Queen's University
33rd Annual Anesthesiology Research Day

Scientific Program Directors and Residency Research Coordinators:

Ian Gilron, MD, MSc, FRCPC

Elizabeth VanDenKerkhof, RN, MSc, DrPH

Scientific Adjudicators:

Cara Reimer, MD, FRCPC

Cathy Cahill, PhD

Donald R. Miller, MD, FRCPC (Guest)

Department Head:
Joel Parlow, MD, MSc, FRCPC

Residency Program Director:
Michael Cummings, MD, FRCPC

Postgraduate Medical Secretary:
Kim Asselstine

Director of Clinical Research:
Brian Milne, MD, MSc, FRCPC

Research Committee Chair:
Ramiro Arellano, MD, MSc, FRCPC

Research Facilitator:
Rachel Phelan, MSc

Research Coordinator:
Debbie DuMerton Shore, RN, CCRP

Research Nurse:
Beth Orr, RN, CCRP

Research Nurse:
Sarah Walker, RN, MSc

Research Nurse:
Cindy Sabo, RN

Institutional support:
Queen's University **Kingston General Hospital** **Hotel Dieu Hospital** **Providence Care**

**** The Royal College of Physicians & Surgeons of Canada, Region 3 Advisory Committee, has provided a continuing medical education grant in support of this meeting.****

Held at Donald Gordon Centre, Kingston, Ontario, CANADA, March 30, 2012.

Supported by Educational Grants from:

Eli Lilly
Purdue Pharma
Novo Nordisk
Pfizer
Arrow (Division of Teleflex Medical)
Hospira
Abbott
GE
Merck

Programme booklet cover design by Ian Gilron

Queen's University 33rd Annual Anesthesiology Research Day

SCIENTIFIC PROGRAMME OUTLINE

0900 – 0910 Opening Remarks
– Dr. Joel Parlow

0910 – 0930 Research Day Introduction

– Dr. Ian Gilron

0930 – 1030 Oral presentations

1030 – 1100 Poster presentations and nutrition break

1100 – 1130 Oral presentations

1130 – 1300 * LUNCH (provided) *****

1300 – 1430 Oral presentations

1430 – 1500 Poster presentations and nutrition break

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

The Judges will be:

Dr. Donald Miller, Professor, Department of Anesthesiology, University of Ottawa

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

Dr. Cathy Cahill, Associate Professor, Queen's Department of Anesthesiology & Perioperative Medicine

---

1500 **Dr. Donald Miller,** Professor, Department of Anesthesiology, University of Ottawa, Speaker of the Royal College of Physicians & Surgeons of Canada, Region 3 Advisory Committee

"*Updates on Reporting Transparency, Ethical Dilemmas and Misconduct in Biomedical Publication – The Editor's Perspective*"

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

Oral Presentations

Jessie COLLINGS, PGY3
"Comprehensive sonoanatomy module to reduce duration of training and increase accuracy of neuraxial block performance" (proposal)

Tricia DOYLE, PGY3
"**A Survey of Health Professional Education in Patient Safety at Queen's University**" (proposal)

Luis Enrique CHAPARRO, Research Fellow
"**Pharmacotherapy for the prevention of chronic pain after surgery: a Cochrane Systematic Review**"(data presentation)

Alex FLOREA, PGY2
"**Impact of beta-blockade on cerebral ischemia during carotid endarterectomy**" (data presentation)

Rebecca GERLACH, PGY4
"Rationalizing a standard approach to the surgical airway: A review of technique and evidence for efficacy" (review presentation)

Brian GRANT, PGY4
"**Impact of spontaneous versus evoked neuropathic pain on daily function**" (data presentation)

Erika NGUYEN, PGY2
"Surgical vs. classical approach to TAP blocks: A randomized controlled study" (proposal)

Yasser HAYAT, PGY3
"**The economics of drug wastage**" (update)

Patrick GRENIER, PhD Candidate, Queen's Biomedical & Molecular Sciences
"**Systemic administration of ultra-low dose alpha 2-adrenoreceptor antagonist atipamezole attenuates morphine tolerance and enhances opioid analgesia in neuropathic pain states**"
(data presentation)

Judy MAROIS, PGY2
"**The Effect of Intraoperative Labetalol on Time to Discharge and Hemodynamic Stability in Laparoscopic Cholecystectomy**"(proposal)

Jeff SAMPSON, PGY4
"**Evaluating Junior Resident Readiness for Independent Anesthesia Call Duties With Simulation**" (proposal)

Karen WONG, PGY3
"**Do Antidepressants reduce post-operative pain? A systematic review.**" (data presentation)

Poster Presentations

Patrick GRENIER, PhD Candidate, Queen's Biomedical & Molecular Sciences
"**Glial Modulation suppresses modality-specific tactile allodynia in a model of neuropathic pain**"
(poster presentation)

Alex MATTIOLI, PhD Candidate, Queen's Biomedical & Molecular Sciences
"Ultra-low dose naloxone modulates opioid tolerance independently of Toll-like receptor 4" (poster)

Edmund ONG, PhD Candidate, Queen's Biomedical & Molecular Sciences
"**Delta opioid receptor trafficking is altered following prolonged morphine treatment**" (poster)

Liuia XUE, Queen's Biomedical & Molecular Sciences
"**Use of Conditioned Place Preference paradigm to measure the negative affect of chronic pain**" (poster)

Critical Appraisal Essays

Karmen Krol, MD, PGY-1, Queen's Anesthesiology
"*Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy*."
Anesth Analg. 2007 Nov;105(5):1255-62.

Nicole McFadden, MD, PGY-1, Queen's Anesthesiology
"The perioperative dialogue reduces postoperative stress in children undergoing day surgery as confirmed by salivary cortisol."
Pediatric Anesthesia 2011; 21:1058-1065.

Vanessa Sweet, MD, PGY1, Queen's Anesthesiology
"Incidence and impact of distracting events during induction of general anaesthesia for urgent surgical cases"
Eur J Anaesth 2010 Aug; 27(8): 683-9

Maggie Thomson, MD, PGY-1, Queen's Anesthesiology
"Caudal Normal Saline Injections for the Treatment of Post-Dural Puncture Headache."
Pain Physician 2011; 14:2781-279.

"Comprehensive sonoanatomy module to reduce duration of training and increase accuracy of neuraxial block performance"

Jessie Collings PGY3

Research supervisors: Dr Shyam, Dr Murdoch, Dr McMullen; thanks to Rachel Phelan, Val Wilson

The traditional method for neuraxial regional analgesia relies on palpation of landmarks which may not be accurate or evident, especially in cases of obesity and scoliosis. Even the most experienced anesthesiologists incorrectly estimate the interspace level by palpation 71% of the time (1). Uncertainty of anatomy can result in numerous puncture attempts, trauma to neurovascular structures, and unintentional dural puncture. Ultrasound can increase accuracy in identifying intervertebral levels to 76% compared to 30% with palpation (2). Studies on obstetric patients show that ultrasound also results in better blocks, fewer complications, and increased overall patient satisfaction. Anesthesia trainees had a higher success rate and steeper learning curve with ultrasound-guided epidurals compared to the group that was taught the traditional palpation technique for needle insertion (3). However, ultrasound use in neuraxial regional blocks is still usually reserved for only the most difficult patients.

The overall goal of the current study is to increase the accuracy and reduce the time required to master ultrasound-guided neuraxial blocks in the lumbar region. The project evaluates the efficacy of our educational module at increasing competence and confidence for accurate lumbar ultrasound performance in our anesthesiology residents. The module is designed to describe the role of ultrasound for spine demarcation before placement of a neuraxial block and to familiarize residents with ultrasound technology and techniques. Through use with normal models, residents will become confident with using ultrasound to identify sonoanatomy and optimal needle insertion point before attempting to use it on difficult patients.

Our module encompasses 3 methods of training: 1) verbal instruction, 2) instructor-guided lumbar ultrasound performance on a model (7 residents,1 hour per week for 4 weeks), and 3) unlimited access to our interactive laptop-based training application. Our outcomes for assessment are: 1) ability to identify the L3 /4 interspace in the paramedian longitudinal view, 2) ability to identify the optimal insertion site in the transverse view, and 3) ability to measure the depth of the dura/ligamentum flavum in the transverse view Prior the completion of the module, the residents fill out a survey addressing their own estimation of competence, potential adoption into practice, most useful/least useful aspects of the course, etc. Some limitations in our study design include a small number of residents and the use of the same models each week, which may lead to memorization of their anatomy by the residents scanning them. We also need to ensure our assessment outcomes are objective and reproducible. We have completed the four week teaching module with our residents and over the next few months, we will be doing data collection, analysis and interpretation. Our goal is to repeat an assessment of knowledge and survey in 3 months time. Results from this pilot can be used to design a multicenter, fully powered investigation to determine the full impact of our comprehensive training module. We can also use this module to teach staff who are unfamiliar with the use of ultrasound for neuraxial techniques.

References:

1. Broadbent CR, Maxwell WB, Ferrie R, Wilson DJ, Gawne-Cain M, Russell, R. Ability of anesthetists to identify a marked lumbar interspace. Anaesthesia 2000; 55: 1122-6.

2. Watson MJ, Evans S, Thorp JM. Could ultrasonography be used by an anaesthetist to identify a specified lumbar interspace before spinal anesthesia? Br J Anaesth 2003; 90: 509-11.

3. Grau T, Bartusseck E, Conradi R, Martin E, Motsch J. Ultrasound imaging improves learning curves in obstetric epidural anesthesia: a preliminary study. Can J Anesth 2003; 50: 1047-50.

A Survey of Health Professional Education in Patient Safety at Queen's University

Patricia Doyle, David Goldstein, Elizabeth VanDenKerkhof, Dana Edge

Background

Safety is central and critical to quality healthcare. With the current efforts to optimize safe, quality care, more attention has been brought to the integration of patient safety into health education curricula. Much of this effort in Canada is underpinned by the Canadian Patient Safety Institute's Safety Competencies Framework. The result of the Institute's study revealed that the integration of patient safety concepts into training has been poor, and launched an initiative which developed a framework composed of six competencies to make patient safety easy to understand and apply at all levels of education. An understanding of current student perspectives on these concepts is necessary in order to integrate these safety concepts and monitor the effectiveness of any changes made. Currently, there is little evidence garnering student perspectives in this domain, particularly amongst medical trainees. The purpose of this study is to understand the quality and content of patient safety education in the medical education at Queen's University.

Research Questions:

1. How do medical trainees describe the patient safety curriculum in the classroom and clinical settings?
2. Is there a relationship between the patient safety curriculum in the classroom and clinical settings?
3. Are there differences in students' perspectives of the patient safety curriculum across stages of training?

Study Design and Methodology:

This study is a cross-sectional web-based survey. All trainees in the undergraduate (n ~436) and postgraduate (n ~406) medical educational programs were invited to complete the online Modified Health Professional Education in Patient Safety Survey. This is a previously validated questionnaire designed to assess students' exposure to the six health safety competencies and students' perceptions on how broader patient safety issues are addressed in their education. Participants were invited via email with two subsequent reminder emails, which directed them to the online questionnaire. A prize incentive was offered for participation. The data collection is occurring from January through March 2012. All data gathered remains confidential. Demographic data will be described using descriptive statistics (mean and standard deviation). For research question #1, frequencies and percentages will be used to summarize findings; for question #2, Spearman rank coefficient will be used, and for question #3, Kruskal-Wallis one-way analysis of variance will be used.

Interim Results

Response rate to date show that 252 medical students (62%) have completed the questionnaire whereas 151 residents (35%) have participated. The questionnaire is available for another 2 weeks, with a targeted response rate of 70%, which was achieved with a previous survey of nursing students. Statistical analysis will follow closure of the questionnaire.

Implications

Results from this study will guide future health safety curriculum development for medical education programs at Queen's University and will serve as a baseline to track trainees' perspectives about patient safety over time. Plans are also underway to conduct an annual national survey of health professional trainees.

PHARMACOTHERAPY FOR THE PREVENTION OF CHRONIC PAIN AFTER SURGERY

Luis Enrique Chaparro, MD: Department of Anesthesiology & Perioperative Medicine. Queen's University, Kingston, Canada.
Shane A. Smith, MSc, MD: Department of Anesthesiology & Perioperative Medicine. Queen's University, Kingston, Canada.
Phil J. Wiffen, BPharm, MSc: UK Cochrane Centre, Oxford, UK
Henry J. McQuay, DM: Nuffield Division of Anaesthetics, Oxford University, Oxford, UK.
R. Andrew Moore, DPhil: Nuffield Division of Anaesthetics, University of Oxford, Oxford, UK.
Ian Gilron, MD, MSc: Departments of Anesthesiology & Perioperative Medicine and Biomedical & Molecular Sciences. Queen's University. Kingston, Canada.

Introduction

Surgery, as a cause of chronic pain, is unique because the injury is planned and predictable [1]. We report here preliminary results of an ongoing systematic review of clinical trials evaluating pharmacotherapy to prevent chronic postsurgical pain in adults.

Methodology

Our review criteria and search strategy included double-blind, placebo-controlled, randomized adult trials of one or more perioperatively administered drugs that measured pain at least three months after surgery [2]. All reviewed trials are graded using the Cochrane risk of bias tool. The primary outcome was defined as the proportion of participants reporting any pain at, or referred to, the anatomical site of the procedure three months after the procedure. The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and PaPaS Trials Register were the databases used for the search strategy. Other trials are currently being searched from reference lists of relevant articles in order to complete this review.

Results

The first iteration of the literature search yielded, thus far, 37 trials that met inclusion and evaluated impact on chronic postsurgical pain following administration of: gabapentin or pregabalin (15 trials), NMDA antagonists (14), opioids (2), NSAIDs (2), corticosteroids (2), and single trials of topical local anesthesia, and allopurinol. Twelve studies followed the patients for 3 months; 17 studies for at least six months; 7 followed the patients for one year and only one for two years.

Discussion

Results of this ongoing systematic review have revealed evidence that NMDA antagonists and gabapentinoids may play a role in reducing chronic pain after surgery. Imminent completion of the trial search and meta-analysis of combinable studies will serve to quantify the impact of these two drug classes on the development of chronic postsurgical pain.

References

[1] Lancet 2006. 367: 1618–25.
[2] Cochrane Database of Systematic Reviews: Protocols 2010 Issue 1 DOI: 10.1002/14651858.CD008307.

Preoperative beta blocker use associated with cerebral ischemia during carotid endarterectomy

Alexandra Florea, Janet van Vlymen, Samia Ali, Donald Brunet, Joel Parlow

Background

Cerebral ischemia is a known complication of carotid cross-clamping during carotid endarterectomy. While selective intra-luminal shunting has been used for cerebral protection, this procedure may not always be effective and carries its own risks. The purpose of this study was to identify potentially modifiable risk factors for intraoperative cerebral ischemia and shunting during carotid endarterectomy.

Methods

We performed a retrospective, case-control chart review of all primary carotid endarterectomies with electroencephalographic (EEG) monitoring and selective shunting performed at our institution between 2000-2010. Operative records were screened for documentation of ischemic EEG changes and shunting at the time of carotid clamping. The remaining charts of patients not requiring shunting were randomized and matched to the shunt cases by year of surgery, and presence or absence of contralateral carotid occlusion. Detailed perioperative data was collected for all shunt and control cases. Results were analyzed using the Mantel-Haenszel test and a multivariable logistic regression model.

Results

The incidence of intraoperative ischemic EEG changes leading to shunt placement gradually decreased by approximately 50% between the first and second 5 year periods of the study, or on average 12% per year (P=0.0032). Chronic beta blocker use was the only preoperative variable that was significantly different between the shunt and control groups, with patients undergoing shunting being more likely to have been receiving beta blockers (33/69 vs 18/69, P=0.01, OR 2.5, 95% CI, 1.2 - 5.1). Intraoperative hemodynamic values were similar for shunt and control groups, as well as for beta blocked and non-beta blocked patients.

Conclusions

The current study found an association between chronic beta blocker use and intraoperative cerebral ischemia in patients undergoing carotid endarterectomy. As this effect did not seem to relate to intraoperative hemodynamics, it is postulated that this observation may involve impaired vasodilation and autoregulation of cerebral blood flow in response to carotid clamping.

