Queen's University
31st Annual Anesthesiology Research Day

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Research Facilitator:
Rachel Phelan, MSc

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.****

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Programme booklet cover design by Ian Gilron

Queen's University *31st Annual Anesthesiology Research Day*

SCIENTIFIC PROGRAMME

0900 – 0910 Opening Remarks
– Dr. Joel Parlow

0910 – 0930 Anesthesiology Research: What's the payoff for the public & for our specialty?

– Dr. Ian Gilron

0930 – 1030 Oral presentations (see list below)

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

1100 – 1200 Oral presentations (see list below)

1200 – 1300 * LUNCH (provided) *****

1300 – 1415 Oral presentations (see list below)

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

1445 – 1530 Oral presentations (see list below)

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

The Judges will be:

Dr. Peter Slinger, Professor, Department of Anesthesia, University of Toronto

Dr. Alison Froese, Professor, Queen's Depts. of Anesthesiology & Perioperative Medicine, Physiology & Pediatrics

Dr. David Goldstein, Associate Professor, Queen's Department of Anesthesiology & Perioperative Medicine

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1515 **Dr. Peter Slinger,** Professor, Department of Anesthesia, University of Toronto, Speaker of the Royal College of Physicians & Surgeons of Canada, Region 3 Advisory Committee

"Advances in Lung Isolation"

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

Order of Oral Presentations

Jason McVicar, PGY3, Queen's Anesthesiology
"**A Clinical Tool to Predict Anxiety at the Induction of Anesthesia in Children**" (research update/data presentation)

Rebecca Gerlach, PGY2, Queen's Anesthesiology
"**Impact of a Simple Preoperative Smoking Cessation Intervention**" (proposal)

T. Alexandra Mattioli, PhD Candidate, Queen's Pharmacology & Toxicology
"**Gliosis Induced By Intrathecal Catheterization Enhances Morphine Tolerance; Ultra-Low Dose Antagonists May Attenuate Tolerance And Gliosis By Independent Mechanisms**" (data presentation)

Tracy Cupido, PGY3, Queen's Anesthesiology
"Trigger Point Injection Study (TPIS)" (data presentation)

Samia Ali, PGY4, Queen's Anesthesiology
"**Factors that may precipitate cerebral ischemia during carotid endarterectomy**" (data presentation)

Brian Grant, PGY2, Queen's Anesthesiology
"**Impact of spontaneous versus evoked neuropathic pain on daily function**" (proposal)

Drew McLaren, PGY3, Queen's Anesthesiology
"**Canadian Anesthesia Workforce Assessment 2010**" (research update/data presentation)

Matthew Langdon, PGY2, Queen's Anesthesiology
"**Does Perioperative Dextromethorphan Reduce Pain Following Pediatric Tonsillectomy?**" (proposal)

Stacy Ridi, PGY4, Queen's Anesthesiology
"**A National Survey Of Medical Student Attitudes Toward The Matching Process**" (data presentation)

Ryan Mahaffey, PGY2, Queen's Anesthesiology
"**Identifying diverse mechanism clusters in human neuropathic pain**" (proposal)

Serena Shum, MD Candidate, Queen's Medicine
"**Retrospective Study of Enhanced Care Units and Surgery**" (proposal)

Jordan Leitch, MSc Candidate, Queen's Center for Neuroscience Studies
"**The fMRI response in the spinal cord and brainstem to peripheral neuropathic pain**" (research update)

Jeremi Mountjoy, PGY4, Queen's Anesthesiology
"**Effects of patient controlled analgesia pump feedback on post-operative pain**" (research update)

Angela Hogan, PGY5, Queen's Anesthesiology
"**Pilot Study on the Use of Inhaled Flolan and its Impact On Separation from Cardiopulmonary Bypass**" (research proposal/update)

Brendan Levac, BSc Candidate, Queen's Life Sciences
"**Ringer's Lactate Is Compatible With SAGM-PRBC For Rapid Transfusion**" (data presentation)

Laura Katz, MSc Candidate, Queen's Psychology
"**Understanding disability in women suffering from Interstitial Cystitis / Painful Bladder Syndrome from a biospsychosocial perspective**" (data presentation)

Poster Presentations

Edmund Ong, PhD Candidate, Queen's Pharmacology & Toxicology
"**Mu/Delta Opioid Receptor Heterooligomer Trafficking in Response to Prolonged Morphine Treatment**" (poster presentation)

Michael Philbrook, MSc Candidate, Queen's Pharmacology & Toxicology
"**Heme-oxygenase Inhibitors: a novel strategy for treating inflammatory and neuropathic pain?**" (poster presentation)

Patrick Grenier, MSc, Candidate, Queen's Pharmacology & Toxicology
"**Delta-Opioid Receptor Trafficking in Neuropathic Pain is Attenuated by Glial Inhibition**" (poster presentation)

Samantha Lecour, Research Technician, Queen's Pharmacology & Toxicology
"**Conditioned Place Preference as a Model to Determine Drug Effectiveness in Relieving Neuropathic Pain**" (poster presentation)

Jess Ginting, Queen's Psychology
"**The Influence of Pain and Spousal Responses to Pain Behaviour on Quality of Life in Chronic Pelvic Pain Samples**" (poster presentation)

Julian deBacker, Honour's Thesis Candidate, Queen's Life Sciences
"**The effects of Dopamine D3 antagonist in the bed nucleus of the stria terminalis on drug-induced reinforcement.**" (poster presentation)

