgesia in spine surgery – A prospective randomized double-blind placebo controlled study"*

Authors : Garg N, Panda NB, Gandhi KA, Bhagat H, Batra YK, Grover VK, Chhabra R.

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Introduction

The aging Canadian population, and its associated increase in comorbidities, is a phenomenon that has been known for many years. According to Statistics Canada, the proportion of Canadians 65 years of age and over is now at 16.1%, up from 7.6% in the 1960s and 15.3% in 2013¹. Operative procedures for degenerative spine disease and disc herniation are most common for those under the age of 60, while spinal stenosis corrective surgery is the main reason for those above 60 years of age². In consequence, anesthesiologists will increasingly care for patients having spinal surgery. Furthermore, pain management will be essential facet of the postoperative care, for obvious ethical reasons, but also given that intractable pain and inadequate pain relief have been shown to contribute to adverse outcomes such as immunosuppression, pulmonary and cardiac complications, increase the risk of deep vein thrombosis, slower recovery and may lead to chronic pain³.

Current pain treatment modalities include regional anesthesia techniques, NSAIDs however the mainstay of pain treatment remains systemic opioids. This class of medication provides effective analgesia yet also carry with them undesirable side effect, ranging from inhibition of bowel function, nausea and vomiting, pruritis, hypotension, sedation. Wheeler and al, systematic review analysed opioid-associated adverse events in postoperative

patients from multiple RCTs, observational studies and case reports and found that as much as 31% of patients reported adverse gastrointestinal events⁴. Although nausea and vomiting are not life threatening side effects, many studies have pointed out that patients often find this adverse effect even more distressing than pain, thus leading to poor patient experiences⁵. Additionally, a more rare but serious complication of high dose opioids is respiratory depression. The incidence of severe respiratory depression with PCA pumps has been reported to be as high as 1 per 10,000 patients⁶. These events are usually associated with an error in management.

Given the undesirable side effects of opioids, both on patient safety and patient experiences, but also keeping in mind that adequate pain relief following spinal surgery is a critical step to prevent adverse outcomes, Garg and al. set to find an alternative and safe adjuvant pain therapy with opioid sparing properties. The authors of the study have used Ketamine, a non-competitive antagonist at the NMDA receptors responsible for nociceptive transmission^{11,12,13,14} and Dexmedetomidine, a highly selective centrally acting alpha- 2-adrenergic agonist that yields analgesic and sedation properties without evidence of respiratory depression, as the analgesics of choice for postoperative pain therapy considering their minimal side effects profile.

66 patients were screened for eligibility and none were excluded, thus all patients were enrolled in the study. Following enrollment, patients were educated on the use of the Numeric Rating Scale, where a pain score of 0 indicates no pain and a pain score of 10 is the worst imaginable pain, before being randomized into 3 groups: K, D and C. This trial was double-blinded as the patients did not know the content of the clear, unmarked syringes and the authors

Methodology

The current study is a single-center, prospective, double-blinded randomised placebo controlled trial. The aim of the study as previously mentioned is to assess the efficacy of opioid-sparing analgesics such as low-dose ketamine and dexmedetomidine infusion in patients undergoing spine surgery.

were blinded as allocation concealment was preserved by using hardware-generated random numbers table and sequentially numbered opaque sealed envelope technique (SNOSE) randomization. Subsequently, 22 patients were randomized in group K (Ketamine group), receiving a bolus 0.25mg/kg IV followed by infusion rate of 0.25mg/kg/h in addition to midazolam 10mcg/kg bolus followed by 10mcg/kg/h infusion (Both drugs in same syringe). The addition of a benzodiazepine is to reduce the incidence of CNS side effects, such as hallucinations, of Ketamine⁷. 22 patients were randomized in group D (Dexmedetomidine group), receiving a bolus of Dexmedetomidine 0.5mg/kg IV over 10 minutes, followed by an infusion rate of 0.3 mg/kg/h . 22 patients were randomized in group C (Control group), receiving volume-matched bolus and infusion of 0.9% normal saline.

Study drugs were started in the

Study Parameters	
Mean, group 1	69
Mean, group 2	4140% dec
Alpha	0.05
Beta	0.2
Power	0.8

<http://clincalc.com/Stats/SampleSize.aspx>

The trial is ethically sound as it was approved by the institutional ethical committee and also after obtaining written informed consent from the patients. As leaving pain untreated would be unethical, all patients received a rescue dose of Morphine 3mg IV should they have a pain score of 4 or more on the Numeric Rating Scale.