RATIONALIZING A STANDARD APPROACH TO THE EMERGENCY SURGICAL AIRWAY: A REVIEW OF TECHNIQUE AND EVIDENCE FOR EFFICACY

Rebecca M. Gerlach MD[1], Kenji Inaba MD[2], Regan J. Berg MD[2], Demetrios Demetriades MD[2]

1. Department of Anesthesiology, Queen's University, Kingston General Hospital, Kingston, ON
2. Division of Trauma Surgery and Surgical Critical Care, Los Angeles County Medical Center – University of Southern California, Los Angeles, CA

Abstract

The patient who cannot be intubated and cannot be ventilated presents an immediate threat to life that, despite multiple advances in the difficulty airway armamentarium, continues to challenge anesthesiologists with the need for an emergent surgical airway. The rarity of this situation, however, is such that no one provider will attain enough clinical experience to be comfortable with the technique, mandating training with cadaveric or synthetic anatomic models to ensure competency. The ideal surgical airway technique should be simple and reliable, easily replicable, fast, and performable under pressure, yet the optimal approach remains controversial. Both percutaneous and open techniques are described, with a significant trend in the anesthesia literature towards less invasive percutaneous approaches in contrast to the open techniques advocated by surgeons. Attempts to compare the efficacy of various techniques are confounded by significant biases, including use of varying synthetic and cadaveric models and varying provider clinical backgrounds and training. The use of several surgical instruments and multiple approaches has clouded the understanding of open cricothyroidotomy for non-surgeons, while percutaneous techniques mandate a baseline skillset and familiarity with commercial kits, and may not be as reliable in a true clinical situation as airway models suggest.

The current systematic literature review surveys the range of advocated techniques and the evidence for their efficacy, incorporating experience from one of the largest Level 1 trauma centers in the United States, to rationalize an optimal approach for obtaining surgical airway access applicable to surgeons and non-surgeons alike. In addition, multiple outstanding research questions including the impact of distorted neck anatomy on the performance of cricothyroidotomy, the role of stress and previous cricothyroidotomy experience on performance, and long-term clinical outcomes of emergency cricothyroidotomy are tabulated and the ongoing attempts by our research group to address these issues are described.

Impact of Spontaneous Versus Evoked Neuropathic Pain on Pain-Related Quality of Life

Grant B, Gilron I, Holden R, Orr E.

Background: A substantial percentage (18-42%) of patients with diabetes suffer from disabling pain due to sensory neuropathy. Neuropathic pain is known to have a significant impact on quality of life and activities of daily living. Given that current pain therapies are inadequate for 40-60% of affected patients, much effort is being invested into the identification of new targets of pain modulation. Research into novel drug therapies for pain is largely based upon animal pain models of stimulus-evoked pain since very few animal models of spontaneous pain exist. Patients with neuropathic pain describe an array of sensory abnormalities. These can be pains of a spontaneous nature (those that arise without external stimulation) and evoked pains (abnormal responses to mechanical or thermal stimuli). Spontaneous pain can be continuous, steady and ongoing, or it can be paroxysmal, episodic and intermittent. The relative impact of spontaneous versus evoked pain on quality of life and activities of daily living is unclear. There have been very few reports on the ability of patients to differentiate between these two types of pain and their relative impact on pain-related quality of life. The purpose of this ongoing investigation is to develop a pool of self-report items and descriptors that will describe functionally-relevant differences between spontaneous and stimulus-evoked pain. We expect this research to lead to the development and validation of a pain measurement inventory that could be used to quantify differential impact of analgesic therapies on spontaneous versus evoked chronic pain.

Methods: Following Research Ethics Board approval and informed consent, adult patients with neuropathic pain who experience daily moderate pain for at least 3 months were recruited. In this prospective study, patients completed a pilot version of the "Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation Pain Questionnaire",a modified Brief Pain Inventory, and the "S-LANSS" neuropathic pain questionnaire.

Results: Preliminary descriptive results of this pilot questionnaire suggest the experience of evoked pain as "often" or more by 57-74% of study subjects and the experience of spontaneous pain as "often" or more by 67-74%. Interestingly, 57% of patients never or only sometimes avoid activities because of evoked pain and 62% say it never or only sometimes interferes with activities. Strikingly, 93% of patients often, very often or always carry on with their regular activities of life despite the pain. The most common factors reported to evoke pain included walking, standing, bedsheets, shoes and socks. The most common situations in which spontaneous pain occurred included watching TV, reading and sitting.

Conclusions: Preliminary results of this pilot questionnaire suggest that subjects with neuropathic pain are able to differentiate between evoked and spontaneous pain both of which appear to be frequent experiences. Given the need to better understand the mechanistic diversity of neuropathic pain and how current and future pain therapies can differentially affect spontaneous versus evoked pain, further development and validation of this type of pain measurement inventory is warranted.

Surgical vs. classical approach to TAP blocks: A randomized controlled study

Erika Nguyen, Tarit Saha, Jasmine Bahrami

Background

TAP blocks have been shown to be superior to intravenous and oral opioids in relieving postoperative pain following various abdominal procedures. The technique was initially described as an anatomical landmark-based approach before the ultrasound guided approach was introduced in 2007 with the expectation of increasing safety and reliability of the TAP block. Recently, a novel technique using an intra-abdominal approach performed by the surgeon has proved to be successful in decreasing postoperative pain following colorectal surgery and cesarean section. It is likely that this approach would be associated with a decreased incidence bowel and organ perforation as it is performed under direct visualization of all abdominal components. On a resources standpoint, a surgical TAP block does not require the involvement of specially trained anesthesiology staff or additional equipment (ultrasound). With a trained surgeon, a TAP block from an intra abdominal approach can be done very quickly, is time efficient and could improve turnover time in OR. Its efficacy over the transcutaneous approach, however, has yet to be proven as no one has compared the two techniques.

Our study aims to demonstrate that the surgical transversus abdominis plane block provides equivalent analgesia to the classical TAP with the added benefits of being a more cost-effective, time-efficient and potentially safer technique.

Methods

After obtaining ethics approval, patients scheduled for elective total abdominal hysterectomy +/- bilateral salpingo-oophorectomy using a Pfannenstiel or low midline incision will be randomized into 3 groups. Group A will receive surgical TAP blocks, group B ultrasound-guided transcutaneous TAP blocks and group C will be a control group. A standard postoperative analgesia regimen that includes a PCA-IV will be ordered for all patients. Our primary end points will be pain scores and hemodynamic values (HR, BP) at different times postoperatively. We will include opioid consumption, patient satisfaction, OR time and incidence of side-effects as secondary end points. Patients with a past medical history of chronic pain, fibromyalgia, inflammatory bowel disease or drug allergy to local anesthetics will be excluded from the study.

We plan to conduct a pilot study in order to determine the feasibility and the sample size required for our project. This will also provide our surgeon(s) an opportunity to get familiar and consistent with the surgical TAP block technique.

References

1. Bharti N, Kumar P, Bala I, Gupta V: The efficacy of a novel approach to transversus abdominis plane block for postoperative analgesia after colorectal surgery. Anesthesia & Analgesia 2011, 112(6):1504-1508.

2. Owen DJ, Harrod I, Ford J, Luckas M, Gudimetla V: The surgical transversus abdominis plane block--a novel approach for performing an established technique. BJOG: An International Journal of Obstetrics & Gynaecology 2011, 118(1):24-27.

The Economics of Anesthesia Drug Wastage

Investigators: Dr. Y. Hayat, Dr. R. Tanzola, Dr. R. Rooney, Dr. Dale Engen

Background: Soaring health care costs have led to an increasing proportion of the federal and provincial budgets being utilized to provide health care services. Both federal and provincial governments have been forcing reductions in health care expenditures. This has lead to hospitals and medical departments, including Anesthesiology, being pressured to bring down their costs and justify expenditures. Anesthetic drugs are a major variable cost for the department and the hospital. Last year total OR anesthetic drug expenditure at KGH was approximately ½ million dollars. More recently we have faced critical shortage of intravenous anesthetic agents that further highlights the need for drug conservation strategies. Gillerman et. al., using a mathematical model, estimated the cost of anesthetic drug wastage to be 26% of an Anesthesiology department's total drug expenditure. At KGH, this wastage could be approximately $125,000. Weinger calculated drug wastage cost per case of US $ 13.51 and estimated potential aggregate annual savings of US $250-$350 million based on the potential cost savings of $10-$15 per surgical case in the USA. Wagner et. al. used regularly drawn drugs including epinephrine, ephedrine, lidocaine, atropine and succinylcholine in their study and estimated total savings of $ 66,000 per year in a tertiary care hospital. However, none of these studies have directly quantified the amount of total drug wastage. Therefore, the purpose of this study was to directly quantify anesthetic drug wastage.

Hypothesis:

At least twenty five percent of the Anesthetic drugs are wasted on a given day

Objective:

To quantify the magnitude of the Anesthetic drugs wastage and to determine the most commonly wasted drugs.
Suggest strategies to improve utilization.

Method:

Following institutional ethics approval, we carried out wasted anesthetics drugs collection study for a two week period starting on January 30th. All opened and incompletely used syringes and vials of anesthetic drugs were collected in marked containers. Investigators went through the collection on daily basis to record quantities of the wasted drugs.

Results:

The following numbers represent minimum anesthetic drug wastage captured for the two week period, excluding controlled drugs, volatiles, oral and infrequently used anesthetic drugs. This is the minimum due to the fact that drugs from some operating rooms were discarded elsewhere and were missed from the study.

- Total projected cost of wasted intravenous anesthetic drugs was $ 45,552

Following drugs were most commonly wasted:

OPERATING ROOM	Unit Acq Cost	Total drug units	Total drugs per year	Total cost
Rocuronium Bromide Inj 10mg/mL - 5mL	$ 5.01	76.10	1978.6	9,902.89
Propofol Inj 10mg/mL - 20mL	$ 2.38	104.55	2718.3	6,457.05
Succinylcholine Chloride Inj 20mg/mL-10mL	$ 3.58	64.80	1684.8	6,031.58
Labetalol	$ 6.90	23.05	599.3	4,136.01
Esmolol HCl Inj 10mg/mL - 10mL	$ 10.22	13.80	358.8	3,666.94
Phenylephrine Inj 10mg/mL-1 mL	$ 1.20	64.20	1669.2	1,996.36
Atropine Sulfate Inj 0.6mg/mL - 1mL	$ 0.74	94.00	2444	1,796.34
Propofol Inj 10mg/mL - 100mL	$ 46.00	1.25	32.5	1,495.00
Glycopyrrolate Inj 0.2mg/mL - 2mL	$ 4.90	9.50	247	1,210.30
ePHEDrine Sulfate Inj 50mg/mL - 1mL	$ 0.67	66.35	1725.1	1,148.92
Midazolam HCl Inj 1mg/mL - 2mL	$ 1.08	40.25	1046.5	1,128.13

Discussion:

This study quantified the magnitude of Anesthetic drug wastage. Current critical shortage of intravenous anesthetic drugs signifies rational use of these drugs. Following strategies will help optimize drug utilization

- Redo study to show impact of conservation strategies on drug wastage post intervention (post critical shortage era)
- Have labeled syringes ready to draw drugs such as Atropine and Succinlycholine as oppose to routinely drawing them
- Draw smaller quantities and save remaining in the vials for later use such as Rocuronium if full 50 mgs is not needed for a patient
- Carry stock of pre-mixed syringes of smaller quantities of Ephedrine and Phenylephrine prepared by OR pharmacy
- Consider purchasing secure anesthetic drug cart management system with option for the storage of pre-drawn unused syringes for later use and to ensure patient safety

Acknowledgements:

Our thanks to Ron Koob, Paula King , Joe Raposo & Joanne Bauder Fobert for their help.

SYSTEMIC ADMINISTRATION OF ULTRA-LOW DOSE ALPHA 2-ADRENORECEPTOR ANTAGONIST ATIPAMEZOLE ATTENUATES MORPHINE TOLERANCE AND ENHANCES OPIOID ANALGESIA IN NEUROPATHIC PAIN STATES

Grenier P (1), Milne B (2), Cahill CM (1,2,3). (1) Department of Pharmacology and Toxicology, (2) Department of Anesthesiology, and (3) Centre for Neuroscience Studies, Queen's University

Two significant obstacles in the therapeutic use of opioid analgesics are the development of tolerance over time and the decreased effectiveness of opioids in the treatment of chronic pain states. Previous studies have investigated the use of spinal administration of ultra-low dose (ULD) a2-adrenergic receptor antagonists to attenuate the development of morphine tolerance. The aim of this study was to confirm the effectiveness of systemic administration of ULD a2-adrenergic antagonist atipamezole in enhancing morphine analgesia in models of opioid tolerance and neuropathic (NP) pain, which has not been previously investigated.

To determine the effects of ULD α2-adrenergic antagonists on the development of opioid tolerance in pain naïve animals, male Sprague-Dawley rats were randomly assigned to groups receiving once daily subcutaneous injections of morphine (5mg/kg), morphine (5mg/kg) plus atipamezole (5ng), atipamezole alone (5ng) or saline vehicle. Thermal tail flick latencies were assessed on day one and day seven over a two hour time course to assess the effect of atipamezole on acute morphine tolerance. Tail flick latencies were also assessed daily, thirty and sixty minutes post-injection for seven days to assess the effect of atipamezole on development of chronic morphine tolerance.
To determine the effect of ULD a-2 adrenergic antagonists on morphine analgesia in a model of NP pain, separate rats were randomly assigned to one of two groups: sham or NP. NP pain was induced through chronic constriction injury (CCI) of the sciatic nerve. Half the animals in each group received once daily subcutaneous injections of low-dose atipamezole (5ng) or saline for eleven days. Thermal and mechanical responses were assessed on days four, seven and ten post-surgery. Once pain hypersensitivity was established, a single injection of morphine (5mg/kg) was administered to all animals, and behaviour was assessed over a two hour time course to determine changes in acute opioid analgesia.

Opioid tolerance developed rapidly over the seven days in morphine-treated animals. In rats co-administered atipamezole, an approximate 30% attenuation of tolerance was observed compared to morphine alone. Neither atipamezole alone nor saline vehicle had any effect on tail flick latencies.
Development of mechanical allodynia was observed in CCI animals over the ten days following surgery, and was significantly attenuated by day ten in those receiving daily low-dose atipamezole compared to saline. No effect on thermal tail flick latencies was observed over the same period.
On day ten, a single acute injection of morphine restored mechanical withdrawal thresholds to pre-surgery baselines in the CCI animals. The duration of the anti-allodynic effects of morphine was significantly prolonged in the animals that had been chronically treated with atipamezole compared to saline. Similarly, following the acute morphine injection, the thermal anti-nociceptive effects were prolonged in the CCI animals treated with atipamezole compared to saline controls.

Chronic systemic administration of ULD a2-adrenergic antagonist atipamezole attenuates the development of morphine tolerance, and enhances and prolongs the anti-allodynic effects of morphine in NP pain states. This may one day prove useful in a clinical setting to enhance the effects of opioid analgesics. Further studies will be performed to determine the mechanism through which adrenergic antagonists modulate opioid receptor activity.

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

Judith Marois, Rob Tanzola and Dale Engen

Background: The surgical stimulus, pneumoperitoneum, results in an elevation of HR and BP assumed to be due to pain and treated by anesthesiologists with opioids. However, the hemodynamic changes occurring in laparoscopic pneumoperitoneum are primarily due to stimulation of the sympathetic system. The logical treatment for hemodynamic changes resulting from non-painful sympathetic stimuli is sympathetic blockade, e.g. esmolol, labetalol, rather than an analgesic. Studies suggest that intraoperative beta-blockade may be a superior management option compared to the current standard of care using opioid for pneumoperitoneum. Intraoperative esmolol has been shown to effectively control hemodynamics, and when compared to opioids, significantly improve postoperative outcomes including decreased early postoperative nausea and vomiting (PONV), decreased postoperative fentanyl and ondansetron use, and shorter time to discharge. Labetalol may be advantageous over esmolol since it controls both heart rate and blood pressure, can be given as a bolus and costs less than esmolol. The purpose of this study is to delineate the potential benefits of beta-blockers for the treatment of intraoperative sympathetic stimulus, demonstrate a relevant impact on patient outcomes, and contribute to the literature in this area. Also, we aim to specifically identify labetalol as a valid beta-blocker treatment.

Hypothesis: We hypothesize that labetalol will be as effective as esmolol in reducing length of stay in the PACU and time to discharge as compared to fentanyl. We hypothesize that labetalol will effectively maintain intraoperative heart rate and mean arterial pressure within 20% of baseline when compared to esmolol as control and fentanyl as standard of care.

Primary outcome: time from arrival in PACU until readiness for discharge from PACU; intraoperative hemodynamics measured by heart rate, mean arterial pressure, systolic blood pressure and diastolic pressure.

Secondary outcome: postoperative nausea and vomiting, pain scores and fentanyl use in PACU, cost of intraoperative fentanyl, labetalol, and esmolol.

Study Design: Patients undergoing elective ambulatory laparoscopic cholecystectomy surgeries will be recruited for a prospective, randomized, double-blinded clinical trial. There will be 3 arms (fentanyl boluses, esmolol infusion, labetalol boluses) and patients will receive the study treatment plus placebo intraoperatively. A blinded observer in PACU will do outcome assessments.
Impact: This study will contribute to the literature in an area that is not well defined, adding to what is known about intraoperative use of beta-blockers, specifically labetalol, which has not been as thoroughly studied as esmolol. It will also provide more information about opioid-sparing anesthetic techniques. Health care costs may also be reduced either through a difference in the medications used or in the time patients spend in hospital postoperatively.