Cindy Chiang, MSc Candidate, Queen's Center for Neuroscience Studies
"**The role of Dopamine D1/D2 receptors in the bed nucleus of the stria terminalis on natural and pharmacological reinforcement**" (poster presentation)

Xenos Mason, Honour's Thesis Candidate, Queen's Biology
"**Cocaine Self-administration reveals a dopamine D1 and Src Tyrosine kinase-dependent long-term potentiation at inhibitory synapses**" (poster presentation)

Michal Krawczyk, MSc Candidate, Queen's Center for Neuroscience Studies
"**Dopamine D1/D2 receptors-induced decrease of NMDA currents in cocaine addicted rats**" (poster presentation)

Critical Appraisals

Jessica Collings, MD, PGY-1, Queen's Anesthesiology
"Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients" Anesthesiology 2009;110:284.

Tricia Doyle, MD, PGY-1, Queen's Anesthesiology
"Effects of age and gender on intravenous midazolam premedication" British Journal of Anaesthesia 2008;101:632.

Yasser M. Hayat, MD, PGY-1, Queen's Anesthesiology
"Early Goal-Directed Therapy In The Treatment Of Severe Sepsis And Septic Shock" NEJM 2001;345:1368.

Karen Wong, MD, PGY-1, Queen's Anesthesiology
"Identification of Patients at Risk for Postoperative Respiratory Complications Using a Preoperative Obstructive Sleep Apnea Screening Tool and Postanesthesia Care Assessment" Anesthesiology 2009;110:869.

Impact of Spontaneous Versus Evoked Neuropathic Pain on Daily Function

Grant B, Gilron I, Orr E.

Background: A substantial percentage (18-42%) of patients with diabetes suffer from disabling pain due to diabetic neuropathy. Painful diabetic neuropathy 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, if any, animal models of spontaneous pain exist. However, patients with painful diabetic neuropathy report pain intensity and pain quality quite diversely suggesting the possibility of different underlying pain mechanisms. Patients with diabetic polyneuropathy describe an array of sensory abnormalities. These can be pains of a spontaneous nature (those that arise without detectable stimulation) and evoked pains (abnormal responses to stimuli). Spontaneous pain can be continuous, steady and ongoing, or it can be paroxysmal, episodic and intermittent. It is not known what impact spontaneous pain versus evoked pain has on quality of life and activities of daily living. It is also not known whether patients can differentiate between the two types of pain and the impact they have on an individual's life.

Study Question & Hypothesis: Does spontaneous pain have as much functional impact on activities of daily living as stimulus-evoked pain in patients with diabetic neuropathy? Our hypothesis is that stimulus-evoked pain has a more negative effect on patients' activities of daily living than spontaneous pain.

Study Design: This is a prospective observational study involving patients with painful diabetic neuropathy. 75-100 adult patients will be recruited with distal, symmetrical sensory diabetic polyneuropathy experiencing daily moderate pain for at least 3 months. Patients will be contacted by phone or mail and informed consent will be obtained. They will then complete questionnaires relating to pain intensity, medication/treatments used for their painful diabetic neuropathy, a neuropathic pain questionnaire, and a questionnaire to quantify the effect of spontaneous and evoked pain on activities of daily living. These questionnaires will be completed on two separate occasions approximately 3 months apart. A subset of patients will be invited to the clinic for an additional sensory examination to map out areas of allodynia and hyperalgesia. The two co-primary outcome measures are: 1) The severity of impairment (0- no impairment; 10-complete impairment) of activities of daily living and 2) The quantitative impact of stimulus evoked pain and spontaneous pain on activities of daily living. Secondary outcome measures: 1) Patients will be able to differentiate spontaneous and evoked pain and 2) Patients will be able to rate the impact of stimulus and evoked pain on their activities of daily living. The proposed timeline will be 1 year.

Impact: The proposed study is innovative in that it closely examines patients' experience of pain (specifically, spontaneous versus evoked pain) and how it impacts their activities of daily living. Given our focus on humans suffering from diabetic neuropathic pain, results from this study will more appropriately guide future research strategies and may emphasize more clearly that experimental models of spontaneous pain are needed.

Impact of a Simple Preoperative Smoking Cessation Intervention

Resident Presenter: Rebecca Gerlach
Supervisor: Janet van Vlymen

Background: Many patients requiring surgery are daily cigarette smokers. It has been shown that smoking predisposes patients to wound infections, myocardial ischemia and post-operative pulmonary complications[1]. Recently, the literature has shown that short-term smoking cessation, for as little as 4-8 weeks before surgery, can significantly decrease complications and improve outcome[2].

For many patients, having major surgery is a "teachable moment" and provides a motivating factor for behavioural change. There have been several trials published demonstrating the success of various smoking cessation interventions in the pre-operative period, both in decreasing smoking rates and subsequent post-operative complications[3],[4],[5],[6]. Currently, there is no organized approach to encourage smoking cessation for patients having surgery at Hotel Dieu Hospital or Kingston General Hospital.

Objectives: We will examine whether a simple, low-cost intervention, incorporated into our existing pre-surgical screening program, can lead to either cessation or a 50% reduction in smoking preoperatively. We will examine whether this change is sustained at 30 days post-operatively. In addition, we will evaluate the impact of this intervention on the length-of-stay, infection rate, and major morbidity after surgery.