Inclusion criteria were patients of ASA class I and II between the ages of 18-60 undergoing elective spine surgery under general anesthesia. The types of elective spinal surgeries were for the most part laminectomies and pedicle screw fixation (Table 1). The following were the exclusion criteria: patients with HTN, CAD, heart blocks or patients on a beta-blocker or alpha-

postoperative period and continued for a total period of 24 hours. Pain-free period, pain scores, rescue analgesic (morphine) requirements, and side effects were noted for 48 hours postoperatively.

The sample size of the study was computed to compare the mean doses required in the K and D groups as compared to the C group. On literature review⁸, the authors found a mean morphine analgesic dose of 69 +/- 30mg required in the control group. They expect a 40% reduction of morphine requirements (thus 41 +/- 20mg) in each of the experimental groups. To detect this difference, the minimum number of subjects for adequate study power (standard of 80%) and 95% confidence level is 18 in each group (see figures below). 22 were enrolled in each group, thus this study has adequate statistical power to detect a difference (type II error).

$$k = \frac{n_2}{n_1} = 1$$

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_1 = \frac{(30^2 + 30^2/1)(1.96 + 0.84)^2}{28^2}$$

$$n_1 = 18$$

$$n_2 = K * n_1 = 18$$

$\Delta = |\mu_2 - \mu_1|$ = absolute difference between two means
 σ_1, σ_2 = variance of mean #1 and #2
 n_1 = sample size for group #1
 n_2 = sample size for group #2
 α = probability of type I error (usually 0.05)
 β = probability of type II error (usually 0.2)
 z = critical Z value for a given α or β
 k = ratio of sample size for group #1 to group #2

2-agonist. Again, it was not mentioned why certain groups were excluded but one can presume that the authors were hoping for a young, healthy patient population. Interestingly of note, all patients screened (n=66) were enrolled in the study.

The current study population differs from what we encounter here in Kingston. The average age was 36 +/- 14, thus none of the studied patients were above the age of 60, the patients were limited to ASA I and II with BMIs of less than 28 and those with either high blood pressure, evidence of coronary disease or even on a beta-blocker were excluded. Thus, the study population consisted essentially of a young and healthy group, not

exactly representative of the older patient population with associated comorbidities we see at KGH having spinal surgery. The clinical conditions encountered in this study are similar to my own practice.

This trial is designed to test the hypothesis. Patients either receiving opioid sparing analgesic or placebo were monitored for pain according to a standardised pain score (NRS) and also opioid side effect in the first 48 hours post-operatively of various spinal surgeries. As part of the study protocol, all patients received a general anesthetic, with a propofol and vecuronium induction followed by maintenance with propofol and nitrous oxide/oxygen. Intraoperative analgesia was given with IV morphine 0.1mg/kg. In the postoperative period (and commencement of the study), hemodynamic parameters were maintained within 20% of baseline with atropine, esmolol, mephentermine or nitroglycerin infusion when needed. The primary endpoint of this study was to compare the pain free interval of the 3 groups, while pain scores, rescue analgesic requirement and side effects were secondary endpoints. The protocol is questionably clinically relevant given that PCA instead of an infusion would be

more in conformity with present-day Canadian anesthesiology practice. Moreover, the methodology is validated and it is detailed enough to be reproducible.

Statistical analysis of this study involved the computation of descriptive statistics using SPSS software. The KS test was used to determine whether the data was normally distributed. Consequently, the quantitative variables, such as pain-free period and rescue analgesic requirements, were obtained using the one-way ANOVA technique to compare means of numerical variables in the 3 groups and are presented as mean and Standard Deviation (SD). Pain scores are described as median and interquartile range. Further, the Kruskal-Wallis test was used to compare pain scores in the 3 groups and this was done as an extension of the Mann-Whitney U test. Difference between groups for qualitative data, such as the side effect of dizziness, hallucinations, nightmares and nausea/vomiting, were assessed using the χ^2 test and are described as frequencies or proportions. Statistical significance was fixed at a two-sided P-value of < 0.05.

Results

The groups studied are well balanced and comparable as outlined in Table 1. The majority of the surgeries performed in all 3 groups were laminectomies or pedicle screw fixation. Additionally, they had similar ASA statuses, age, weight, sex ratio and intraoperative morphine administration. The authors also mention that

the groups were comparable in terms of duration of anesthesia, amount of IV fluids and blood administration, however this was not quantified nor was it mentioned at which point in the surgery the patients received such products.