Acknowledgements: Dale Engen, Rob Tanzola, Debbie DuMerton Shore, Elizabeth VanDenKerkhof, Rachel Phelan, Chris Gray, Queen's University Office of Research Services

Evaluating Junior Resident Readiness for Independent Anesthesia Call Duties With Simulation

Jeff Sampson, Melinda Fleming, and Michael Cummings

Introduction: Currently, Queen's University Anesthesiology and Perioperative Medicine residency program uses two methods to establish whether junior residents are ready for independent anesthesia call duties. The first method of assessment is based on daily evaluations by attending anesthesiologists of residents' clinical performance. The second method is an assessment of the completeness of a checklist[1] covering specific aspects of the on-call practice of junior residents.

The desire for further objective measures of the competence of residents transitioning to independent call duties overlaps with a growing body of medical education literature relating to competency-based postgraduate medical training. Furthermore, the Royal College of Physicians and Surgeons of Canada (RCPSC) continues to increase its use of the competency-based paradigm in specialist training programs. Using the simulation environment to replicate crisis scenarios relevant to anesthesia practice provides a forum for objective assessment of medical expert, procedural, and non-technical competencies.

Research Objective: Establish the validity and reliability of a simulation-based assessment of junior residents' preparedness for independent call duties.

Proposed Study Design: The proposed project is a medical education pilot study. The first iteration of evaluative simulator sessions will occur in July or August of 2012 following completion of the Boot Camp and Airway courses for junior residents. Participants in the simulation project will include junior anesthesia residents at the beginning of their second year of residency training and family practice physicians commencing an additional anesthesia training year. Four simulation scenarios under development will deal with anesthesia crisis management and Advanced Cardiac Life Support content.

The scenarios will require development and validation of a scenario-specific assessment tool to score the medical expert aspect of the project. Employing a modified Delphi technique[2-3] will allow for attainment of expert consensus while developing the valid and reliable standardized scoring system for the assessment tool.

Another assessment model under consideration to evaluate the non-technical skills of study participants, such as communication and leadership, is the Anaesthetists' Non-Technical Skills (ANTS) tool[4]. Also under consideration, in order to gauge overall performance during the evaluative sessions, is the Global Rating Scale currently in use by the Anesthesiology Examination Board of the RCPSC.

Employing the three assessment tools will yield a comprehensive simulation-based assessment of preparedness for independent call duties. Evaluation for statistical concordance between the simulation-based assessment and the current methods of assessment will demonstrate whether evaluative simulator sessions provide a valuable tool for gauging junior resident readiness for independent call duties.

References:

1. Queen's University Anesthesiology and Perioperative Medicine. Competencies Required for Independent Anesthesia Call Duties. http://meds.queensu.ca/anesthesiology/assets/Competencies%20Required%20for%20Independent%20Anesthesia%20Call%20Duties.pdf. Accessed 01 March 2012.
2. Clayton, MJ (1997). Delphi: a technique to harness expert opinion for critical decision−making tasks in education. Educational Psychology, 17(4), 373−386.
3. Scavone, BM, Sproviero, MT, McCarthy, RJ, Wong, CA, Sullivan, JT, Siddall, VJ, & Wade, LD (2006). Development of an objective scoring system for measurement of resident performance on the human patient simulator. Anesthesiology, 105(2), 260–266.
4. Flin, R, Patey, R, Glavin, R, & Maran, N (2010). Anaesthetists' non-technical skills. British Journal of Anaesthesia, 105(1), 38–44.

Do antidepressants reduce postoperative pain? A systematic review.

Karen Wong and Ian Gilron, Queen's University

Introduction: Multi-modal analgesia has long been advocated for treatment of postoperative pain. Though opioids, NSAIDs and acetaminophen have been the mainstay agents in managing postoperative pain, other adjuncts such as anticonvulsants, which have been used successfully in treating chronic pain, have also been efficacious in this setting. Similarly, antidepressants, a cornerstone in the treatment of neuropathic pain as well as chronic pain related to an underlying inflammatory process, may possibly be suitable in the postoperative pain setting. Here, we review the evidence for the use of antidepressants as an analgesic adjunct in postoperative pain.

Methods: The electronic databases EMBASE, MEDLINE, CENTRAL, CINAHL were searched for published randomized, double-blind clinical trials that evaluated the efficacy of antidepressants for treating postoperative pain. The references of these studies were also searched to identify additional trials. Finally, a cited reference search through the Web of Science database was also used. Study outcomes include: 1) validated measures of patient-reported pain intensity and pain relief, 2) validated measures of patient global assessment of efficacy, 3) time to use of rescue medication, 4) number of participants using rescue medication, 5) number of participants with one or more adverse events, 6) number of participants with serious adverse events, 7) number of withdrawals (all cause, adverse events). Two assessors independently review each study to determine inclusion and the Cochrane Collaboration's tool for assessing risk of bias is used to analyze the quality of the included studies.

Preliminary results: 1347 records were found from searching the aforementioned electronic databases, and 1 additional reference was found through a cited reference search. 1318 records were excluded as a result of duplication or non-clinical study (eg. review articles). 29 abstracts were reviewed, 11 were excluded (2 in Italian, 1 in German, 2 in animal models, 4 in non-surgical population, 1 non-randomized observational study, and 1 used medications that were not typically used as antidepressants). 18 full texts were subsequently reviewed, 3 were excluded (1 was an open label study, 2 studied amitriptyline administered in a mixture with ketoprofen and oxymetalozine vs. placebo). 15 randomized, double-blind, placebo controlled trials have been included in this review thus far, describing the experience of 998 patients. 449 patients were randomized to placebo and 564 to treatment. The studies are as follows: 2 compared amitriptyline to placebo, 1 compared bicifadine to both placebo and aspirin, 1 compared bicifadine to placebo and codeine, 2 compared desipramine to placebo, 1 compared duloxetine to placebo, 1 compared fluoxetine to placebo, 1 compared fluradoline to placebo and aspirin, 4 compared tryptophan to placebo, 1 compared venlafaxine to gabapentin and placebo, and 1 compared desipramine to amitriptyline and placebo.

Conclusion: Final literature search and quality assessment of included trials are ongoing. Where appropriate, meta-analyses will be undertaken in order to perform an unbiased evaluation of existing evidence.

GLIAL MODULATION SUPPRESSES MODALITY-SPECIFIC TACTILE ALLODYNIA IN A MODEL OF NEUROPATHIC PAIN

Grenier P (1) and Cahill CM. (1,2,3). (1) Department of Pharmacology and Toxicology, (2) Department of Anesthesiology, and (3) Centre for Neuroscience Studies, Queen's University

Many studies have demonstrated correlations between expression of neuropathic (NP) pain behavior and activation of glial cells in the spinal cord, and some groups have shown metabolic inhibitors of glia attenuate pain responses. PJ34, an inhibitor of Poly-ADP-Ribose Polymerase (PARP) has been shown to inhibit the activation of microglia following ischemia in spinal cord tissue, but few studies have investigated its use in a model of NP pain. Propentofylline (PF), an inhibitor of both astrocytes and microglia, has been shown to be effective in attenuating allodynia and hyperalgesia in rodent models of NP pain. The purpose of this study was to attempt to draw parallels between the actions of PJ34 and PF, both behaviorally and on a molecular level through the use of two pain models and through various sensory testing modalities.

NP pain was induced in male Sprague-Dawley rats through a chronic constriction injury (CCI), either through the tying of loose ligatures around the sciatic nerve (Bennett and Xie model) or by loose constriction of the nerve with a polyethylene cuff (Mosconi-Kruger model). Sham surgeries without nerve manipulation were used as a control. Animals received saline vehicle, PF (10ug) or PJ34 (15ug) through once daily intrathecal injections for eleven days post-surgery, beginning one hour pre-surgery.
Mechanical allodynia was assessed on days 4, 7 and 10 post-surgery using two different testing modalities: the mechanical withdrawal threshold to a series of von Frey filaments, and the number of withdrawals to a single 2g or 12g filament. On day eleven animals were perfused with 4% PFA for immunohistochemistry (IHC) studies of glial activation and neuronal activation via
c-Fos. Fluorescent IHC was performed on spinal cord slices using antibody labeling for microglia (CD11b) and astrocytes (GFAP). DAB IHC was used for c-Fos labeling. Image analysis consisted of quantification of fluorescent intensity of glial labeling and cell counts for c-Fos.

Neuropathy increased microglial and astrocyte activation as evidenced by an increase in immuno-fluorescent labeling. PJ34 produced a significant decrease in microglial labeling compared to saline treatment in NP rats. There was no significant effect on GFAP (astrocyte) labeling between PJ34 and saline. Thus PJ34 is an inhibitor of microglia but not astrocytes. In contrast, PF produced a decrease in both astrocyte and microglial activation in NP rats.
Chronic treatment with both glial inhibitors significantly attenuated the bilateral neuropathy-induced upregulation in c-Fos expression within the spinal dorsal horn. NP animals chronically treated with PF showed a significant attenuation of c-Fos expression to the same levels seen in sham-operated animals, while PJ34 was not able to attenuate c-Fos expression to sham levels. This may suggest astrocytes are playing a bigger role in neuronal activation in NP pain than microglia. Neither glial inhibitor had any effect on c-Fos expression compared to saline in sham animals.
Nerve injury through both the Bennett and Xie and the Mosconi-Kruger models produced mechanical allodynia by seven days post-surgery. Chronic treatment with PF did not reverse mechanical allodynia in either surgical model compared to saline. Chronic treatment with PJ34 did not have an effect on the mechanical withdrawal thresholds, but did have a significant effect on the number of withdrawals to a 12g von Frey filament in both NP models.

These studies highlight the importance of methodology in quantitative sensory testing. Investigating the differences between these two mechanical testing modalities may highlight a difference in the neurons involved and may help give an understanding of the mechanism through which glial inhibition affects neuronal activation in chronic pain states.

A RANDOMIZED CONTROLLED TRIAL OF DEXTROMETHORPHAN VERSUS PLACEBO FOR POST TONSILLECTOMY OR ADENOTONSILLECTOMY PAIN CONTROL IN CHILDREN

Investigators: Dr. Rachel Rooney, Dr. Matthew Langdon, Queen's Anesthesia
Research Nurses: Beth Orr, Debbie Dumerton Shore, Queen's Anesthesia

Research Progress Update: Trial Now Underway at Hotel Dieu Hospital…

Anesthesia Protocol

PURPOSE:

To test the hypothesis that the addition of dextromethorphan pre op and 8 hours post op to standard treatment will lower post op pain scores and decrease the amount of post op opioids required by children after tonsillectomy.

Patient Population: Age 3-12, ASA 1-2, tonsillectomy, adenotonsillectomy

Pre-operatively in SDAC (administered by study nurses):
Dextromethorphan 1mg/kg syrup or placebo syrup in equivalent volume orally

Induction:
Inhaled sevoflurane with or without nitrous oxide, IV induction with propofol
Acetaminophen 20mg/kg PR prior to the start of surgery

Intra-operative:
Inhaled sevoflurane or desflurane and/or muscle relaxant at the discretion of the attending anesthesiologist

IV Fentanyl for intra operative pain control as required

IV Dexamethasone 0.1 mg/kg maximum 4 mg, at the beginning of surgery.

IV Ondansetron 0.15 mg/kg maximum 4 mg, just before completion of surgery

**Please no other analgesic drugs during surgery (e.g. no ketorolac, no ketamine, no remifentanil)

Post-operatively:
IV Morphine 0.01-0.03 mg/kg IV PRN or Fentanyl 0.25 mcg/kg PRN in PACU
Dosing may be adjusted slightly for ease of drug dilution in the PACU

EPACU pain and nausea medication will be pre ordered according to study protocol.

Drs. Rooney and Langdon will be managing all postoperative pain and nausea issues in EPACU instead of the surgeons. If any questions arise that are not straightforward please direct them to Dr Rooney or Langdon. Thank-you in advance for your participation in this study!

Ultra-low dose naloxone modulates opioid tolerance independently of Toll-like receptor 4

T. A. Mattioli[1], B. Milne[1,2], C. M. Cahill[1,2], *[1]Biomedical and Molecular Sciences, Queen's University, Kingston, ON, Canada, [2]Anesthesiology, Queen's University, Kingston, ON, Canada*

Aim of Investigation: Ultra-low doses (ULD) of the opioid receptor antagonists, naltrexone and naloxone, augment the analgesic actions of morphine, block the induction of tolerance, and reverse established tolerance. The mechanism(s) by which this phenomenon occurs is still largely unknown. A recent publication reported novel antagonism of Toll-like receptor 4 (TLR-4) by the opioid receptor inactive (+) stereo-isomers of naltrexone and naloxone. Activation of glial TLR-4 triggers gliosis and the release of pro-nociceptive substances, contributing to the generation of chronic pain states and potentially to the development of opioid tolerance. Thus, the present study aims to elucidate the specific role of TLR-4 in the development and maintenance of tolerance to morphine analgesia.

Methods: Adult male C3H/HeOuJ (wild type; WT) or C3H/HeJ (TLR-4 knockout; KO) mice (20-25g) were administered morphine (MS; 10 mg/kg), MS and (-)naloxone (NLX; 1ng/kg), MS and (+)NLX (1ng/kg), or saline (SAL) intraperitoneally, once daily for five days. Thermal nociception was assessed on days 1, 3 and 5 by tail flick test (hot water immersion, 50˚C). Statistical significance was defined as P-value <0.05.

Results:
No difference was observed in acute morphine analgesia between the WT and TLR-4 KO mice, with each strain achieving approximately 100% MPE on day 1. Following 5 days of MS administration, the degree of tolerance was not significantly different between WT and KO mice (41 vs 46 % MPE respectively). Systemic administration of (-)NLX attenuated the development of morphine tolerance in WT mice compared to those receiving MS only ($p<0.05$). In KO mice, there was also no difference between day 1 and day 5 responses in animals treated with MS and (-)NLX suggesting that (-)NLX remained effective in attenuating tolerance in mice lacking TLR-4 receptors. The ULD opioid antagonist effect appears to be stereo-selective, as (+)NLX (opioid receptor inactive) did not attenuate tolerance in WT (48% MPE) or KO (60% MPE) mice compared to controls treated with MS only. Moreover, day 5 antinociceptive responses of MS and (+)NLX treated animals were significantly decreased from respective day 1 responses ($p<0.01$ WT; $p<0.05$ KO).

Conclusions: The stereo-selectivity of the ULD effect suggests that opioid antagonists do not modulate opioid tolerance via TLR-4 as hypothesized. Tolerance was still attenuated in TLR-4 knockout mice (C3H/HeJ) by (-)NLX; thus, an alternate mechanism of action must be responsible for the prevention and reversal of analgesic tolerance by ULD opioid antagonists.

Delta Opioid Receptor Trafficking Is Altered Following Prolonged Morphine Treatment

EW Ong (1) and CM Cahill (1,2,3). (1) Department of Biomedical and Molecular Sciences, (2) Department of Anaesthesiology, and (3) Centre for Neuroscience Studies, Queen's University, Kingston, Canada.

Aim of Investigation

The post-internalisation trafficking of endogenous neuronal delta opioid receptors (DOR) was examined in dorsal root ganglia (DRG) neurons following prolonged morphine treatment.

Methods

Primary dorsal root ganglia neuron cultures were treated with morphine (10uM) or vehicle for 48 hours, followed by acute DAMGO, Deltorphin II (DELT), SNC80, or vehicle (all 1 uM) for 60 minutes. DOR and markers of early endosomes (Rab5), recycling endosomes (Rab11), and lysosomes (LAMP1) were immunofluorescently double-labelled and imaged by confocal laser scanning microscopy. Associations between DOR and each marker were assessed by colocalisation analysis.

Results

Prolonged morphine treatment increased DOR colocalisation with early endosomes and lysosomes but not recycling endosomes following acute vehicle treatment. Acute DELT markedly decreased DOR colocalisation with lysosomes in prolonged vehicle treated neurons; this decrease was blunted following prolonged morphine treatment. Acute DELT increased DOR colocalisation with early endosomes in prolonged vehicle treated neurons. This was reversed following prolonged morphine treatment, where acute DELT decreased DOR colocalisation with early endosomes. Acute DELT increased DOR colocalisation with recycling endosomes following each prolonged vehicle and morphine treatments. Acute SNC80 decreased DOR colocalisation with recycling endosomes in prolonged vehicle treated neurons, with little change to colocalisations with early endosomes or lysosomes. In contrast, following prolonged morphine treatment, acute SNC80 increased DOR colocalisation with recycling endosomes and decreased colocalisation with early endosomes and lysosomes. In prolonged vehicle treated neurons, acute DAMGO decreased DOR colocalisation with both early and recycling endosomes. This was reversed following prolonged morphine, where acute DAMGO increased DOR colocalisation with early and recycling endosomes.