Methods: All adult smokers will be identified by the pre-surgical screening nurse when the anesthetic questionnaires are received in Central Registration. Patients will be telephoned by a research nurse to obtain verbal consent and will be randomly assigned to an intervention or non-intervention group. Patients will be excluded from the study if they are less than 18 years of age, if their surgery is scheduled in less than one week, or if they are currently receiving an educational program.

Patients randomized to the intervention group will receive advice and information about the benefits of smoking cessation from the research nurse and a recommendation to contact the Smokers Helpline and their family doctor if they require prescription cessation aids. The intervention group will also receive weekly email reminders of the benefits of smoking cessation. During their usual Pre-Surgical Screening Nursing assessment, smoking cessation advice and information will again be reinforced. Patients randomized to the non-intervention group will receive the usual preoperative advice currently provided by the nurses in Pre-Surgical Screening.

All patients participating in the study will complete a survey with a blinded research nurse preoperatively on the day of surgery. A thorough smoking history will be collected and will include: recent smoking history, previous attempts to quit, use of cessation aids, reduction in tobacco use, and duration of cessation. A reduction of tobacco use by 50% will be considered a significant reduction and cessation for at least one week before their surgery will be considered cessation.

All inpatients in both groups will receive a post-operative consult with the smoking cessation program at KGH. This program is currently being introduced in the surgical population. Charts will be reviewed at the time of discharge to determine length-of-stay, infection rates, and identify any major morbidity (e.g., myocardial infarction, pneumonia etc). All patients will be contacted by phone at 30 days to determine smoking cessation, hospital readmission, and postoperative wound infection.

Power Analysis: A sample size of 68 people per group was calculated using a 20% difference in smoking cessation between the two groups with 80% power and a p-value of 0.05.

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Pilot Study on the Use of Inhaled Flolan and its Impact On Separation from Cardiopulmonary Bypass

Dr. Angela Hogan and Dr. Ramiro Arellano

Background: Inhaled Flolan (epoprostanol) administered to patients with pulmonary hypertension either before cardiopulmonary bypass for cardiac surgery, or after cardiac surgery, has been shown to be safe and effective. Pulmonary hypertension and right heart failure are associated with difficult separation from CPB and inhaled Flolan could facilitate this process.

Objective: To determine the impact of inhaled Flolan on ease of separation from CPB during cardiac surgery.

Hypothesis: inhaled Flolan administered before or after CPB could help facilitate weaning from CPB during cardiac surgery.

Method: Retrospective chart review of at least 20 patients who underwent cardiac surgery with cardiopulmonary bypass at Kingston General Hospital from 2006 until present, and who received inhaled Flolan. Demographic, hemodynamic (including data from pulmonary artery catheters and TEE if available), oxygenation status, timing and dose of administration, type of anesthetic and monitoring, type of cardioplegia, CPB and cross-clamp times, any difficulties in separation from CPB, morbidities and mortalities in the perioperative period up to 30 days, time to extubation, ICU and hospital length of stay, as well as any detectable side-effects possibly linked to the administration of inhaled Flolan will be documented. Difficult separation from CPB will be defined as SBP <80 mmHg; pulmonary artery diastolic pressure or pulmonary artery capillary wedge pressure >15 mmHg; use of inotropic or vasopressive support (NE >0.05 mcg/kg/min, dopamine >5mcg/kg/min, dobutamine >5mcg/kg/min, epinephrine >0.05 mcg/kg/min, milrinone bolus > 50mcg/kg then >0.5 mcg/kg/min, phenylephrine >2.5 mcg/kg/min, isoproterenol >0.01 mcg/min and methylene blue (any dosage)).

Canadian Anesthesia Workforce Assessment 2010

Drew McLaren, Rob Tanzola, Liz Vandenkerkhof and Dale Engen.

Purpose

Adequate health care delivery involves planning for the future and ensuring sufficient medical specialists are available to fulfill clinical need. Previous evaluations of the Canadian anesthesiology workforce have demonstrated current provider shortages and have also estimated future deficiencies. However, there has been no recent assessment to evaluate if the demand of the national anesthesia workforce is being fulfilled. In part with conventional anesthesia providers, the use and design of anesthesiology care teams and anesthesiology assistants are increasing across the country. To date, there has never been a national review of the use of anesthesiology assistants or their impact on the demand of other anesthesiology providers. The purpose of this study is to re-evaluate the current status of the Canadian anesthesiology workforce, as well as assess the use of anesthesiology assistants nationwide and determine their impact on national provider shortages.

Methods

All licensed health care facilities potentially employing anesthetic services have been identified. A two part questionnaire will be mailed to each institution in the spring of 2010. The first half of the questionnaire is unchanged from the 2002 survey completed by Engen *et al*. This portion evaluates the current national anesthesia workforce and estimates the future need in five years. The second half the questionnaire evaluates the national use of anesthesiology assistants. Questions are directed at the specific roles and spectrum of care that anesthesiology assistants are fulfilling at each institution. Furthermore, institutions are asked to estimate the impact that anesthesiology assistants have had on the demand for other anesthesiology providers.

Does Perioperative Dextromethorphan Reduce Pain Following Pediatric Tonsillectomy?