TABLE 1. Comparison of Patient Characteristics

Patient Characteristics	Group C	Group D	Group K	P
Age (y)	36.32 ± 14.32	36.73 ± 14.77	36.45 ± 13.39	0.995
Sex (male/female) (n)	16/6	14/8	13/9	0.627
Weight (kg)	65.27 ± 15.54	65.68 ± 14.01	61.45 ± 14.60	0.580
BMI (kg/m ²)	24.77 ± 4.56	24.8 ± 3.09	24.68 ± 5.38	0.997
ASA status (I/II) (n)	19/3	22/0	19/3	0.192
No. disks/vertebrae involved	2.23 ± 1.85	2.14 ± 1.16	2 ± 1.34	0.887
Type of surgery (n [%])				
Laminectomy and excision	15 (68.2)	11 (50)	10 (45.5)	0.506
Pedicle screw fixation	4 (18.2)	8 (36.4)	8 (36.4)	
Decompression and stabilization	2 (9.1)	0	1 (4.5)	
Detethering	0	1 (4.5)	0	
Discectomy	1 (4.5)	1 (4.5)	2 (9.1)	
Excision of tumor	0	1 (4.5)	1 (4.5)	
Vertebral levels (n)				
Dorsal	7	6	11	0.324
Lumbar	13	8	7	
Dorso-lumbar	1	5	3	
Lumbo-sacral	1	2	1	
Sacral	0	1	0	
Intraoperative morphine (mg/kg)	0.111 ± 0.017	0.108 ± 0.015	0.110 ± 0.022	0.874

Values expressed as mean ± SD.

A total of 66 patients were randomized in 3 groups as previously mentioned, however none were excluded and none were lost to follow up. The fact that none were lost to follow up is not surprising as the study

was in the first 48 hours of the postoperative period, thus significantly reducing the chance of longitudinal loss.

In table 2, we can appreciate the results of the

primary endpoint amongst the 3 groups. The mean pain-free periods (the time to first-time morphine use) in the ketamine group (860 minutes) and the dexmedetomidine group (580 minutes) were longer than in the placebo group (265 minutes) during the 48-hour observation

period, with a P-value < 0.002. Further, while it was significantly different between groups K and C (P =0.001) and also between groups D and C (P=0.018), the difference between the two experimental groups (K and D) were comparable (P=0.307).

TABLE 2. Pain-free Period and Rescue Analgesic Requirement

Parameters	Group C	Group D	Group K	P
Total pain-free period (min) (median and interquartile range) in 48 h; upper and lower limits of interquartile range	265.26/295; 760/0	580/1470; 2880/0	860/2628; 2880/60	0.002
Rescue morphine requirement at 12 h (mg)	3.75 ± 2.525	1.64 ± 2.167	0.14 ± 0.640	0.000
Rescue morphine requirement in first 24 h (mg)	15.64 ± 9.31	6.89 ± 5.886	2.45 ± 2.067	0.000
Rescue morphine requirement in first 48 h (mg)	21.09 ± 12.88	7.98 ± 7.724	2.59 ± 1.974	0.000

Data represented as mean ± SD.

Rescue morphine requirements were significantly higher in the placebo group at all times except at 0 hours, as evidence by a cumulative morphine requirement at 24 hours of 15.64 ± 9.31mg, compared to 6.89 ± 5.88mg in group D and 2.45 ± 2.06mg in group K (P-value < 0.05) and at 48 hours group C 21.09 ± 12.88mg, group D 7.98 ± 7.72mg and group K 2.59 ± 1.97mg (P-value < 0.05). Of interest to this study, 5 patients in group D and 7 in group K did not require any morphine during the study period.

Pain scores in the experimental groups were significantly decreased as compared to the placebo group except at 0 hours.

Discussion

The main conclusion of the study is that Ketamine and Dexmedetomidine infusion in the postoperative period of spine surgery reduces the morphine requirements and also results in better post-operative analgesia compared to morphine alone. The authors mention that Ketamine decreased morphine requirement by 74% and dexmedetomidine decreased it by 54%. How they obtained these numbers is a mystery to me, as they have not demonstrated their calculations. The cumulative morphine at 48 hours for the control group was 21.09mg, as compared to 7.98mg for the Dexmedetomidine group and 2.59mg for the Ketamine group. On literature review, some studies have shown a reduction of the cumulative opioid requirement, by as much as 5-20mg, with the addition of Ketamine to an opioid based PCA as well as a small improvement but statistically significant of postoperative pain⁹. Ketamine has been shown to be a good analgesic in experimental animal trials, however has had mixed results in clinical trials in terms of effectiveness. A systematic review of randomised trials by *Carstensen and al.* exposed this controversy as 6 of the studies included showed significant improved postoperative analgesia with the

Drug profile side effects were compared in the 3 groups. The authors mention that the sedation score in the three groups differed significantly but they have not demonstrated this result in any table or graph. However, they do mention that NONE of the patients in the study required airway management. Additionally, opioid side effects such as nausea and vomiting were comparable in all 3 groups (P > 0.05) with a greater incidence of dizziness (n=4) and vomiting (n=3) in the Ketamine group. Hemodynamic profiles were comparable except for systolic blood pressure in the control group, which was significantly higher at all times except 0 hours (P=0.001)

addition of ketamine to opioids, nonetheless 5 studies showed no significant clinical improvement¹⁰.