Conclusions

DOR post-internalisation trafficking is typically considered to proceed via early endosomes towards ultimate degradation in lysosomes. Following prolonged morphine treatment, we observed increased DOR internalisation and degradation. Acute treatment of neurons with two DOR agonists, DELT (a peptide) and SNC80 (a small molecule), revealed interesting differences. In prolonged vehicle treated neurons, DELT markedly reduced DOR-lysosome association; it instead promoted DOR recycling. SNC80 did not alter degradation and, in fact, reduced recycling. In prolonged morphine treated neurons, both promoted DOR recycling. Acute treatment of neurons with DAMGO, a mu opioid receptor agonist, had little effect on DOR association with lysosome. In prolonged vehicle treated neurons, DAMGO reduced DOR association with both early and recycling endosomes. However, in prolonged morphine treated neurons, the effect was reversed and DAMGO promoted DOR internalisation and recycling. Prolonged morphine treatment alters DOR internalisation trafficking both constitutively and in response to agonist-induced activation.

Use of Conditioned Place Preference Paradigm to measure the Negative Affect of Chronic Pain

Lihua Xue, Samantha LeCour, Claire Magnussen, Stephanie Metcalfe, Patrick Grenier, Anne Sutherland, Mary C. Olmstead and Catherine M. Cahill

Introduction: In addition to the obvious sensory disturbances that accompany neuropathic (NP) pain, this condition is associated with an important affective state. The emotional component of NP pain has been largely unexplored in the basic science field despite its obvious relevance to clinical conditions. The negative affect, or how much the pain is 'bothersome', significantly impacts the quality of life of the sufferer, and leads to the common co-morbidities of psychiatric disorders such as depression; patients with NP pain are twice as likely to suffer from depression and anxiety. In the present study we have used a paradigm that has traditionally been used as a measure of rewarding/reinforcing properties of drugs to capture the affective or tonic aversive component of persistent on-going pain. We hypothesized that drugs that are analgesic would produce a rewarding effect in chronic pain, but not sham animals.

Methods: Three groups of animals were used in the present study: pain-naïve, sham, and NP. Neuropathy was induced by chronic constriction of the common sciatic nerve. Animals underwent surgery (or not) 6 days prior to habituation, and conditioning to either drug or vehicle in a three-chambered compartment of a conditioned place preference paradigm. Conditioning was preformed over 8 days period using an unbiased, balanced paradigm where animals received drug and vehicle on alternative days. Post-conditioning testing was performed in drug-free states to determine the amount of time spent in either the drug or vehicle-paired compartment.

Results: Intrathecal administration the alpha 2 adrenergic receptor agonist, clonidine (13ug) or the delta opioid receptor agonist, deltorphin (30ug) produced a place preference in NP, but not sham animals. This result indicates that a reinforcing effect of a drug that is attributed to removal of the tonic aversive nature of pain can be detected in animals with on-going pain. Consistent with the literature, morphine dose-dependently produced reward in pain-naive animals. However, the dose response curve was significantly shifted to the left in NP animals and higher doses that were required to produce a preference in pain-naïve animals appeared to become somewhat aversive in the NP group. Finally, we determined how long the preference lasted (the rate of extinction) by daily exposure the apparatus without drug exposure. Pain-naive animals showed a significant increase in the amount of time in the morphine-paired compartment over the first 4 days, whereas animals with chronic pain lost their place preference within the second trial.

Conclusions: Together these data suggest that the conditioned place preference paradigm can capture the affective, tonic aversive nature of pain and its inclusion in preclinical screening of novel analgesics may better predict their effectiveness than traditional threshold assays of pain hypersensitivity. Additionally, while opioids have been shown to be less effective in treating NP pain compared to other pain types, our data suggests that morphine is more effective at low doses in modulating the aversive component of nerve injury and that higher doses of opioids, which are rewarding in pain-free states, may exacerbate the negative affect associated with nerve injury.

Critical Appraisal

By: **Karmen Krol**, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication title: "***Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy***."

Authors: ***Collard V, Mistraletti, G, Taqi A, Asenjo JF, Feldman LS, Fried GM, Carli F.***

Anesth Analg. 2007 Nov;105(5):1255-62.

Introduction

Anesthesiologists reading the title of this article for the first time would, without doubt, find it somewhat compelling. Conceptually, it's the sort of stuff that, perhaps if slightly simplified, would grab the attention of hospital administration as well given that one thing sparing another might be good for a bottom line somewhere in these fiscally restrained times. Indeed, the perioperative context of this study – ambulatory laparoscopic cholecystectomy – has well benefitted from advances in surgical and anesthetic technique, such that this progress can coincided with reduced procedural costs, reduced in-hospital time and the commensurate institutional cost savings therein, and increased patient satisfaction (1,2). The downstream results of this include the advent of minimally invasive "fast track" surgery and accelerated postoperative recovery periods, allowing centers to manage these cases on an outpatient or day surgery basis (1). Cholecystectomy is one of the most common intra-abdominal surgical procedures and the minimally invasive laparoscopic approach has become the standards of care in Canada (1,2). The main problem is that, despite the advances made that have safely facilitated this procedure, postoperative nausea and vomiting, pain, medical complications, and urinary retention remain rather common, and can be sufficiently severe so as to lead to an unanticipated hospital admission rate of approximately 5% (2).

Safe discharge of a patient from an ambulatory procedure suite requires complete recovery from anesthesia, effective postoperative analgesia balanced with hemodynamic stability and a minimum of other adverse symptoms. Opioids, a mainstay of perioperative pain management, are problematic in the context of postoperative analgesia for ambulatory laparoscopic cholecystectomy because 1) they are associated with increased risk of postoperative nausea and vomiting (PONV), and hemodynamic and/or respiratory abnormalities that would prevent safe discharge; 2) are less efficacious for postoperative analgesia than expected (1,3). Three components to the postoperative pain experience following laparoscopic cholecyctectomy have been described: a dominant incisional pain; deep visceral pain; and referred shoulder pain (4). Intuitively, this collective of distinct symptoms calls for analgesic approaches targeting the separate modalities represented. One obvious benefit to multimodal management is the potential for opioid sparing, thus mitigating some of the risk of adverse effects that would stall or prevent the safe discharge of the postoperative ambulatory patient.

It has been suggested that using short-acting opioids intraoperatively like remifentanil would serve the need for treating the painful stimuli of pneumoperitoneum and laparoscopic cholecystectomy, while limiting the presence of opioid-related side effects into the postoperative period (5,6). The authors of the paper also describe the use of β-adrenergic antagonism during surgery over the last ten years; that the utility lies in reducing the stress response and the commensurate perioperative hemodynamic changes in patients. Esmolol in particular, classified as an ultra short acting and cardioselective β-adrenergic antagonist, has been proposed as an alternative to intraoperative opioids in ambulatory anesthesia, as it has been found to facilitate fast tracking of patients postoperatively (7-9).

The specific hypothesis that these investigators sought to test was "(patients undergoing laparoscopic cholecystectomy) receiving intraoperative esmolol infusion would benefit from a significant opioid-sparing effect in the postoperative period" (1). If indeed the use of adrenergic blockade as part of safe, opioid-free ambulatory anesthesia in outpatient laparoscopic cholecystectomy spares the postoperative use of opioid, it would be expected that there be a concurrent prevention of anticipated opioid related side effects (notably PONV). Conceivably, this would facilitate throughput in the ambulatory surgical setting. Provided that this mode of management does not cause any

additional adverse symptoms, and at least maintains the acceptable standards of postoperative analgesia, this hypothesis would prove valuable in the efforts to further advance the efforts to deliver safe and efficacious ambulatory anesthesia in this context.

Methodology

This study is a prospective, randomized and observer-blinded cohort study with three groups. The "control" group (n=30) received regular (every 30 minutes) doses of fentanyl 50 μg IV; a second group (n=30) receiving first an initial dose of esmolol 1.0 mg/kg, then a continuous IV esmolol infusion of 5-15 μg/kg/min; and a third group (n=30) that received an initial dose of remifentanil 1.0 μg/kg then a continuous IV infusion of remifentanil 0.1-0.5 μg/kg/min. All other components of the provided general anesthesia were appropriate and standardized, including premedication, end-tidal concentration of desflurane (targeted to 4%-8%, to maintain adequate depth of anesthesia and prevent intraoperative awareness), neuromuscular blockade, and its indicated reversal, temperature, monitoring, IV fluid and rate of administration (Normal Saline, 6 mL/kg/hr), as well as analgesic adjuncts and empiric antiemetic therapies (acetaminophen 1.3 g; dexamethasone 8 mg, ketorolac 30 mg, and droperidol 0.625 mg). Surgically, all patients received similar sites of operative incisions, first infiltrated with 2% lidocaine, pneumoperitoneum was maintained at 12 mmHg with carbon dioxide, positioning for all patients was identical and all received 0.25% Bupivicaine + 1:200,000 epinephrine injections into the incisions at the and of the procedure.

Three anesthesiologists, who were instructed to follow study design but who did not participate in preoperative or postoperative assessments, provided general anesthesia to each of the groups of patients. Patients were transferred to the PACU where they were monitored by nurses unaware of the study hypothesis. The anesthetic records were not made available to the nursing staff or involved Research Fellow, ostensibly to prevent bias, and the nursing staff did not interact with the anesthesiologists involved in the study. PACU nurses re-evaluated patients every 5 minutes, or sooner at the patient's request. Fentanyl was prescribed in a standard manner, dosed 25 μg IV every 5 minutes up to a maximum of 200 μg/hr, for postoperative pain only if the reported pain level was 3/10 or greater at rest, utilizing the verbal rating scale (VRS). The White-Song scoring system seeks to quantify the postoperative suitability for patients to bypass a recovery period in the PACU and proceed directly to a step-down facility in anticipation of faster discharge home, or, depending on the centre, discharged home directly from the PACU. The system assesses patient level of consciousness, capacity for physical activity, hemodynamic and respiratory status and stability, as well as postoperative pain and emetic symptoms (1, 10). Achieving a score of 12/14 is deemed a safe threshold for fast-track path to discharge for a patient having received general anesthesia; in the current study, time to a score of 12/14 was measured for patients in each of the three groups.

122 patients were initially approached for enrollment in the study. 21 refused to participate, 11 did not meet inclusion criteria, leaving 90 patients to be enrolled. Exclusion criteria for the study were: <18 yrs or >85yrs; ASA status ≤ II; a history of hepatic, renal or cardiac failure; organ transplant; diabetes; morbid obesity; chronic use of opioids or β-adrenergic antagonists; known asthma or reactive airways disease; severe mental impairment; allergy to local anesthetics; inability to comprehend pain assessment. The 90 enrolled patients were, before the induction of general anesthesia, randomly assigned to a study group by a computer-generated block randomization schedule to compose three equal groups of 30 patients each. The apparently a priori power analysis of the sample sizes in this study verifies that 30 subjects in each group were sufficient for the detection of at least 40% reduction in postoperative fentanyl use in the PACU with an adequate power of 0.8 and probability of type-1 error of 0.05 (1); congruent with a related study examining patients undergoing general anesthesia for gynecological laparoscopic surgery (7). The primary outcome for the study was the amount of fentanyl used for postoperative pain relief in the PACU (1). Secondary outcomes were the incidence of postoperative nausea and vomiting, the use of ondansetron in the recovery room, patients' White-Song score, and time spent in the PACU. The breadth of collected data certainly seems appropriate and informative: patient demographics, history of PONV, motion sickness, smoking, duration of surgery and anesthesia, amount of fentanyl, esmolol, and remifentanil used intraoperatively, amount of IV fluids given intraoperatively, amount of fentanyl used in the PACU, time spent in the recovery room until discharged home, VRS, incidence of PONV, pruritis and urinary retention, and the White-Song score. The data expression and statistical analyses are similarly appropriate, using analysis of variance (ANOVA) with multiple comparisons between groups and post-hoc analyses intended to separately acknowledge data that follow, or do not follow normal distributions (instead of assuming normal distributions throughout the data).

The reviewed article certainly represents anesthetic approaches that are achievable and relevant in a variety of settings, from academic centres to smaller community hospitals with outpatient or day surgical programs. The main components of classical general anesthesia are employed in the study with experimental variations that, with evidentiary support, are within reasonable

parameters that they uphold a standard of care to the patient participants in this study. However, I think that the study design is inevitably flawed in its refusal to include a cohort of patients that receive neither opioid nor β-adrenergic antagonists, as a true control of the interventions targeting each of the different modalities (nociception and increased sympathetic outflow). The study maintains ethical standards by not having such a group, since patients undergoing laparoscopic cholecystectomy without intention of either of the stated treatments would be subjected to intraoperative care that is deliberately below acceptable standards. Other than this (necessary) compromise, the design is clearly intended to test the stated hypothesis and therefore further advance the field to the benefit of ambulatory anesthesia and surgical practice. The inclusion criteria are appropriately rigorous in the sense that patients fulfilling those criteria are representative of the intended ambulatory patient population; ie, healthy adults with minimal comorbid disease. The methodology is described in adequate detail so as to be fundamentally reproducible, with drugs, their doses and routes of administration clearly described, surgical technique, etc. Various omissions (e.g., specific makes and models of anesthetic machines and ventilators, infusion pumps, commercial sources of drugs, IV fluids) are likely acceptable ones and any variations conferred by presumably properly functioning or standardized examples of similar equipment/sources of consumables is not likely to affect the clinical outcomes or significance of treatment differences, either experimentally or in daily practice.

Results

Five patients in total were excluded from postoperative analysis. Three patients in the "control" group (receiving intraoperative fentanyl) and two from the group receiving intraoperative remifentanil group were excluded because their surgeries were converted form laparoscopic to open procedures. The authors do not account for what, if any, impact this would have on the overall statistical power of their analyses, since this small reduction from the sample sizes represents a failure to achieve their designated "minimally acceptable" power of 0.8. However, the three groups are statistically alike in all designated variable except that there was a significantly larger proportion of women to men in the remifentanil group (27 vs 3) as compared to the fentanyl (19 vs 11) and esmolol (17 vs 13) groups. Demographic and medical historical data for each of the three groups are easily compared in table form. Similarly, VRS and White-Song scores are appropriately documented for all three groups in table form, as are (separately) the primary and secondary outcome measures, and the comparisons of each treatment group to the "control" group, and to each other.

The average amount of fentanyl used in the PACU was significantly lower in the esmolol group (91.5 μg) than the amounts used on average in the other two groups (168.1 μg and 237.8 μg). The incidence of nausea was significantly less frequent in the esmolol group and the number of patients receiving ondansetron, and the total amount of ondansetron administered for persistent nausea were both lower in the esmolol group when compared to both other groups in this study. There was no difference on these latter parameters when comparing only the fentanyl and remifentanil-treated groups. There were significantly more patients with a White-Song score >12 at 1 minute after arrival to the PACU in the esmolol group (21 patients) when compared to the remifentanil group (9 patients) and the time interval between arrival in the PACU and discharge home was significantly shorter in the esmolol group (120 minutes) when compared to the other groups (180min and 162.5 min for the fentanyl and remifentanil groups, respectively).

Discussion

The main conclusion of the study is that an intraoperative, continuous infusion of esmolol with no additional opioids contributes to a significant opioid-sparing effect during the immediate postoperative period, and furthermore, that this coincided with significantly lower incidence of postoperative nausea and the need for anti-emetic medication, as well as faster time to patient discharge (1). The data, as presented, clearly support this conclusion and the effects noted are both statistically and clinically significant. In doing so, the data support the hypothesis but also extend the importance of the contribution to the field that this study makes. The significant differences in the secondary outcomes that the esmolol treatment conferred on the study patients are parameters that collectively identify a defined role for this anesthetic approach in ambulatory laparoscopic cholecystectomy. Lower need for opioids, lower incidence of adverse symptoms (PONV), faster time to discharge home are all desirable outcomes in the ambulatory setting.

The authors do not appear to dedicate a great deal of effort to explaining how their treatment would subserve such desirable outcomes. They identify the obvious abrogation of increased sympathetic activity lent by β-adrenergic antagonism in the context of the anxiety associated with surgery, and suggest that blunting the sympathetic responses that occur, to noxious stimuli (incisions, pneumoperitoneum, etc) may reduce the overall nociceptive experience and thus reduce the need for postoperative opioids. They decline to rectify the putative cardioselectivity of esmolol with a global antagonism of sympathetic tone but instead postulate that esmolol may be acting in the CNS to block the specific contributions to nociception of the hippocampus.

However, the final point on this postulate notes that there is disputed evidence that esmolol has the capacity to cross the blood-brain barrier an therefore it is not known whether it can exert any meaningful effect on central adrenergic activity and nociception. Another possible explanation advanced in the paper is based on the assumption that β-adrenergic antagonists have been shown to decrease their own metabolism, and that of other drugs, likely by reducing hepatic blood flow (11). This at least seems plausible, given the anticipation for a reduced cardiac output with esmolol infusion and possible redistribution of organ perfusion, and the result may very well be changes in the pharmacokinetics of analgesic drug metabolism (12).