Langdon M, Rooney R

Background: Tonsillectomy is a common pediatric surgical procedure which is associated with moderate to severe postoperative pain. Attempts at providing safe and adequate analgesia have been unsuccessful. Treatment with opioid and non-steroidal anti-inflammatory agents, although widespread, has been controversial due to potential central nervous system effects and increased risk of postoperative bleeding. The N-methyl-D-aspartate (NMDA) antagonist, dextromethorphan (DM), has been shown to modulate pain processes and reduce post-surgical pain and opioid consumption with few side effects. This drug may prove to be an effective and safe alternative for the treatment of post-tonsillectomy pain in children.

Knowledge Gap: The perioperative use of NMDA antagonists as pain adjuncts is increasing, but few studies address the specific use of many of these agents in pediatric surgery. Previous studies on the preoperative use of oral DM provide limited data and confounding results. Single-dose administration, variable use of intraoperative opioid, insufficient postoperative follow up, and smaller sample sizes may add limitations to these studies. New research addressing some of these concerns may lead to a better understanding of the perioperative use of DM in pain management for a common pediatric surgery.

Hypothesis: We predict that the perioperative administration of DM will reduce pain associated with pediatric tonsillectomy.

Primary Outcome: Pain severity

Secondary Outcomes: Postoperative nausea and vomiting, rescue opioid use, respiratory depression, bleeding

Study Design: After obtaining ethics committee approval and parental consent we plan to recruit 125 patients, ASA class I and II (ages 3-12 years old) who are having tonsillectomy and/or adenotonsillectomy, into a prospective, blinded, randomized control trial. Patients will receive either study drug (DM) or placebo preoperatively, followed by a standardized anesthetic protocol including the use of inhaled gases, opioid and steroids. A second dose of study drug or placebo will be administered early in the recovery period, along with rescue opioid and anti-nausea medications if needed. Patients will be assessed, by post anesthetic care nurses at determined intervals, for pain (using the 'Faces' pain scale), vomiting, respiratory depression, bleeding and opioid consumption. A follow up phone call after 24 hours to assess similar outcomes at home will also be performed. Based on previous assessments of pain using similar measurement tools we will consider a 20% decrease in pain severity as clinically significant.

Identifying Diverse Treatment-Response Clusters in Neuropathic Pain

Ryan Mahaffey

Supervisor: Ian Gilron

Introduction:

As one of several treatment strategies for neuropathic pain, pharmacotherapy includes a variety of different drugs including antidepressants, anticonvulsants and opioids. Tailoring individualized treatment according to analgesic response, co-morbidities and other contraindications can be quite challenging, take several months to arrive at a helpful regimen, and, in the process, result in periods of time when the patient suffers from intolerable side effects and/or inadequate pain relief. Therefore, any knowledge that facilitates more rapid prediction of efficacy and tolerability with a particular drug would greatly improve patient care.

It has been postulated that a mechanism-based classification of pain will allow for the matching of pharmacologic agents with specific pain mechanisms. The results of this study are expected to increase the understanding of specific pain mechanisms and their corresponding response to specific treatment modalities. The research project being proposed is a secondary analysis of two previous studies investigating single vs. combination therapy in the treatment of neuropathic pain. The first study investigated gabapentin and morphine – both as individual agents as well as in combination – in the treatment of neuropathic pain (diabetic neuropathy or postherpetic neuralgia). The second study investigated nortriptyline and gabapentin in a similar manner. The initial studies found that combination regimens were more efficacious than either drug alone. These two studies have opened the door to a secondary analysis with a number of interesting research questions.

Research question:

1. Is there a correlation between a positive response: A) to gabapentin versus that of morphine and B) to nortriptyline versus that of gabapentin?

2. When investigating multiple pain quality descriptors (e.g. burning pain) from patient-reported completion of the Short-form McGill Pain Questionnaire is there a difference in treatment response to each pain quality descriptor between Morphine vs. Gabapentin and Gabapentin vs. Nortriptyline?

Hypotheses to be tested:

1. It is hypothesized that a response (or lack thereof) to one drug predicts the response to another drug in neuropathic pain.

2. It is hypothesized that there will be a difference between the efficacy of Morphine vs. Gabapentin and of Gabapentin vs. Nortriptyline for the reduction of multiple patient-reported Short-form McGill Pain Questionnaire pain quality descriptors.

Proposed study design:

We propose to conduct secondary analyses of data from two previously conducted neuropathic pain clinical trials. The two studies were both prospective randomized double-blind crossover studies. The data mining will consist of correlation analysis for Q1 and paired T-tests for Q2.

Project timeline:

Given that necessary data and statistical methods for this investigation already exist, feasibility is not a concern and the study could be completed within the next 6 months.

Factors that may precipitate cerebral ischemia during carotid endarterectomy

Ali S, Parlow J, Brunet D.

BACKGROUND: The substantial benefits attained from carotid endarterectomy (CEA) have been well established; however it is well known that this operation carries a significant risk of cerebral ischemia. The use of shunts to maintain cerebral perfusion during the course of this surgery has been in practice for decades, but also carries the risk of complications which include air or plaque embolization, intimal tears and carotid dissection. While some surgeons routinely insert shunts and others do not, the middle ground approach is selective shunting based on monitoring cerebral perfusion. This is the practice at our institution where cerebral perfusion is monitored by the use of intraoperative electroencephalography (EEG).

There are several patients (e.g. age, co morbidities, location and laterality of stenosis) as well as anesthesia related factors that may contribute to cerebral ischemia. The aim of this quality assurance pilot study is to attempt to identify factors that may predispose to cerebral ischemia during CEA at our institution.