Although the study drugs have a good safety profile, the authors ignored the fact that the Ketamine group had a higher side effect profile than the control group. They mention that postoperative complications were similar in all 3 groups (however with a P-value of > 0.05, the statistical significance is questionable) with a slightly more incidence in group K. There were 4 patients who developed dizziness and 3 with vomiting as compared to 1 and 1 respectively in the control group. Thus, the results do not address one of the stated hypotheses of the study being that alternative analgesics such as Ketamine and Dexmedetomidine would have opioid sparing properties. Ketamine is known to have multiple dose-dependant side effects, including neuropsychiatric effects as well as nausea and dizziness. A proposed hypothesis is that opioid receptors are involved in the complex pharmacological effects of Ketamine (*Freo, 2002*). The dose required for adequate analgesia remains unclear and perhaps with more studies we will be able to better define the adequate analgesic

dose with the hope of reducing it thus further decreasing the opioid side effects. Of interest, many studies have looked at the side effect profile with the addition of Ketamine to opioid-based PCAs in the postoperative period. *Wang and al.* systematic review concluded that the addition of Ketamine to Hydromorphone/Morphine PCA reduced the incidence of PONV by an absolute reduction risk of 8.9%⁹. We assume that the reduced incidence is secondary to the reduced morphine requirement.

The clinical significance of this study for our practice is difficult to assess. The current study population is rarely what we encounter coming in for elective spinal surgery at most Canadian hospitals; therefore it is difficult to extrapolate if this particular pain management regimen will be effective. One has to wonder if the young and healthy population of this study require less analgesic than the population we actually manage in our hospitals. Additionally, it is our standard of practice to offer PCA following spinal surgery so it is difficult to know if the pain scores would have been the same if the patient themselves controlled the timing of doses. That being said, this study raises the possibility of utilising dexmedetomidine for more than just sedation and safe extubation purposes in the ICU. As we know, the cost of this drug at our institution is high, however should there be more research on the safe analgesic profile for this promising drug, perhaps it would be more readily available (push for obtaining generic drug?).

I have identified a few limitations to this study in addition to those mentioned by the authors. One of the major limitations is there is no record of preoperative pain; therefore we have no baseline pain level. Additionally, the nature of the disease (disk pathology) in the present population would require higher analgesic doses due to preoperative sensitisation. As discussed in the methodology, the population tested is young (average age 36 ± 14), non-obese and without significant cardiovascular comorbidities which renders postoperative pain more straightforward, thus can the results be extrapolated to the average patient we see walking through the OR doors in our Canadian facilities? The analgesic administration mode was by infusion with

breakthrough rescue morphine, although we know PCA provides better pain relief and it is a standard of care. In the study, subjects had to wait until they reached a pain score of 4 and THEN receive a pre-fixed dose of 3mg IV morphine. I suspect that they would have required less opioids should a PCA been implemented. The study period was limited to the first 48 hours postoperatively, thus we do not know the pain status or side effect profile beyond that time. As previously mentioned, all patients screened for eligibility were randomized, raising the question of systemic bias. Due to the small size of the study, the types of surgery were not necessarily similar as there is a lack of information surrounding the surgical and anesthetic components of the perioperative component; the surgical instrumentations and complexity of the surgeries were not mentioned, the timing at which the 0.1mg/kg IV morphine dose was given (induction? Emergence? Throughout?) is unclear, the use of other adjuncts in the perioperative and postoperative period, such as acetaminophen/NSAIDs were not noted.

The take-home message that I concluded from this article, and also from reading around the subject, is that postoperative analgesia is a critical element in managing patients undergoing spine surgery and should be approached as a multimodal analgesic model. Alternative analgesics, such as Ketamine and Dexmedetomidine, are safe and effective in reducing but not completely eliminating morphine requirements, however this specific study was not convincing that they had opioid sparing properties. As previously stated, the data on Ketamine as an effective analgesic remains controversial and needs more clinical trials. A few questions remain: Can this straightforward approach also be effective in patients at high-risk of postoperative opioid-resistant pain (cancer patients, chronic pain, opioid dependant)? Also, it has been claimed that Ketamine is able to reduce the chance of progressing to chronic pain, however we are still awaiting definitive clinical trials to support this. In my future practice, I will certainly consider Ketamine and Dexmedetomidine as analgesic adjuncts to be utilised as part of a multimodal approach of acute pain in the postoperative period.

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