A possibility that the authors do not describe is that the intraoperative use of fentanyl and remifentanil has produced opioid tolerance and/or opioid-induced hyperalgesia (13), whereas the esmolol-treated group had no exposure to potent intraoperative opioids, at any dose, and therefore was spared this confounding effect. This would also help explain why the remifentanil-treated group showed the greatest postoperative fentanyl usage and the lowest number of patients with a White-Song score of >12 at one minute after arrival in PACU. The downstream delays in discharge home (relative to the esmolol-treated patients may reflect the additional time needed for analgesic adjuncts (acetominophen, ketorolac) to exert their effects. What, if any, effect the phenomena of opioid tolerance, and opioid induced hyperalgesia are exerting in this paradigm is rather unclear and deserves future study. The results of the current study are in agreement with other investigations showing postoperative opioid sparing in patients treated with esmolol infusions in gynecological intra-abdominal surgery (8,9), however these studies employed fentanyl as part of the induction of anesthesia, although not as an ongoing component of intraoperative management. Importantly, this study is the first to use esmolol to replace any and all intraoperative opioids, and show a significant reduction in the amount of postoperative fentanyl used, and postoperative adverse symptoms.

This represents an important contribution to approaches and management of ambulatory populations scheduled for surgery. Another avenue of future research is undoubtedly the applicability of this approach to other ambulatory procedures. It certainly appears to have a great deal of merit and, although I haven't been in this gig for long enough to define my own "practice" per se, this approach will probably be a component of my future career, given the appropriate patient(s), surgical procedures and setting. It seems clear that there is a role for drugs like esmolol (and presumably other β-adrenergic antagonists) as part of multimodal anesthesia/analgesia to support the safe but expedient workflow of patients through ambulatory surgery.

References

1. Collard V, Mistraletti, G, Taqi A, Asenjo JF, Feldman LS, Fried GM, Carli F. Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. Ambulatory Anesthesiology; 105(5): 1255-62.
2. Lau H, Broks DC. Contemporary outcomes of ambulatory laparoscopic cholecystectomy in a major teaching hospital. World J Surg 2002;26:1117–21
3. Zhao SZ, Chung F, Hanna DB, Raymunso AL, Cheung RY, Chen C. Dose-response relationship between opioid use and adverse effects after ambulatory surgery. J Pain Symptom Manage 2004;28:35– 46
4. Bisgaart T. Analgesic treatment after laparoscopic cholecystec- tomy. Anesthesiology 2006;104:835– 47
5. Song D, White PF. Remifentanil as an adjuvant during Desflu- rane anesthesia facilitates early recovery after ambulatory surgery. J Clin Anesth 1999;11:364 –7
6. Song D, Whitten CW, White PF. Remifentanil infusion facilitates early recovery for obese outpatients undergoing laparoscopic cholecystectomy. Anesth Analg 2000;90:1111–3
7. Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast track outpatient gynecologic laparoscopic surgery. Anesth Analg 2001;92:352–7
8. White PF, Wang B, Tang J, Wender RH, Naruse R, Sloninsky A. The effect of intraoperative use of esmolol and nicardipine on recovery after ambulatory surgery. Anesth Analg 2003; 97:1633– 8
9. Chia YY, Chan MH, Ko NH, Liu K. Role of beta-blockade in anaesthesia and postoperative pain management after hysterec- tomy. Br J Anaesth 2004;93:799–805
10. White P, Song D. New criteria for fast-tracking after outpatient anesthesia: a comparison with the Modified Aldrete's scoring system. Anesth Analg 1999;88:1069–72
11. Wood AJ, Feely J. Pharmacokinetic drug interactions with propanolol. Clin Pharmacokinet 1983;8:253– 62
12. Avram MJ, Krejcie TC, Henthorn TK, Niemann CU. Beta- adrenergic blockade affects initial drug distribution due to decreased cardiac output and altered blood flow distribution. JPET 2004;311:617–24
13. Pranevicus P. Non-Opioid anesthesia with esmolol avoids opioid-induced hyperalgesia and reduces fentanyl requirement after laparoscopy (Letter to Editor). Anesth Analg. 2009 Mar;108(3):1048

Critical Appraisal Essay

By: **Nicole McFadden**, MD, PGY-1, Queen's Anesthesiology

Publication title: "***The perioperative dialogue reduces postoperative stress in children undergoing day surgery as confirmed by salivary cortisol***."

Authors: ***Wennström B, Törnhage C-J, Nasic S, Hedelin H, Bergh, I.***

Pediatric Anesthesia 2011; 21:1058-1065.

Background:

It is well recognized that undergoing surgery creates anxiety for many patients and this may be particularly true for pediatric patients who lack the capacity to fully comprehend the process. In addition to being unpleasant and frightening to a child, perioperative anxiety has also been shown to negatively affect postoperative outcomes such as pain, emergence delirium, and behavioural problems (1). With rates of preoperative anxiety among children as high as 60% and evidence documenting these negative outcomes, much research has been conducted to develop and evaluate methods of reducing anxiety and improving outcomes (2-4). While such research is often considered 'soft', one cannot overlook the impact such factors have on other more 'hard' outcomes such as length of hospital stay and functional recovery (5). Having undergone surgery as a child myself and recalling my own experience, this is an area of personal interest and an area I see opportunity to make a difference in my future practice.

Introduction:

This study was conducted in Sweden by authors from the Departments of Anesthesia, Pediatrics, and Urology at Skaraborg Hospital in Skövde, as well as the Centre for Research and Development at Skaraborg Hospital, the School of Life Sciences at Skövde University, and the Institute of Health and Care Sciences at the University of Gothenburg. The background to the study hypothesizes that children feel more confident and less anxious when they are informed about what is going to happen prior to the event. The authors recognize that anesthesiologists often have no contact with children prior to the day of surgery and limited contact on the day of surgery to explain the events. The study, therefore, seeks to answer the question of whether a specific clinical, scientifically-based model of information sharing and continuity of care known as the Perioperative Dialogue (PD) reduces anxiety and stress in children undergoing day surgery. While this is in many ways a qualitative outcome, the authors have performed a randomized controlled trial using salivary cortisol as an objective quantitative measure of perioperative stress. The title of the paper adequately identifies both the research question and study population while indicating the final results in statement form; i.e. the perioperative dialogue (the intervention) reduces postoperative stress (the outcome) in children undergoing day surgery (the population) as confirmed by salivary cortisol (the outcome measure).

Methodology:

The population studied in this prospective randomized controlled trial included 93 children scheduled for elective day surgery under general anesthesia at Skaraborg Hospital in Sweden between 2007-2010. Inclusion criteria required the children be between age five and eleven years and identified as ASA class I-II. Limitations of this sample include the fact that it was drawn from a single centre which may introduce certain population-specific confounders, that there were more males than females (79 versus 14), and that it is overall a small sample size. Of the 93 children assessed for eligibility, none were excluded or declined to participate. The children were randomized to three groups using a random selection table although the authors do note that 'occasional consideration had to be taken to staff scheduling'. This is not explained further and it is unclear how this may affect the reliability of the results but should be taken into consideration. The three study groups included a control group receiving standard perioperative care, a group receiving preoperative information in advance in addition to standard perioperative care, and a group receiving the perioperative dialogue which included the same preoperative information as in group two. All three groups were reported to receive the same preoperative information, the differences being when they received it, by whom, and with or without the perioperative dialogue. The experiment groups are explained in the section on the study groups and the basic points of the preoperative information and perioperative dialogue are also outlined in tables. Due to the nature of the interventions in this study, neither the participants nor the investigators were blinded. This is another source of potential bias in the study as the main author was responsible for both allocating patients to groups and providing the PD to children in the experimental group.

It could potentially have been possible to blind the individuals assessing postoperative pain and interpreting the salivary cortisol results to reduce this source of bias.
Thirty-one patients were allocated to each of the three groups. Table 2 reveals no statistically significant differences between groups on the possible covariates of age, weight, sex, duration of anesthesia, duration of surgery, or previous experience of hospital care. There were, however, statistically significant differences between the number of children undergoing different types of surgery between the groups which may affect the results as certain surgeries may be more anxiety-provoking. These differences and how they were analyzed for statistical significance are clearly outlined in Table 2 and though many possible covariates are identified the reader must always be aware that there may be more.

Aside from the experimental interventions, common treatment methods between all groups are described including premedication, induction and maintenance drugs. Some differences in treatment exist for different surgeries, for example regional anesthesia was used for certain procedures, and given that types of surgery varied between groups, this could also affect results as all participants were not treated equally.

Salivary cortisol concentration was used as the primary outcome marker for anxiety in this study, however three additional measures were used as secondary outcomes to further quantify the results; the Wong-Baker FACES Pain Rating Scale, postoperative morphine use, and duration of stay in PACU. Salivary cortisol has been validated as an easy-to-collect, noninvasive biological marker of stress, however, strategies for collection must be standardized and possible confounders including diurnal variations, age, weight, and recent meals must be controlled for (6, 7). The sampling procedure in this study is explained in terms of timing of samples, sampling method, and specific equipment used. The W-B scale is also explained. It is noted, however, that for both salivary cortisol sampling as well as the W-B scale, assessments were only drawn when the child expressed willingness to cooperate. While this may be an important ethical point, it does create the possibility that results are affected by not having standardized testing times and instead relying on subjective willingness.

As with all studies involving children, the issue of consent arises. In this case, the control group was stated to receive the standard preoperative care of Swedish public hospitals and obviously the anticipated outcome was that the intervention groups would have a more positive outcome. Therefore no participants were receiving less than the current standard of care though the risk that the intervention groups may be adversely affected still existed. Nonetheless, the study was approved by the Regional Ethics Board of Gothenburg University, informed consent was obtained from parents, and, where age-appropriate, written or dialogued consent from the children as well.

Results:

Thirty-one patients were allocated to each of the three study groups. There was only one patient lost to follow-up, this patient from the control group. However 51 of the total 369 salivary samples collected were excluded based on insufficient volume for testing, often because the child was too sick to cooperate due to postoperative nausea and vomiting or pain. The excluded samples are outlined in the allocation flow chart in Figure 1. The number of remaining samples were still similar between groups; 105, 100, and 113 in the control, information, and PD groups respectively, however so many excluded samples, especially from sick patients, may skew the results. All patients were analyzed by intent to treat with no cross-over.

The salivary cortisol measurements at each of the four sampling points as well as the mean sampling times and number of valid measurements for each group are presented in Table 3. From this table we can see that there were no statistically significant differences in salivary cortisol levels between groups at the first three sampling times; the outpatient surgery department, preoperatively on the day of surgery, and just prior to induction. This is important to note as the results section only describes the statistically significant difference in the postoperative measurements, with the PD group having lower cortisol concentrations. This table also shows that differences in sampling times were not statistically significant. These results are depicted graphically in Figure 2, again revealing no real difference between groups for the first three measurements, with the PD group being significantly lower at the postoperative measuring point. Cortisol concentrations were reported to decrease in 96% of children in the PD group compared to 72% in the control group and 63% in the preoperative information group, results that are not clear from Figure 2 which only reflects mean measurements.

The authors acknowledge that the distribution of types of surgery was not equal between groups and note that the median cortisol levels differed between types of surgery. This was addressed by a stratified analysis that reduced discrepancy between groups with respect to type of surgery, concluding that the decrease in cortisol concentrations in the PD group was still statistically significant, though the details of this analysis are not provided. It is also noted that fewer children in the PD group received regional blocks though this was not found to be statistically significant.
Secondary outcome data are presented in Table 4, which reveals a statistically significant reduction in morphine

dose in the PD group. No statistically significant differences were found in number of patients receiving morphine, W-B pain scores, or duration of PACU stay. W-B scores were, however, higher in children receiving morphine and a positive correlation was found between morphine consumption and salivary cortisol concentrations though this is not evident from the separate data tables.

The data are presented in easy to interpret table format including means and standard deviations or confidence intervals as well as P-values. The raw data is not presented, however, and it is not always clear how some of the statistics and percentages in the results section were calculated, such as the correlation between morphine consumption and salivary cortisol concentration. Figure 2 is also somewhat deceiving as it represents mean cortisol values whereas the results section describes a 72% and 63% reduction in cortisol concentration from baseline to postoperative recovery in the control and information groups, respectively.

Discussion:

The main conclusion of this study was that children who received the perioperative dialogue had lower salivary cortisol concentrations postoperatively, extrapolated as a reduction in postoperative stress and anxiety. Interestingly, there was no difference in pain scores between the groups even though those in the PD group received less morphine. The authors explain this finding by hypothesizing that children in the PD group were better able to cope with the situation and therefore required less analgesia. They cite other studies with similar findings such as reduced morphine requirements despite no differences in pain scores when music was used postoperatively (8).

While the results of this study initially appear convincing based on the data provided, many possible sources of error and bias have been identified including small sample size, no blinding, differences in types of surgery between groups, and variations in sampling times based on patients' willingness. The authors have attempted to control for some of these limitations, however the results need to be interpreted within the context of possible error.

Even if one were to accept the results as valid despite these limitations, there may be more challenges to applying these results in practice. One of the main questions that arises throughout this report is around the specifics of the perioperative dialogue. One can gather the general gist of the PD as a process for maintaining open communication between patient and practitioner as well as continuity of care with that same practitioner throughout the child's perioperative experience. The basic steps of the PD at each point of the surgical timeline are outlined in Table 1, however these are very broad generalizations and it is unclear how much inter-provider variability might exist in implementing these guidelines. Further, these steps seem to be relatively common sense practices that any compassionate care provider would attempt to follow, especially when dealing with children, within the time constraints of the healthcare system.

Perhaps then this reveals the bigger issues of incorporating the perioperative dialogue into practice, those of cost-effectiveness and time restraints. It seems reasonable to assume that most anesthesiologists and nurses recognize that children may be anxious about surgery and will try to answer their questions, provide information, and build a trusting relationship with the child. It is also undeniable, however, that there is often limited time in which to do this and currently the surgical department is not set up to provide continuity of care between the various areas. As identified in this report, employing Child Life Specialists or restructuring surgical departments so that the same nurses can follow patients throughout their stay are possible ways of ensuring better continuity of care and providing the perioperative dialogue. Further studies would be needed to analyze the cost-effectiveness of these measures.

An alternative solution identified in this report involves using salivary cortisol measurements as a way to identify patients with high stress responses and directing more time and effort to managing these patients. While this may help patients with very high levels of anxiety and perhaps be more cost-effective in terms of staffing, it would require screening everyone with salivary cortisol measurements and would not help make the surgical experience better for all patients.

In conclusion, many possible sources of bias and error have been identified in this study that may limit its reproducibility and validity. The findings are still interesting, however, and the underlying question of how to reduce perioperative anxiety bears significance for all anesthesiologists. Further research in this area and openness to change in the structure of the perioperative environment have the potential to improve the surgical experience for all patients.

References

1. Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. Pediatrics 2006;118:651–8.
2. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adol Med 1996;150:1238–45.
3. McCann M, Kain Z. Management of preoperative anxiety in children: an update. Anesth Analg

2001;93:98–105.
4. Wright KD, Stewart SH, Finley GA, Buffett-Jerrott SE. Prevention and intervention strategies to alleviate preoperative anxiety in children: a critical review. Behav Modif. 2007 Jan;31(1):52-79.
5. Rosenberger PH, Jokl P, Ickovics J. Psychosocial Factors and Surgical Outcomes: An Evidence-Based Literature Review. J Am Acad Orthop Surg. 2006 Jul;14(7):397-405.
6. Hanrahan K, McCarthy AM, Kleiber C, Lutgendorf S, Tsalikian E. Strategies for salivary cortisol collection and analysis in research with children. Appl Nurs Res. 2006 May;19(2):95-101.
7. Weibel L. Methodological guidelines for the use of salivary cortisol as biological marker of stress. Presse Med. 2003 May 24;32(18):845-51.
8. Nilsson S, Kokinsky E, Nilsson U, et al. School-aged children's experiences of postoperative music medicine on pain, distress, and anxiety. Pediatr Anesth 2009; 19: 1184-1190.

Critical Appraisal Essay

By: **Vanessa Sweet**, MD, PGY1, Queen's Anesthesiology

Publication title: ***"Incidence and impact of distracting events during induction of general anaesthesia for urgent surgical cases"***

Authors: ***G.L. Savoldelli, J. Thieblemont, F. Clergue, J. Waeber, A. Forster and P. Garnerin***

Eur J Anaesth 2010 Aug; 27(8): 683-9

INTRODUCTION

Patient safety and systematic human error reduction are becoming increasing popular topics in medicine, and particularly within the field of anaesthesiology.[1,2] Much of the research in this area has stemmed from similar work in the aviation industry where concepts such as the 'sterile cockpit' have been developed.[3,4] While research into human factors in errors is certainly important, even with a well-defined systematic approach to the delivery of an anaesthetic, the potential for error is never completely eliminated. The operating room is a very busy environment with many people doing various tasks, some of which may interfere with one another and ultimately result in outcomes that are harmful to patients.