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

METHODOLOGY AND RESULTS: After obtaining approval from the ethics committee, a retrospective chart review of all 106 patients undergoing first time carotid endarterectomy over a two year period from Jan 2007 to Jan 2009 was conducted. Summary EEG data, with all instances of ischemic events recorded was reviewed, as was the anesthetic management.

It was previously determined that our local incidence of cerebral ischemia with cross-clamping, leading to shunt placement was 13%. However in the course of this review we identified 9 cases that required shunt placement, indicating a slightly lower incidence of 8.5%.

Among the cases identified, a descriptive analysis of the following variables will be conducted:

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

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

REFERENCES:

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

Retrospective Study of Enhanced Care Units and Surgery

Serena Shum, Rob Tanzola, Dale Engen, Mike McMullen

Introduction

Enhanced Care Units (ECUs) are an expensive and scarce resource. Surgeries are often cancelled due to their unavailability. The decision to allocate an ECU bed for a patient requires careful consideration of a multitude of factors. Furthermore, there exists a difference between surgical and medical use of ECUs. Medically, patients are admitted if they are in extremis, whereas postoperative surgical patients are often placed there for monitoring. This chart review will examine ECU use at Kingston General Hospital (KGH) by surgical patients over a three to six month period. The study will identify patient demographics and co-morbidities, markers reflecting their course in surgery, indications for ECU admission, length of stay in ECU, interventions required while in ECU, and their disposition post-ECU.

The purpose of this study is to determine the characteristics of these patients and elucidate how many of these patients had interventions that required actually required ECU post-operatively.

Methodology

A retrospective chart review is employed to address the research question. Eligible patients were those who underwent elective surgeries with an ECU room booked pre-operatively. We included patients from November 2009 to May 2010. Patient data was then extracted from KGH's electronic records system. Subsequently, further detail regarding ECU stays was elicited from the nursing progress notes, which remain in paper format. A total of 100 patients will be reviewed.

Data

Pre-Operative Data

Pre-operative data included patient demographics (age, sex, surgical procedure received, and the American Society of Anesthesiologists, or ASA score), the reason for the ECU booking and the service requesting (anesthesia or surgery), and whether the surgery was canceled due to ECU unavailability. Data regarding patient co-morbidities included cardiovascular (stable/unstable coronary artery disease, current/remote congestive heart failure, left ventricular dysfunction, arrhythmia, and valvular disease) and respiratory (pulmonary hypertension, controlled/uncontrolled obstructive sleep apnea, obstructive and restrictive lung disease, asthma, COPD, current smoking) conditions. Where available, the severity of obstructive sleep apnea is captured by the AHI score and that of obstructive lung disease by $FEV_{1.}$ The presence and nature of any neuromuscular conditions was also recorded.

Intra-Operative Data

The surgical Apgar score was developed (Gawande, Kwaan, Regenbogen, et al. 2007) and validated (Regenbogen, Ehrenfeld, Lipsitz, et al. 2009) as an outcome score that surgical teams could calculate to accurately grade a patient's condition and chances of major complications or death post-operatively. It is 10-point scale based on estimated blood lost, lowest mean arterial pressure and lowest heart rate intra-operatively. The Surgical Risk Score, or SRS (Sutton, Bann, Brooks et al. 2002), is a validated score (Brooks, Sutton & Sarin 2005) intended to provide an accurate prediction of mortality based on clinical data. It is derived from the addition of three other scores: Confidential Enquiry into Perioperative Deaths (CEPOD), the American Society of Anesthesiologists (ASA), and the British United Provident Association (BUPA).

Post-Operative Data

The patients' course in the Post-Anesthetic Care Unit (PACU) was deduced from the employment of interventions including intubation, ART and/or CVP lines, CPAP/BIPAP and vasopressor use. The patient's condition, including temperature, presence of respiratory distress, diuresis and acidosis were also noted. Aldrete scores upon admission and discharge were recorded along with the discharge BP, HR, and O_2 sat as well as the level of O_2 they received. Post-operative lab values were also extracted. These include complete blood counts, electrolytes, arterial blood gases, clotting ability, and markers of renal function. Details regarding cardiac, respiratory, and neurologic complications occurring in ECU were examined. These include hypotension, extreme heart rates, arrhythmia, chest pain / angina, desaturation, dyspnea, new CPAP/BIPAP use, signs of or treatment for congestive heart failure, acidosis, renal failure, mental status changes, administration of blood products, volume, vasopressors, and pain control. The involvement of the RACE Team and the occurrence of code blues were also noted. Finally, the length of ECU stay and post-ECU destination were recorded.

Trigger Point Injection Study (TPIS)

Tracy Cupido
Supervisor: Dr. Richard Henry; March 5, 2009

Background: The cost of treating osteoarthritis (OA) in the U.S. increased by 53% from 1996-2004, with the largest proportion of this increase coming from the inflating cost of prescription medications. During the same period, the number of joint replacements has also been on the rise, with knee replacements showing the highest growth. One of the key diagnostic features of OA is pain, without which many patients would not be candidates for surgery. The pathogenesis of chronic knee pain is not completely understood, but in addition to OA, trigger points have also been implicated as one possible cause. If we can identify and treat trigger points that are causing knee pain we can relieve the suffering of many individuals experiencing chronic pain. Myofascial trigger points (MTrP) are hyper-irritable areas within taut bands of skeletal muscle or fascia. They are painful on compression and may give rise to characteristic patterns of referred pain, tenderness, autonomic nervous system symptoms and restricted range of motion. Recognition of MTrP has led to various strategies to attempt to relieve pain.