At the time this study was conducted, some previous work had been done which investigated issues relating to workplace distractions in healthcare, particularly within the emergency department, and during various surgical procedures. These studies found high incidences of distractions, and have begun to draw on the 'sterile cockpit' of aviation, and suggest a movement toward a similar approach in medicine during any critical periods of patient care.[5-7]

Within anaesthesiology specifically, some work had been done looking at the effect of ergonomics and human factors on anaesthesiologists and their level of vigilance. This particular research group had conducted a small pilot study and published the abstract,[8] however, there were no other studies at the time that had looked at the incidence and impact of distracting events during induction.

This study seeks to quantify the incidence of distracting events during induction of general anaesthesia for urgent surgical cases, and to characterize the impact of such events on the patient as well as the anaesthetic team. Specifically, the authors categorize distracting events according to their origin, source, nature, frequency and duration, as well as the consequence of such events on the task each anesthetic team member is performing and on patient outcome.

In this study, there is no formal hypothesis being tested. In characterizing the incidence and impact of distracting events as described above, the authors are taking on the important task of beginning to understand the nature and consequence of distracting events during induction in order that further work may be done to minimize their negative consequences. The two key critical phases in anaesthesia are induction and emergence, and therefore it would be useful to look at these phases first, in much the same way that the 'sterile cockpit' addresses take-off and landing.

The observational data from this study has the ability to inform future studies that look more in depth at specific identified distractors as well as allow for the development and implementation of strategies to minimize the incidence and impact of such distractors, hence, optimizing patient outcomes.

METHODOLOGY

This study is a prospective, observational and descriptive study. As such, there are no experimental groups. Because it was not an experimental study and therefore there were no interventions or exposures, there was no true blinding to be done. It is certainly worthwhile noting, however, that all anaesthetic team members provided written informed consent to be observed by the investigators, and as such were fully aware of the goals of the current study.

The population was a total of 37 anaesthetic teams (either one or two physicians and a nurse or two physicians) formed from a group of 29 anaesthetic team

members (11 senior residents, 5 consultants and 13 nurse anaesthestists) and 37 patients to whom teams administered a general anaesthetic (a total of 38 inductions were observed, however, one was excluded due to technical difficulties with the video recording).

The investigators studied only the induction phase of the general anaesthetic, defined as the time from patient arrival in the induction room to the fixation of the endotracheal tube. The induction phase was chosen as it is a critical time during the delivery of an anaesthetic and requires a great deal of "trust and calm, as well as constant vigilance by the anaesthetic team".

Interestingly, these inductions were all for urgent surgeries, however only surgeries that occurred during the working day were selected, and on the basis of convenience depending on investigators' availability. The authors offered no explanation as to why urgent surgeries were selected over routine/elective cases, as the latter would certainly be more numerous.

While the study was descriptive only, and hence doesn't require a specific sample size as there is no need for statistical power to detect an effect, the authors did not provide support for their sample size. A subsequent study looking at critical phase distractions in anaesthesia cites a similar sample size[2] whereas studies quantifying distractions during surgical procedures cite a wider range of sample sizes.[5,9]

Urgent procedures do not make up the majority of the surgical procedures that occur in most hospitals, so the sample is therefore not similar to my own practice. Furthermore, the inductions recorded in the study took place in a dedicated anesthetic induction room, which are not commonplace in North America.

The study received approval from the Chairman of the Ethics Committee and the Medical Director of the Geneva University Hospitals. Certainly, for ethical reasons, the issue being investigated would not necessarily lend itself well to an experimental study design. The work, however, is important for laying the framework for future studies that seek to optimize patient safety.

The study protocol does allow for the determination of incidence and impact of distracting events, within the limits of the authors' scoring system. Of concern, however, is that the study design does not enable the investigators to look at any patient outcomes that occur beyond the end of the induction period. It presupposes that the effects of any distractions during the induction period will only manifest during the induction period (and not during maintenance, emergence, post-operative periods). As such, the study protocol does not necessarily allow the investigators accurately capture the impact of distracting events during induction on patient outcomes.

The authors presented the definitions used for their original scoring system, which was designed to categorize and analyze distracting events. Some of the definitions within the scoring system, however, were either not particularly detailed or leave open significant room for subjectivity on the part of the individuals scoring the videos (hence decreasing reproducibility). Two investigators jointly reviewed videos, however, inter-rater reliability of the scoring system was not reported in the paper, nor did they specify how disagreements on scoring were resolved.
While this scoring system/set of definitions has not been formally validated prior to use in this study, the authors based their choice of categories on previous studies looking at healthcare workplace interruptions, two of which dealt specifically with interruptions within the operating room.

The clinical relevance of the protocol is quite good with respect to describing the origin and source of distracting events. I would suggest that the clinical relevance of the protocol with respect to impact of distracting events on the anaesthetic team and the patient is somewhat weaker. Impact of distracting events on the anesthetic team may not be outwardly observable (i.e., a video recording may not capture inattentiveness). Furthermore, limiting the period of observation to the induction phase may prevent the investigators from capturing patient outcomes that do not present until later in the maintenance or emergence phases, yet were attributable to distractions that occurred during induction.

The authors used descriptive statistics to analyze both the frequency and duration of distracting events, as well as their consequences on the anesthetic team and on the patient. Given the descriptive and observational nature of the study, this is an appropriate analysis of the data gathered. This does, however, prevent the authors from being able to comment as to whether the effects of origin and source on the frequency, duration, or consequences of such distracting events are statistically significant or not.

RESULTS

The authors reported the duration and frequency of all distracting events during inductions, as well as on the basis of the origin of the distracting event (internal/external) as well as their sources (team members/equipment/alarms/workspace/external staff/ patient/other). At least one distracting event was present for an average of 39.5% of the total duration of the anesthetic induction.

While distracting events internal to the anesthetic team

were more frequent and of greater duration than those external to the team. Overall, the most frequent source was the "intrusion" of a non-member of the anesthetic team, with inappropriate actions of anesthetic team members (including non-patient related conversations) a close second.

Also detailed were the frequency and duration of consequences on anaesthetic team members (multitasking/task switching/brief break in attention/suboptimally performed task/suspending task) according to the origin and source of the distracting events. They further presented data illustrating the consequences of distracting events according to the role of the anaesthetic team member (airway manager vs. drugs manager). Interestingly, over 80% of all distracting events had an observable impact on at least one of the anaesthetic team members.

With respect to the impact of the distractions on the patient, the majority had no observable impact during the duration of the induction phase. A negative impact on patient management was observed following 21.5% of the distracting events, and positive impact on patient management was observed in 7.2% of cases. A larger percentage of the distracting events originating internal to the anaesthetic team had an impact on patient care than did the distracting events originating external to the anaesthetic team. This included both negative impacts upon patient care (e.g., inadequate preoxygenation, lack of light in the laryngoscope, etc.) as well as positive impacts upon patient care (e.g., patient repositioning, airway examination, etc.)

Importantly, however, statistical analysis was descriptive only. Therefore, this study is unable to provide evidence as to whether the effects of origin and source on the frequency, duration, or impact of distracting events are statistically significant.

DISCUSSION

Because this is an observational and descriptive study, it is limited with respect to the conclusions that can be drawn. That being said, it does provide some very interesting and thought-provoking data.

The authors demonstrate that distracting events are both frequent and diverse during the inductions of general anesthesia that they studied. Distracting events were most frequently due to intrusion of external staff, carelessness/inappropriate action of the team members, and inappropriate behaviour from the patient (though the authors did not provide an example of what might constitute "inappropriate patient behaviour" during induction). Furthermore, the most distracting events from the perspective of consequence on team function were phones/beepers, team members, and equipment. They also found that interruptions from external staff had minimal impact.

The results of this study do address the stated purpose of the investigation. While the descriptive statistics do lend support the conclusions drawn by the researchers, as mentioned previously, there was no formal statistical hypothesis testing. Therefore, while the authors suggest their findings represent true differences, their analysis did not allow them to determine whether any of their findings are truly statistically significant.

The authors compared their results to those of a previous study looking at interruptions and distractions within the operating room[5]. Both studies cited a high incidence of distracting events, however, the current study's finding that interventions from external staff had limited impact was in contradiction with the Healey *et al*. study. The authors explain this apparent contradiction as being a result of their operating room configuration, where patients are induced in an induction room that is also used as a storage room and transit route for patients leaving the operating room. This would certainly explain the high incidence of distractions from external sources, but it does not explain why these distractions were of minimal consequence.

There are several further limitations to the study, some of which are addressed by the authors. First, as mentioned previously, the scoring method has not previously been validated for studying distracting events in the delivery of a general anaesthetic. An integral part of the validation of any novel scoring system is determining the inter-rater reliability. This was not formally measured in this study. It would be particularly important to do this before use of this scoring system in subsequent studies, as there is a large degree of subjectivity involved in this type of scoring, particularly with respect to assessing the impact of the distracting events.

The authors also discuss the possibility of the impact of obervation on participants' behaviour. All members of the anaesthetic team provided informed consent to be observed, and there is no indication that the participants were unknown to the investigators. The authors acknowledge that a 'Hawthorne effect' is a possibility. To my mind, however, this lack of anonymity in combination with awareness that one is being observed as well as the knowledge of why one is being observed would significantly increase the likelihood participants would be especially vigilant. As such, the study may not have detected consequences that would have occurred had participants either been anonymous to the video raters or were blinded to the purpose of the observation.

Little attention was paid to the distinction between 'good' and 'bad' distracting events, or creating a rigorous definition of what constitutes a true

'distraction'. As well, the definition of beneficial patient outcome was somewhat weak. For example, within the definitions of this study, an alarm for decreasing $Sp0_2$ would be considered a distraction, but one could argue that this is not a distraction at all, but rather, an appropriate re-director of attention. The authors also stated that phone calls to "obtain additional patient information" were distracting events with positive patient outcomes. Such phone calls may indeed result in positive outcomes, but it would depend on the actual content of the phone call. For example, a phone call to alert the anaesthetic team of relevant medication allergies may be very different from a phone call to clarify the patient's date of birth.

The generalizability of the paper is limited due to the restriction of measured patient outcomes to the induction phase, a decision for which the authors offered no particular explanation. Many potentially serious complications could arise as a result of distractions during induction but not present until after the induction phase. Additionally, the inductions took place within dedicated anaesthetic induction rooms, which are not commonplace in many areas. The origins and sources of distractions may be very different depending on the physical configuration of the room in which an induction occurs as well as the other activities occurring simultaneously and therefore competing for the attention of those within the anaesthetic team.

As a first study, however, of distractions in anaesthesia, the authors have addressed some very significant issues. This is an important step in improving patient safety. It is essential that as a profession we identify sources of potential safety compromise in order to remediate them. The authors present a novel scoring system to be used for this purpose. While they only looked at one phase of an anaesthetic, it is an important starting point as induction is inherently high risk.

From here, there remain questions for future work such as determining the incidence and impact of distractions during all of the phases of anaesthesia, as well as for different surgical indications and with different operating room configurations. Once this work has been done, it will have laid the groundwork for developing strategies to minimize the incidence of distracting events as well as minimize their impact by helping anaesthesia and operating room staff to develop effective strategies for coping with distractions and effective multi-tasking. Some of this work has already begun since this paper's publication.[2]

APPLICABILITY

In reviewing this study, I have gained a greater awareness of the various sources of distractions as well as their potential impact on my patients and on me. Although it is a small observational study, it raises key issues that need to be addressed in order to continue to foster a culture of patient safety within anaesthesia. While these issues will need to be studied formally, it is worthwhile incorporating the current knowledge into my clinical practice. Vigilance on my behalf with respect to minimizing potential distractions during the delivery of an anaesthetic and garnering the cooperation of other operating room staff in this matter will be an important step toward furthering patient safety. As more rigorous studies are completely, I anticipate we will learn more of the specifics of distractions in the operating room and also have more tools at our disposal to prevent these distractions and mitigate their effects on our patients.

REFERENCES

1. Phipps D, Meakin GH, Beatty PCW, *et al*. Human factors in anaesthetic practice: insights from a task analysis. *Brit J Anaesth* 2008; **100**: 333-43.
2. Broom, MA, Capek, AL, Carachi P, *et al*. Critical phase distractions in anaesthesia and the sterile cockpit concept. *Anaesthesia* 2011; **66**: 175-9.
3. Sumwalt, RL. *Aviation Safety Reporting System Directline Issue 4 1993. The Sterile Cockpit.* http://asrs.arc.nasa.gov/publications/directline/dl4_sterile.htm (accessed 2012/2/5)
4. Dismukes K, Young K, Sumwalt R. Cockpit interruptions and distractions: effective management requires a careful balancing act. *ASRS Directline* 1998; **10**:4-9.
5. Healey AN, Sevdalis N, Vincent CA. Measuring intra-operative interference from distraction and interruption observed in the operating theatre. *Ergonomics* 2006; **49**:589-604.
6. Brixey JJ, Robinson DJ, Johnson CW, *et al.* Towards a hybrid method to categorize interruptions and activities in healthcare. *Int J Med Inform* 2007; **76**:812-20.
7. Hohenhaus SM, Powell SM. Distractions and interruptions: development of a healthcare sterile cockpit. *Newborn Infant Nurs Rev* 2008; **8**:108-10.
8. Thieblemont J, Salvodelli GL, Garnerin P, *et al.* High incidencec of distracting events and diverted time during induction of general anesthesia for urgent surgical cases. *Eur J Anaesthesiol* 2007; **24**: 187-88.
9. Persoon MC, Broos HJHP, Witjes JA, *et al.* The effects of distractions in the operating room during endourological procedures. *Surg Endosc* 2011; **25**: 437-43.

Critical Appraisal Essay

By: **Maggie Thomson**, MD, PGY1, Queen's Anesthesiology

Publication title: "***Caudal Normal Saline Injections for the Treatment of Post-Dural Puncture Headache***"

Authors: ***Susanne Abdulla, Walied Abdulla, Regina Eckhardt***

Pain Physician 2011; 14:2781-279.

Lumbar puncture (LP) and spinal anesthesia are two procedures that require access to cerebral spinal fluid (CSF) and consequently penetration of the dura (Miller et al 2010). LP and spinal anesthesia procedures are not without risk or complication. A common problem following penetration of the dura is development of headache. Such headaches are termed postdural puncture headaches (PDPH) (Miller et al 2010). The mechanism for these headaches is unknown, however several theories have been postulated as to how they develop. While modern LP and spinal anesthesia techniques have decreased PDPH incidence, it remains an important complication of these procedures. PDPH is both an intense and debilitating event and current treatment is not always successful (Turnbull and Shepherd, 2003). Treatment is therefore an important topic of research, and the paper describes a less-studied approach to treatment.

Carried out by Drs. Susanne Abdulla, Walied Adbulla, and Regina Eckhardt of Germany, the study was published in Pain Physician in 2011. All authors are affiliated with Martin Luther University and are members of the Department of Anesthesia and Intensive Care Medicine at the teaching hospital associated with the University, Klinikum Bernberg. There was no external funding for the project.

Introduction:

The International Headache Society has classified PDPH in the group of headaches caused by low CSF pressure (Headache Classification Committee, 1988). Requirements for this classification include:

a. Bilateral headache that develops less than 7 days after spinal puncture
b. Occurs or worsens less than 15 minutes after assuming upright position and disappears or improves less than 30 minutes after resuming recumbent position
c. Disappears within 14 days after spinal puncture.

The authors are evaluating a less-studied treatment for PDPH, specifically the effectiveness of caudal saline injections as a therapeutic approach for PDPH.

The pathophysiology of PDPH has yet to be determined, and indeed treatment of the condition is not optimal. Several theories as to how and why PDPH develops have been postulated. One theory discusses the possibility that when approximately 10% of cerebrospinal fluid (CSF) is lost following dural puncture, orthostatic headache results (Carson and Serpell, 1996). However, certain patients lose more then 10% and do not develop PDPH. There are therefore likely individual characteristics that have roles in whether patients develop PDPH (Liu et al 2008).

Another theory for PDPH development is that the downward pull on pain-sensitive structures when the patient assumes an upright position generates the pain (Amorim and Valenca, 2008; Frank, 2008). When CSF volume is low, gravity causes CSF to move into the spinal dural sac when the patient is in an upright position – thus, the brain loses buoyancy. The sagging brain creates tension on the meninges, vessels and nerves, resulting in PDPH. This has been demonstrated radiologically for PDPH (Rozen et al 2008).

It has also been postulated that intracranial blood volume increases to compensate for lost CSF, and this process leads to PDPH (Amorim and Valenca, 2008). Venous and arterial dilation in a setting of CSF hypovolmemmia may be mediated by adenosine receptors, which may provide a basis for the therapeutic use of caffeine (Lin and Geriderman, 2002).