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

Secondary Study Questions: What proportion of patients waiting for TKA has trigger points as a source of their knee pain? What is the effect of myofascial trigger point injections on pain-related interference of activity, intensity and range of motion? What is the feasibility of administering the following measures to pre-operative TKA patients who are found to have myofascial trigger points: baseline demographics questionnaire (BDQ); brief pain inventory (BPI) short and long; short form McGill pain questionnaire (SF-MPQ) and timed up and go (TUG).

Study Design: We completed a prospective observational study. Patients were recruited from a wait list with an indication for TKA of OA. The following baseline data measurement tools were completed before assessment by a physician: BDQ, BPI, SF-MPQ and TUG. Patients were then evaluated for the presence of trigger points that may have been causing knee pain. All of the subjects were found to have trigger points. When trigger points were identified, their location was recorded on a schema of the knee and they received trigger point injections by a single practitioner. Data was collected immediately after injection and during follow-up visits in 1, 2, 4 and 8 weeks after the initial injection. During each follow up visit patients were re-evaluated and the study intervention was applied as appropriate. All patients were discharged after the 8 week follow-up.

Results: Pre-injection average pain intensity decreased over the course of the study. Post-injection average pain intensity was less than pre-injection, and post-injection scores were stable until the last visit when it increased. The same trend was seen with pain intensity, except that post-injection interference with mood was higher post injection. Both sensory and affective pain decreased over the course of treatments. Overall, sensory pain remained moderate and affective pain remained mild.
Scores on timed up and go (TUG) decreased from the first to the last visit.

Conclusion: The effect of injecting trigger points in patients with knee pain can be evaluated with the use of BDQ, BPI long and short, SF-MPQ and TUG. A larger sample size and multiple practioners evaluating and treating trigger points needs to be investigated before conclusions can be drawn from this data.

Gliosis Induced By Intrathecal Catheterization Enhances Morphine Tolerance; Ultra-Low Dose Antagonists May Attenuate Tolerance And Gliosis By Independent Mechanisms.

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Abstract: Ultra-low doses (ULD) of the opioid antagonists naloxone and naltrexone inhibit the development of spinal morphine antinociceptive tolerance. It is unknown if these antagonists inhibit tolerance via actions at opioid-receptors or via an alternate pathway, such as toll-like receptor 4 expressed on glia. In the present study, we determined whether ULD naloxone inhibited the development of opioid analgesic tolerance via a stereo-selective effect and what effects this treatment has on morphine-induced astrogliosis. Unlike the racemic mixture, the opioid receptor inactive isomer, (+)naloxone, does not attenuate tolerance when co-administered with chronic intrathecal morphine, therefore suggesting classic opioid receptor involvement. Chronic morphine administration induces spinal astrogliosis in tolerant animals. Activated astrocytes are characterized by increased production of glial fibrillary acidic protein (GFAP) and increase in cell size. 3-D images of astrocytes constructed from lumbar spinal cord sections taken from animals administered chronic morphine had significantly larger volumes compared to saline controls ($p<0.001$). Co-injection of ULD (+/-)naloxone attenuated this increase in astrocyte volume ($p<0.01$) and did not differ from controls. Co-injection of ULD (+)naloxone also attenuated the morphine-induced increase in volume ($p<0.001$). Neither racemic nor (+)isomer of naloxone had a significant effect on astrocyte volume compared to saline controls. Thus, inhibition of glial activation by ultra-low dose naloxone may not be causal to inhibiting the development of antinociceptive tolerance.

Chronic administration of morphine via intrathecal catheter resulted in a greater loss of morphine antinociception compared to delivery via lumbar puncture (LP). Catheterization induces spinal gliosis similar to that produced by chronic morphine treatment (via LP), and may, therefore, contribute to the observed increase in analgesic tolerance. In contrast to morphine-induced astrogliosis, treatment with ULD (+/-) naloxone or (+) naloxone had no effect on catheter-induced gliosis. The effect of morphine-induced antinociception was evaluated in naïve, catheterized and sham surgery animals. Acute administration of morphine (via LP) produced no difference in antinociception between naïve, catheterized and sham operated rats ($p>0.05$). However, morphine-induced antinociception following chronic morphine treatment (1 μg, i.t. by LP, 4 days), was significantly greater in sham and naïve rats ($p<0.05$ and $p<0.01$ respectively) compared to catheterized animals. Hence, the presence of the catheter facilitated the development of opioid antinociceptive tolerance. Taken together, these results suggest glial activation is involved in the development of opioid tolerance, but ultra-low dose antagonists may inhibit tolerance via an alternate mechanism.

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A National Survey Of Medical Student Attitudes Toward The Matching Process: Factors Influencing Choice Of Residency

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ABSTRACT

Purpose: The purpose of this study was to explore the attitudes of Canadian medical students toward the residency matching process and to define the relative importance of these attitudes in decision-making.

Method: Canadian medical students who were interviewed for the Queen's University anesthesia and urology residency program for the 2009 match were invited to complete an online, anonymous, cross-sectional, self-report questionnaire. The survey included open-ended questions as well as closed-ended questions using a 5-point Likert scale. Descriptive and quantitative statistics were used to analyze the relative importance of attitudes toward the matching process. For ease of analysis, descriptive differences between responses were reported as an agreement score that combined the agreement responses of 1 and 2 or the disagreement responses of 4 and 5.

Results: The overall response rate was 85% (87 total responses). There was no statistically significant difference in response rates between the 2 specialty groups or in their responses with regard to factors relating to ranking decisions. The factors that appeared to play a more significant role in ranking included quality of staff (91% agreement), quality of residents (81% agreement), and the "feel" of the program (76% agreement). Factors that were considered less important included the desires of partners and family members and amenities of the city where the residency position was located. There was an apparent difference in the stated goals of the interview process between the 2 groups ("selling" oneself to the program, $p < 0.014$), which may be a reflection on the format of interviews between the 2 specialties. Overwhelmingly, both groups thought that talking to residents was the most beneficial aspect of the interview process, although there appeared to be some ambivalence about the importance of the interviews with regard to final rank-order list (45% agreement). Insights from this and future surveys could improve our specialty programs interview process as well as our ability to match the right candidate to the right program

Conclusion: Insights from this and future surveys could improve our specialty programs interview process as well as our ability to match the right candidate to the right program

A Clinical Tool to Predict Anxiety at the Induction of Anesthesia in Children

Jason McVicar, Ted Ashbury, Brian Milne, Elizabeth Van Den Kerkhof

Pediatric surgery can be a stressful experience not only for the child, but also the parent(s) and the medical staff. One of the greatest challenges in pediatric anesthesiology is dealing with the combative child prior to the induction of anesthesia. Unfortunately, even the most experienced pediatric anesthesiologists cannot predict how a child will react at the time of induction or how long the induction process will take.

The most widely accepted approach to prevent anticipated adverse reactions is to prescribe preoperative anxiolytic or sedative medications such as midazolam. The potential benefits of administering sedative medications must also be weighed carefully against the potential side effects which may include paradoxical excitement, delayed recovery, nightmares, food rejection and increased anxiety. Sedation should be reserved only for those children who are identified as high risk for adverse behaviours. Currently, there is no effective tool for predicting anxiety or adverse behaviours in children. The objective of this study is to develop a parental questionnaire to predict which children are at risk for adverse behaviours at the induction of anesthesia.

Using best evidence, we created a rapid assessment questionnaire consisting of only eight questions to determine which children are at greater risk for adverse behaviours and, thus, might require sedative premedications. These questions incorporate elements of specifically identified risk factors for adverse behaviour such as young age, previous anesthesia, previous negative medical experience, poor reaction to prior vaccinations and demonstrated overt dependency on their parents were the most predictive factors.

Our study design is an observational cohort design. Two hundred pediatric patients, 4-10 years of age scheduled for surgery at in Kingston, Ontario, are being recruited. The current anesthesiology practice at our medical center does not involve routinely sedating children and most children are brought to the operating room with one parent where the child experiences an inhalational anesthetic induction with a combination of sevoflurane and/or nitrous oxide with intravenous catheter placement after induction.

On the day before their scheduled surgery, the parents of patients will be contacted by telephone to have the study explained. On the day of surgery a research associate will administer the questionnaire to the parent and passively observe the child to obtain the research standard modified Yale Preoperative Anxiety Scale (mYPAS) score in the preoperative holding area. The research associate who is blinded to the results of the questionnaire will passively observe the child to obtain an independent mYPAS score at the time of anesthetic mask presentation for induction of anesthesia. Children who receive sedation will be excluded from the study.

Factor analysis, correlation and the kappa statistic will be used to validate the new tool against the mYPAS.

Interim Results: 55 participants have been approached, none have declined, 11 were excluded after receiving sedation, and there have been two other exclusions (response rate=76%). There is minimal missing data. The parents answered the questionnaire forced yes/no questionnaire on paper and occasionally would give an ambiguous answer.

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

Jeremi R. Mountjoy, John Murdoch, Rosemary Wilson and Ian Gilron

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

The fMRI response in the spinal cord and brainstem to peripheral neuropathic pain

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Introduction

Neuropathic pain (NP) is caused by nervous system lesions due to trauma or disease, and is characterized by:[1]

- *Spontaneous pain* in the absence of visible tissue damage or noxious stimuli
- *Pathological amplification* of pain response to noxious (hyperalgesia) or innocuous stimuli (allodynia)

Approximately 5% of the American population suffers from NP,[2] commonly describing the pain as burning, tingling, and electric shock sensations,[3] as well as "punishing-cruel" and tiring-exhausting"[4] on the McGill Pain Questionnaire (MPQ).[5] In this study, we used spinal fMRI to investigate spinal cord (SC) and brainstem responses to peripheral NP in a clinical population (median nerve neuropathy).

Methods

Subjects (controls and patients diagnosed with carpal tunnel syndrome - CTS) reported pain levels of 2, 4, and 6 out of 10 when noxious pressure was applied to the volar forearm. These reported pressures were used as the stimuli for the block paradigm.