An additional theory involves hypersensitivity to substance P. A three-fold increase in PDPH has been demonstrated when CSF levels of substance P are low (Clark, 1996). A final mechanism may simply be related to thickness of the dura. Thicker areas are thought to be less likely to leak CSF, therefore PDPH incidence can depend on location of dural puncture (Turnbull and Shephard, 2003).

Treatment of the condition has been attempted with both non-interventional and interventional techniques.

Hydration with oral (PO) or intravenous (IV) fluids are often given to patients to reduce incidence and severity of PDPH. It is thought that hydration may increase rate of CSF production and reduce CSF hypotension (Sudlow and Warlow, 2006). A study by Dietrick and Brandt in 1988 – one of the few studies assessing usefulness of hydration for PDPH treatment – found no difference in occurrence of PDPH with increased hydration following LP. This intervention is common and conservative, however there is little supporting evidence for its use as a treatment modality in PDPH (Sandesc et al 2005).

Bed rest has been thought to provide symptomatic relief but is not curative of headache. Little clinical evidence supports it as a means of treatment (Jones, 1974).

Posture is also thought to be important. Often patients will have already identified the supine position as offering relief before the intervention of an anesthetist. The prone position has also been advocated as it increases intra-abdominal pressure which is transmitted to the epidural space and may alleviate headache, however a study in adults did not demonstrate significant headache relief in this position (Handler et al 1982).

Analgesia utilizing paracetamol, NSAIDs and other supportive measures such as antiemetics that are useful in relieving nausea associated with PDPH are often prescribed. These measures are purely supportive and may control symptoms, thus reducing need for aggressive therapy. Few studies have assessed their usefulness in PDPH. They are generally not thought to provide complete relief (Flaaten, 1987).

Caffeine has been studied as a treatment modality for PDPH (Sechzer and Abel, 1978, Camann et al 1990). Caffeine, a central nervous system stimulant, is thought to cause intracranial arterioles to constrict, alleviating headache (assuming headache is caused by CSF loss and consequent intracranial blood vessel dilatation to compensate for volume loss) (Sechzer, 1979).

Epidural blood patch has been demonstrated to be one of the most effective, though most aggressive forms of treatment for PDPH. We choose to treat persistent PDPH aggressively due to severe and even fatal complications after PDPH. These more important complications include subdural haematomas, intracerebral haemorrhages (Van de Veltde et al 1999) and cranial nerve palsies (Carrero et al 1998). Epidural blood patch has a success rate of 70-98%, though does carry a small risk of serious complications including radicular pain, cranial nerve palsies, irritation, elevated intracranial pressure, paraparesis, cauda equina syndrome, infection and subdural hematoma (Frank, 2008).

Epidural injection of saline has been studied as a treatment for PDPH. Similar to the EBP, injection of saline is thought to create increased mass effect, restoring normal CSF dynamics. In 2011, Katayama et al demonstrated that continuous epidural saline infusion treatment for dural puncture was a relatively safe and effective treatment for PDPH (Katayama et al 2011). Similarly, Crawford reported infusion of Hartmann's solution over a twenty-four hour period as an effective measure for treatment in 1972 (Crawford, 1972).

Caudal injection of normal saline in place of epidural infusion has also been described, however has been largely out of practice for some time. Little work has been done on the treatment modality since the 1950s when the technique was first described (Murry et al 1956). The hypothesis tested in the present study is that caudal saline injection will improve, though perhaps not fully relieve, PDPH-associated pain. The study aims to define another treatment modality to effectively treat PDPH, and, if successful, would add to our list of possible PDPH treatments, and perhaps find a better, more effective, treatment modality.

Methodology:

The study is prospective and observational, taking place over a fifteen year time period. There was no randomization within the trial. The trial was not blinded for, according to the authors, ethical reasons. The population studied is human. No controls and no comparison group were utilized.

Only patients at the Klinijum Bernburg Hospital were involved in the study. Specifically, patients undergoing abdominal and bone surgery or receiving analgesia for a therapeutic intervention and who had spinal or epidural anesthesia resulting in severe PDPH were eligible. Severe PDPH was defined by clinical history of dural puncture associated with severe postural symptoms in patients who were disabled in their daily activities and needed to stay in bed for most of the day. Caudal normal saline injection was offered only to patients with an unbearable headache, refractory to any conservative treatment and aggravated by changing from supine to upright position as well as coughing and straining, with headache onset not more than three days after dural puncture. Patients with defective hemostasis, suspected infection at site of injection, and with a body temperature over thirty-eight degrees Celsius, or a history of headache and/or difficult anatomic conditions were not eligible. Finally, patients under 18 were included.

The study had a sample size of fifty-six patients. This group comprised all individuals who developed severe PDPH following dural puncture at the hospital, though excluded two who had a history of headache, and two with difficult anatomic conditions (ie. severe ossifications and obesity).

The cases of PDPH in the study varied based on procedure leading to the complication. For instance, twenty of the fifty-six cases were following spinal anesthesia. These cases varied based on gauge of needle utilized. Four cases involved used of a 22-gauge needle, four cases involved a 26-gauge needle, and eight a 27-gauge needle. Thirty-six cases occurred after use of spinal catheters for spinal anesthesia. Four cases followed inadvertent dural punctures during epidural catheter placement. The researchers did not have information as to how the procedure became complicated for each of their study participants.

There were no discernable ethical concerns noted in this study.

The protocol described is fairly detailed, lacking only an explanation as to how caudal normal saline was specifically injected. Some further information would have been helpful for anyone hoping to reproduce or continue their work. Criteria for inclusion and exclusion to the study is well described, and reproducible.

Primary endpoint was improvement of headache. The authors considered partial resolution of headache as successful treatment. The study is well designed to test the hypothesis and the protocol is clinically relevant. Given the fairly basic focus of the study, the statistics involved were simple and appropriate.

Results:

Given that data collected were fairly easy to interpret in text-form, the simple tables and graph provided prove sufficient. It would have been interesting to have a table or graph demonstrating number of interventions or volume of saline required based on initial cause of PDPH (ie. spinal anesthesia vs. inadvertent dural puncture during epidural). Number of interventions or volume required based on patient characteristics (ie. body habitus, age etc) would also have been interesting to include.

Findings demonstrated that pain intensity decreased on average 70% with 80mL saline injection, but that this volume did not completely resolve headache. Injection of 100mL of normal saline resulted in an average of 85% reduction in pain, though again did not completely resolve headache. Only one patient required a single injection, with eighteen requiring four, and four patients requiring an EBP when normal saline injection failed.

Discussion:

The principal conclusion of the study is that caudal saline injection does have some success in decreasing discomfort associated with PDPH. The treatment generally necessitates several injections of normal saline before adequate control of the headache is achieved. The authors briefly discuss how normal saline improves headache and why its effect is initially transient. Specifically, they state that normal saline dissipates through tissue planes and is rapidly re-absorbed, dispersing quickly from the epidural space, and re-expanding the subarachnoid space resulting in return of headache. This is an accepted theory in the current literature (Morewood, 1993) and adequately explains the findings in the study, given that the majority of subjects required multiple interventions to relieve headache.

The fact that caudal normal saline injection only completely resolved headache after a single intervention in four patients was not a significant focus of the discussion. Most patients required two or more interventions to control their headache. Given that the other interventional treatment option for PDPH, EBP, is known to relieve headache in 90% of patients after one intervention (Abouleish et al 1975), it seems reasonable to assume that some patients might prefer EBP to repeated saline injections. It does not appear that patients in the present study were offered EBP until such time as normal saline injections had failed as treatment. A study comparing the two interventional treatments would be necessary for clinicians to determine which to use in clinical practice. Only one study currently exists on the topic, and is limited by its sample size. It demonstrated increased effectiveness of EBP in headache relief. EBP did, however, result in increased back pain relative to the caudal injection group (Kakinohana et al 2001).

The side effect profile of caudal normal saline injections is briefly discussed in the paper. From a clinical perspective, it is important to note the differences in secondary effects after normal saline injection relative to EBP. The most severe complication of caudal normal saline injection appears to be intraocular hemorrhage, caused by precipitous rise in intracranial pressure (Clark and Whitwell, 1961). The present study saw patients complain of an unpleasant sensation of warmth and tightness down their legs during the procedure, but reported no intraocular hemorrhages. Following EBP, rare subdural hematomas have been documented, as have radicular pain, cranial nerve palsies, meningeal irritation, elevated intracranial pressure, and cauda equina syndrome (Frank, 2008). EBP has been fairly extensively studied and consequently we may be more aware of its serious complications then those of the less-studied caudal normal saline injection technique. Nevertheless, clinicians and patients should be aware of each side effect profile before determining which, in any, intervention they will undergo.

Another point of discussion that is only briefly mentioned are the basic risks associated with multiple interventions, including pain at the site of injection, risk

of infection, bleeding etc. One would assume that the increased number of interventions required with caudal normal saline injection would increase these inherent risks. Patient discomfort during these repeated sessions is clearly a concern. Patients would have to be made aware before beginning normal saline injections that they may require several similar interventions. The present study did not note any serious concerns relating to multiple interventions.

At first glance, it was not clear as to why the authors were spending valuable discussion space examining their findings regarding patient characteristics as they relate to incidence of PDPH. Indeed, they were right to do so if they hope other researchers will continue and expand their work. The authors demonstrate that the study group utilized is representative of those generally affected by PDPH: more women, and more middle-aged and young adults were affected. Similar demographics were noted in other studies (Wu et al 2006). This study can thus act as an important point of comparison for future work on the topic.

A clear limitation of the study is that it was not randomized or double-blinded, nor did it have a control group. Sample size was also limited.

Applicability of the paper:

While I have learned a great deal from this paper, this paper will not alter my clinical practice at present. A randomized, prospective, controlled study is necessary, as is some knowledge as to long-term outcome following treatment. A study comparing EBP to caudal normal saline injection would also be of interest. This study has, despite its limitations, added to the little knowledge we had on the effectiveness of caudal normal saline injections, and can certainly act as a comparison for future studies.

Citations:

1. Miller RD, Eriksson LI, Fleisher LA, Wiener-Krinish JP, and Young WL. Miller's Anesthesia, 7th ed. Churchill Livingstone, Elsevier. 2010.
2. Turnbull DK, and Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. Br J Anaesth 2003;91:718-729.
3. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia. 1988; 8: 1–96.
4. Carson D, Serpell M. Choosing the best needle for diagnostic lumbar puncture. Neurology 1996; 47: 33–37.
5. Amorim JA, Valença MM. Postdural puncture headache is a risk factor for new postdural puncture headache. Cephalalgia. 2008;28:5-8.
6. Rozen T, Swidan S, Hamel R, Saper J. Trendelenburg position: A tool to screen for the presence of a low CSF pressure syndrome in daily headache patients. Headache. 2008;48:1366-1371
7. Lin W, Geiderman J. Medical myth: Fluids, bed rest, and caffeine are effective in preventing and treating patients with post-lumbar puncture headache. West J Med. 2002;176:69-70.
8. Clark JW. Substance P concentration and history of headache in relation to postlumbar puncture headache: Towards prevention. J Neurol Neurosurg Psychiatry. 1996;60:681-683
9. Jones RJ. The role of recumbancy in the prevention and treatment of postspinal headache. Anesth Analg 1974; 53: 788–95.
10. Handler CE, Smith FR, Perkin GD, Rose FC. Posture and lumbar puncture headache: a controlled trial in 50 patients.J R Soc Med 1982; 75: 404–7.
11. Flaatten H, Rodt S, Rosland J, Vamnes J. Postoperative headache in young patients after spinal anaesthesia. Anaesthesia 1987; 42: 202–5.
12. Sechzer PH. Post-spinal anesthesia headache treated with caffeine. Evaluation with demand method. Part 2. Curr Ther Res 1979; 26: 440–8.
13. Sechzer PH, Abel L. Post spinal headache treated with caffeine: evaluation with demand method. Curr Ther Res 1978; 24: 307–312.
14. Camann W, Murray R, Mushlin P, Lambert D. Effects of Oral Caffeine on Postdural Puncture Headache: A Double-Blind, Placebo-Controlled Trial. 1990. Anesth Analg 70 : 181-4.
15. Carrero EJ, Agusti M, Fabregas N, Valldeoriola F, Fernandez C. Unilteral trigeminal and facial nerve palsies associated with epidural analgesia in labour. 1998. Can J Anesth 45:898-897.
16. Van de Velde M, Corneillie M, Vanacker B, Stevens E, Verhaeghe J, Van Assche A, Vandermeersch E. 1999. Treatment for postdural puncture headache associated with late postpartum eclampsia. Acta Anaesthesiol Belg 50: 99-102.
17. Murry WE, Busch Jr RB, Denson JS. Successful treatment of postlumbar puncture headaches. Amer J Surg 1956; 91:394-495.
18. Crawford JS. The prevention of headache consequent upon dural puncture. Br J Anaesth 1972; 44:598-599.
19. Abouleish E, De la Vega S, Blendinger, Tiong-Oen T. Long term followwp of epidural blood patch. Anesth Analg 1975;54:459-63.
20. Clark CJ, Whitwell J. Intraocular haemorrahge after epidural injection. Br Med J 1961; I: 1612
21. Frank RL. Lumbar Puncture and Post-Dural Puncture Headaches: Implications: treatment of PDPH. J Emerg Med 2008;35:149-157.
22. Turnbull DK, Shepherd DB. Post-dural puncture headache: Pathogenesis, prevention and treatment. Br J Anaesth 2003;91:718-719.
23. Kakinohana M, Odo Y, Matsuda S, Taira Y, Sugahara K. Epidural injection with saline for treatment of postspinal headache Comparison with epidural blood

patch. J Anesth 2001;15:185-187.
24. Wu CL, Rowlingson AJ, Cohen SR, Michaels RK, Courpas GE, Joe EM, Liu SS. Gender and post-dural puncture headache. Anesthesiology 2006;105:613=618.
25. Van de Velde M, Schepers R, Berends N, Vandermeersch E, De Buck F. Ten years of experience with accidental dural puncture and post-dural puncture headache in a tertiary obstetric anesthesia department. J Obstet Anesth 2009; 17:329-335.
26. Katayama T, Hirai S, Hamanaka Y, Fukui T, Itou S, Hatooka S, Mitsudomi T. Effect of the continuous epidural saline infusion for patients with postdural puncture headache after pulmonary resection. Kyobu Geka 2001;64:1071-5.
27. Morewood GH. A rational approach to the cuase, prevention and treatment of postdural puncture headache. Can Med Assoc J 1993;149:1087-1094.

Queen's University Department of Anesthesiology Publication List – 2010-2012 [page 1/4]

(in alphabetical order of 1st author, Department members/cross-appointees highlighted in bold)

Arellano R, Nuromohamed A, Rumman A, **Milne B, Tanzola R**, Point of care transthoracic echocardiography as an alternative to transesophageal echocardiography to confirm internal jugular guidewire position, Canadian Journal of Anesthesia,59:103–104, 2012.

Alvarez A, Aristizabal SP, **Chaparro LE**, Ramirez LJ, Sarassa C. Congenital Indifference to pain. Rev Col Anest. 2010 38 (4): 528-535.

Cahill CM, Taylor A. 2011. A Piece of The Puzzle is Revealed for Delta Opioid Analgesia. *Pain* 152(6):1217.

Cahill CM and Stroman P. 2011. Mapping of neural activity produced by thermal pain in the healthy human spinal cord and brainstem: a Functional MRI Study. *Magnetic Resonance Imaging*. 29(3):342-352.

Cawthorn T, **Phelan R**, Davidson J, **Turner K**. Retrospective analysis of perioperative ketorolac and postoperative bleeding in reduction mammoplasty Can J Anesth, in press, 2012.

Chan P, Graf P, Enns M, Delva N, **Gilron** I, Lawson JS, Gosselin C, Patry S, Milev R, Jewell M, Martin B. The Canadian Survey of Standards of Electroconvulsive Therapy Practice: A Call for Accreditation. Can J Psychiatry 2012 (In Press).

Chaparro LE, Lezcano W, Alverez HD, Joaqui W. Analgesic effectiveness of Dipyrone (Metamizol) for postoperative pain after herniorrhaphy: a randomized, doublé blind, dose response study. Pain Pract 2012 Feb;12(2):142-7.

Chaparro LE, Gallo T, Gonzalez NJ, Rivera MF, Peng PW. Effectivenes of combined haloperidol and dexamethasone versus dexamethasone only for postoperative nausea and vomiting in high-risk day surgery patients: a randomized blinded trial. Eur J Anaesthesiol. 2010 Feb; 27(2): 192-5

Chaparro LE, Muñoz Y, Gallo CA, Alvarez HA, Restrepo SM, Perez N, Restrepo L. Pain and Sensory Symptoms Following Augmentation Mammaplasty: A Long-term follow up study with intraoperative Ketamine use. Rev Col Anest. 2010 38 (2): 204-212.

Chaparro LE, Grisales DS, Montes DM, Gutierrez JP, Valencia AM. The avoidance of neuromuscular paralysis in outpatients requiring endotracheal intubation temporarily increases the incidence of postoperative laryngeal symptoms: quasi-experimental study. Rev Col Anest. 2010 38 (3): 335-346.

Chaparro-Gómez LE, Calvache España JA, Arbeláez León LM. Coadjuvant analgesics for cancer pain: using the clinical queries PubMed tool. Cir Cir. 2010 Mar-Apr;78(2):185-90.

Chen C-H., Boag AH., Beiko DT., Siemens DR., **Froese A**., Isotalo PA. Composite paraganglioma-ganglioneuroma of the urinary bladder: a rare neoplasm causing hemodynamic crisis at tumour resection. Canadian Urological Association Journal. 2010 In press.

Chenier-Hogan N, Brown CA Dr, Hains SM, **Parlow** JL. Heart Rate Variability Response to Standing in men and Women Receiving d,l-Sotalol Following Coronary Artery Bypass Graft Surgery. Biol Res Nurs. 2011 Feb 28.

Darwish H, Mundell G, **Engen D**, Lillicrap D, Silva M, James P. Early intraoperative blood collection does not affect complete blood counts, von Willebrand factor or factor VIII levels in normal children. J Pediatr Hematol Oncol. 2011 Jan;33(1):47-9.

Delva NJ, Graf P, Patry S, Gosselin C, Milev R, **Gilron I**, Martin B, Lawson JS, Enns M, Jewell M, Chan P. Access to electroconvulsive therapy services in Canada. J ECT. 2011 Dec;27(4):300-9.

Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, Chappell A, Chartier K, Cleeland CS, Costello A, Cowan P, Dimitrova R, Ellenberg S, Farrar JT, French JA, **Gilron I**, Hertz S, Jadad AR, Jay GW, Kalliomäki J, Katz NP, Kerns RD, Manning DC, McDermott MP, McGrath PJ, Narayana A, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Reeve BB, Rhodes T, Sampaio C, Simpson DM, Stauffer JW, Stucki G, Tobias J, White RE, Witter J. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain 2010;149(2):177-93.

Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, **Gilron I**, Jensen MP, Katz NP, Raja SN, Rappaport BA, Rowbotham MC, Backonja M, Baron R, Bellamy N, Bhagwagar Z, Costello A, Cowan P, Fang WC, Hertz S, Jay GW, Junor R, Kerns RD, Kerwin R, Kopecky EA, Lissin D, Malamut R, Markman JD, McDermott MP, Munera C, Porter L, Rauschkolb C, Rice A, Sampaio C, Skljarevski V Sommerville K, Stacey BR, Steigerwald I, Tobias J, Trentacosti AM, Wasan AD, Wells GA, Williams J, Witter J, Ziegler D. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. PAIN (In Press) 2012.

Furlan A, **Chaparro LE** et al. A comparison between enriched and non-enriched enrolment randomized withdrawal trials of opioids for chronic non-cancer pain. Pain Research & Management. 2011 Sep-Oct;16(5):337-51..

Ghazni NF, **Cahill CM**, Pukall C, Stroman PW. 2010. Altered spinal cord and brainstem activation in response to peripheral sensitization to sensory stimuli in healthy humans: a spinal fMRI study. American Journal of Neuroradiology 31(4):661-7.

Queen's University Department of Anesthesiology Publication List – 2010-2012 [page 2/4]

(in alphabetical order of 1st author, Department members/cross-appointees highlighted in bold)

Gilron I, Attal N, Bouhassira D, Dworkin R. Neuropathic pain assessment. In: Handbook of Pain Assessment, 3rd Edition, DC Turk, R Melzack, Editors Guilford Press, 2010.

Gilron I, Jensen MP. Clinical trial methodology of pain treatment studies: Selection and measurement of self-report primary outcomes for efficacy. Regional Anesthesia and Pain Medicine 2011 (In Press).

Gilron I, Johnson A. Economics of chronic pain: How can science guide health policy? Can J Anesth. 2010;57(6):530-8.

Gilron I, Moore RA, Wiffen PJ, McQuay HJ. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database of Systematic Reviews: Protocols 2010 Issue 1 DOI: 10.1002/14651858.CD008307

Gilron I, Wajsbrot D, Therrien F, Lemay J. Pregabalin for Peripheral Neuropathic Pain: A Multicenter, Enriched Enrollment Randomized Withdrawal Placebo-controlled Trial. Clin J Pain 2011 27(3):185-93.

Gilron I, Wiffen PJ, Moore RA. Combination pharmacotherapy for the treatment of neuropathic pain in adults (Protocol). Cochrane Database of Systematic Reviews: Protocols 2011, Issue 1 DOI: 10.1002/14651858.CD008943.

Gilron I. Clinical Pharmacology of Antidepressants and Anticonvulsants for the Management of Pain. In: Pain 2010 - An Updated Review, Refresher Course Book. J Mogil Editor, IASP Press, 2010.

Gilron I. Drug discovery (In Press). In: Neuropathic Pain: Mechanisms And Management, DM Simpson, JC McArthur, RH Dworkin, Editors Oxford University Press, 2010.

Gilron I, Tu D, Holden R. Sensory and affective pain descriptors respond differentially to pharmacological interventions in neuropathic conditions. Clin J Pain 2012 (In Press).

Ginting JV, **Tripp DA**, Nickel JC, Fitzgerald MP, Mayer R. Spousal support decreases the negative impact of pain on mental quality of life in women with interstitial cystitis/painful bladder syndrome. BJU Int. 2010 Nov 2. doi:10.1111/j.1464-410X.2010.09846.x.

Gupta A, Mulder J, Gomes I, Rozenfeld R, Bushlin I, Ong E, Lim M, Maillet E, Junek M, **Cahill CM**, Harkany T and Devi LA. 2010. Opioid Receptor Heteromer Up-regulation by Chronic Drug Administration. Science Signaling 3(131):ra54.

Harrison MB, **Vandenkerkhof EG**, Hopman WM, Graham ID, Carley ME, Nelson AE & the Canadian Bandaging Trial Group. The Canadian Bandaging Trial: Evidence-informed leg ulcer care and the effectiveness of two compression technologies. BMC Nursing 2011m 10:20 http://www.biomedcentral.com/1472-6955/10/20.

Harrison MB, **VanDenKerkhof EG**, Hopman WM, Graham ID, Lorimer K, Carley M. Evidence-informed Leg Ulcer Care: A Cohort Study Comparing Outcomes of Individuals Choosing Nurse-led Clinic or Home Care. Ostomy Wound Management. 2011:57(8), 38-45.

Hayton SJ, Lovett-Baron M, **Dumont EC**, Olmstead MC. Target-specific encoding of response inhibition: Increased contribution of AMPA to NMDA receptors at excitatory synapses in the prefrontal cortex. J Neurosci, 2010, 30(34): 11493-500.

Herman KM, Hopman WM, **VanDenKerkhof EG**, Rosenberg MW. Physical activity, weight status and health-related quality of life in Canadian adults. Medicine & Science in Sports & Exercise. Published ahead of print, 01/10/2011, doi: 10.1249/MSS.0b013e31823a90ae.

Hopman WM, Harrison MB, Carley M, **VanDenKerkhof EG**. Additional Support for Simple Imputation of Missing SF-12 Survey Data. ISRN Nursing, vol. 2011, Article ID 752320, 4 pages, 2011. doi:10.5402/2011/752320.

Hsieh AY, **Tripp DA**, Ji LJ, Sullivan MJ. Comparisons of catastrophizing, pain attitudes, and cold-pressor pain experience between chinese and European Canadian young adults. J Pain. 2010 Nov;11(11):1187-94. Epub 2010 May 8.

Krawczyk M, Georges F, Sharma R, Mason X, Berthet A, Bézard E, **Dumont EC**. A double-dissociation in catecholaminergic modulation of synaptic transmission in the oval bed nucleus of the stria terminalis. J Neurophys, 2011, 105: 145-153. Epub 3 November 2010.

Krawczyk M, Sharma R, Mason X, DeBacker J, Jones A, **Dumont EC**. A switch in the neuromodulatory effect of dopamine in the oval BST associated with cocaine self-administration. 2011 (In press), The Journal of Neuroscience.

Leung L, **Cahill CM**. 2010. TNFa in neuropathic pain – a review. J Neuroinflammation 7:27 (epub).

Levac B., Parlow JL., Van Vlymen J., James P., Tuttle A., Shepherd L. Ringer's lactate is compatible with saline-adenine-glucose-mannitol preserved packed red blood cells for rapid transfusion. Can J Anaesth 2010 57(12):1071-7.

Queen's University Department of Anesthesiology Publication List – 2010-2012 [page 3/4]
(in alphabetical order of 1st author, Department members/cross-appointees highlighted in bold)

Mailis-Gagnon A, Nicholson K, **Chaparro LE**: Patient complaints against the staff of a tertiary pain clinic over a 9 year period: a cross sectional study. Pain Res Manage 2010. Jan-Feb; Feb; 15 (1): 17-23.

Mattioli TA, Sutak M, **Milne B, Jhamandas K, Cahill CM**. Brief report: intrathecal catheterization influences tolerance to chronic morphine in rats. Anesth Analg. 2012 Mar;114(3):690-3.

Mattioli TA, **Milne B, Cahill CM**. Ultra-low dose naltrexone attenuates chronic morphine-induced gliosis in rats. Molecular Pain 6:22, 2010.

McKechnie K, Froese A. Ventricular tachycardia after ondansetron administration in a girl with undiagnosed long QT syndrome. Can J Anaesth: 57(5):453-7, 2010

Milne B, Sutak M, **Cahill CM, Jhamandas K**. 2011. Low dose alpha-2 antagonist paradoxically enhances rat norepinephrine and clonidine analgesia. *Anesthesia & Analgesia*. 112(6):1500-1503.

Milne B. Nitrous oxide (laughing gas) inhalation as an alternative to electroconvulsive therapy. Medical Hypotheses 74: 780-781, 2010.

Milne B, VanDenKerkhof EG, Phelan R, Nakatsu K. Does Carbon Monoxide Play a Role in Cigarette Smoke Dependence? Addiction Research and Theory. 2011 July 19. [Epub ahead of print].

Muscedere J, Rewa O, **McKechnie K**, Jiang X, Laporta D, Heyland D. Sub-Glottic Secretion Drainage for the Prevention of Ventilator Associated Pneumonia: A Systematic Review and Meta Analysis. 2011 (In Press). Critical Care Medicine.

Nickel JC, **Tripp DA**, Pontari M, Moldwin R, Mayer R, Carr LK, Doggweiler R, Yang CC, Mishra N, Nordling J. Psychosocial phenotyping in women with interstitial cystitis/painful bladder syndrome a case control study. J Urol. 2010 Jan;183(1):167-72.

Parlow J, Gilron I, Milne B, Dumerton-Shore D, Orr E, Phelan R. Cardiopulmonary bypass does not affect plasma concentration of preoperatively administered gabapentin. Can J Anaesth. 2010 Apr;57(4):337-42. Epub 2010 Jan 29.

Payne DM, Hamilton A, **Milne B, Tanzola R**, O'Reilly M., Intra-operative Diagnosis of Unroofed Coronary Sinus Following Aortic Valve Replacement, Annals of Thoracic Surgery 93:296-297, 2012.

Raphael M, **Jaeger M**, **VanVlymen J**. Easily adoptable total joint arthroplasty program allows discharge home in two days. Canadian Journal of Anesthesia: 58(10); 2011, 902-910

Reitsma M, Tranmer J, Buchanan D, **VanDenKerkhof EG**. The prevalence of chronic pain and pain-related interference in the Canada population from 1994 to 2006. Chronic Diseases in Canada. 2011:31(4):157-164.

Reitsma M, Tranmer J, Buchanan D, **VanDenKerkhof EG**. Sociodemographic predictors of chronic pain in Canadians: A gender-based analysis. Pain Research and Management, In press 2012

Reitsma M, **VanDenKerkhof EG**, Johnston S, Hopman W. Does health-related quality of life improve in women following gynaecological surgery? Journal of Obstetrics and Gynaecology Canada, 2011, 33(12):1241-1247.

Simchison BL. Harassment from misguided mayoral candidate. CMAJ 2010 182(11):1213.

Sivilotti MLA, Messenger DW, **van Vlymen J**, Dungey PE, Murray HE. A comparative evaluation of capnometry versus pulse oximetry for the detection of respiratory events during procedural sedation and analgesia on room air. Canadian Journal of Emergency Medicine 2010; 12: 397-404.

Srikandarajah S, **Gilron I**. Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: a fundamental distinction requiring standardized measurement. Pain 2011;152:1734-9.

Stutzman SS., Brown CA., Hains SM., Godwin M., Smith GN., **Parlow JL**., Kisilevsky BS. The effects of exercise conditioning in normal and overweight pregnant women on blood pressure and heart rate variability. Biol Res Nurs 2010 12(2):137-48.

Tanzola R, Erb J, Endersby R, Milne B. Transesophageal echocardiography images of pulmonary artery compression by benign follicular lymphoid hyperplasia. Can J Anaesth 57:1042-1043, 2010.

Tanzola R, Milne B, Hamilton A. Transesophageal echocardiography of a dislodged left atrial appendage thrombus and its subsequent surgical removal during coronary artery bypass graft surgery. Journal of the American Society of Echocardiography 23, Issue 9, 1008.e1-1008.e3, 2010.

Tanzola R., Milne B., Ventricular Tachycardia, 5-Minute Anesthesia Consult. Singh-Radcliff ND (eds.). Lippincott Williams & Wilkins, In Press 2012.

Turner KE. Book Review: From Craft to Specialty - A Medical and Social History of Anesthesia and Its Changing Role in Health Care: David Shephard in association with Alan Sessler, Francis Whalen and Tuhin Roy. Thunder Bay, Ontario: York Point Publishing, 2009. Can J Anaesth 2010 57(5):523.

Turner K. Remembering David Shephard, MB FRCPC (1930-2011). Can J Anaesth. 2012 Mar 13. [Epub ahead of print]

Queen's University Department of Anesthesiology Publication List – 2010-2012 [page 4/4]
(in alphabetical order of 1st author, Department members/cross-appointees highlighted in bold)

VanDenKerkhof EG, Friedberg E, Harrison MB. Prevalence and risk of Pressure Ulcers in Acute Care Following Implementation of Practice Guidelines: Annual Pressure Ulcer Prevalence Census 1994-2008. Journal of Healthcare Quality. 2011:33(5);58-67.

VanDenkerkhof EG, Hopman WM, **Goldstein DH, Wilson RA**, Towheed TE, Lam M, Harrison MB, Reitsma ML, Johnston SL, Medd JD, **Gilron, I**. Impact of perioperative pain intensity, pain qualities and opioid use on chronic pain after surgery: A prospective cohort study. Regional Anesthesia and Pain Medicine, 2012;37:19-27.

VanDenKerkhof EG, Macdonald HM, Jones GT, Power C, Macfarlane GJ. Diet, lifestyle and chronic widespread pain: results from the 1958 British Birth Cohort Study. Pain Research and Management. 2011:16(2):87-92.

VanDenKerkhof EG, Peters M, Bruce J. Chronic pain after surgery: Time for standardization? A framework to establish core risk factor and outcome domains. The Clinical Journal of Pain, In press 2012

Vandyk A, Brenner I, Tranmer J, **VanDenKerkhof EG**. Depressive symptoms before and after elective hysterectomy. Journal of Obstetric, Gynecologic and Neonatal Nursing. 2011:40(5):566-576.

Wai EK, Sathiaseelan S, O'Neil J, **Simchison BL**. Local administration of morphine for analgesia after autogenous anterior or posterior iliac crest bone graft harvest for spinal fusion a prospective, randomized, double-blind, placebo-controlled study. Anesth Analg. 2010 Mar;110(3):928-33. Epub 2009 Dec 30.

Walker S, Hopman W, Harrison M, **Tripp D**, **VanDenKerkhof EG**. Pain and Psychological Characteristics in Women Waiting for Gynaecological Surgery. Journal of Obstetrics and Gynaecology Canada, In Press 2012.

Watson CPN, **Gilron I**, Pollock B, Lipman AB, Smith M. Antidepressant Analgesics (In Press). Textbook of Pain, 6th Edition, M. Koltzenburg, S. McMahon, Editors Elsevier Press, Philadelphia 2012.

Watson CP, **Gilron I**, Sawynok J, Lynch ME. Nontricyclic antidepressant analgesics and pain: Are serotonin norepinephrine reuptake inhibitors (SNRIs) any better? Pain 2011;152:2206-10.

Watson CPN, **Gilron I,** Sawynok J. A qualitative systematic review of head-to-head randomized controlled trials of oral analgesics in neuropathic pain. Pain Res Manage 2010;15(3):147-57.

Zamora JE, Nolan RL, **Sharan S**, Day AG. Evaluation of the Bullard, GlideScope, Viewmax, and Macintosh laryngoscopes using a cadaver model to simulate the difficult airway. J Clin Anesth. 2011 Feb;23(1):27-34.