Imaging Parameters

- 3T Siemens Magnetom Trio
- Half-fourier single-shot fast spin-echo (HASTE)
- TE=38msec, TR=1sec used to obtain proton-density-weighted images
- FOV=28cm x 14cm, matrix=192x96, nine 2-mm thick contiguous slices
- Stimuli applied in block paradigm

Results

Brainstem (Rostral Pons): In the peripheral NP state, a decreased quantity of active voxels was observed, in addition to notable areas of negative (blue) signal intensity change adjacent to areas of positive (orange) signal intensity change (See group analysis below).

Pain = 2
Control

Pain = 2
Peripheral NP

Cervical Spinal Cord: In controls, positive signal intensity change was observed in the ipsilateral dorsal horn at pain level = 2, whereas negative signal intensity change was observed at pain level = 6. In contrast, in peripheral NP subjects, positive signal intensity change was observed in the spinal cord at all pain levels.

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Ringer's Lactate Is Compatible With SAGM-PRBC For Rapid Transfusion

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Introduction: Standard guidelines for blood administration state that Ringer's lactate (RL) should not be co-administered with packed red blood cells (PRBC) due to a potential risk of clotting, although this has been disputed in a number of studies.(1) In resuscitation of hypovolemia, RL may be favoured over normal saline (NS).(2) The purpose of this study is to determine whether RL can cause clotting when co-administered with PRBC stored with the currently used preservative, SAGM, during rapid transfusion.

Methods: Following institutional ethics approval, 20 units of SAGM preserved PBRC were used during this two phased study. Phase 1: Samples from 12 units of PRBC were serially diluted from 0-97.5% by volume with RL and NS, and incubated for 30 min. These were passed through 40μm filters and examined visually for clots. Additional samples were frozen and batch analyzed at a later date, using an enzyme linked immunosorbent assay (ELISA) to measure F1+2, an index of thrombin generation. Finally, the remaining 150 mL of the PRBC units were diluted and flushed with crystalloid through a blood warmer and filtered for clots, using a rapid transfusion model. Phase 2: In order to determine whether prolonged incubation may have an effect on clotting, 8 further units were serially diluted to 25-95% by volume with RL only, incubated for 30, 60, 120, 180 and 240 minutes, then filtered and inspected for clot formation. The ELISA studies were repeated on fresh samples, and analyzed within 90 min of mixing. Finally, ionized and total calcium concentration were determined on the dilutions.

Results: Phase 1: No filtered clots were observed at any dilution with either NS or RL, or during the simulated transfusion. In the stored, frozen samples, F1+2 ranged from 2.28 to 154.37 pmol/L in NS dilutions, and 2.80 to 1675.93 pmol/L in RL dilutions (Figure below). Phase 2: No clotting was observed in any filter at 30 or 60 min incubation. At 240 minutes, evidence of clotting was seen in most dilutions. ELISA analysis at 90 minutes showed F1+2 values ranging from 2.02 to 228.74 pmol/L. These values were all below physiological levels as established by past studies. Ionized calcium was significantly lower in the samples that had shown clotting.

Discussion: In this comprehensive in-vitro study, utilizing both macroscopic and molecular methods, no clotting was observed at any dilutions of RL with SAGM- preserved PRBC within 60 min. However, with extended incubation, it was shown that RL could cause clotting. The results concur with previous studies that RL can be co-administered with PRBC for rapid transfusion. Calcium containing solutions should be avoided for slow (>60 minutes) transfusion.

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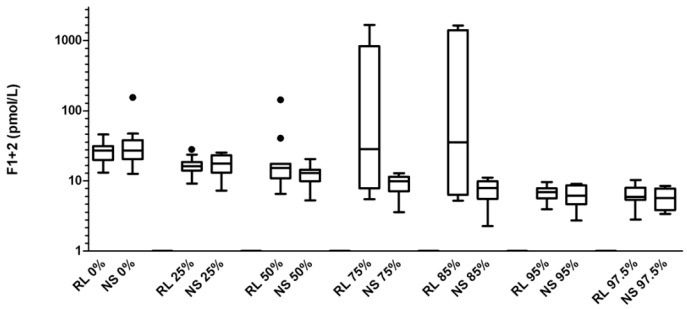

Understanding disability in women suffering from Interstitial Cystitis / Painful Bladder Syndrome from a biospsychosocial perspective

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Introduction: Interstitial Cystitis / Painful Bladder Syndrome (IC/PBS) is a painful and often refractory medical condition affecting 2.7-6.5% of North American women. Disability is a significant issue in women with IC/PBS, but no study has examined the predictors of disability. This study investigated a biopsychosocial model of disability, focusing on the psychosocial predictors, while controlling for demographics, pain and disease-specific symptoms. Disability was represented by voluntary life activities (i.e., family/home responsibilities, social, recreational, occupation and sexual behaviors), and obligatory activities (i.e., self-care, life support activities).

Methods: Ethically approved questionnaires were completed by 190 women diagnosed with IC/PBS from urology clinics in Canada, US and Germany. Demographic (age, education, partner status), disease-specific (O'Leary Sant IC Symptoms and Problem Index) and psychological data (Center for Epidemiological Studies Depression Scale, State Trait Anxiety Index, Pain Catastrophizing Scale, Social Support) was collected. Disability was assessed using the Pain Disability Index. Multiple hierarchical regression modeling was employed.

Results: There were no significant differences in disability across countries ($F=.64$, $p=.528$) and variables that did not correlate with disability were removed from regressions modeling. The first regression model included education, IC/PBS symptoms and problems, pain, catastrophizing and depression predicting voluntary and obligatory disability. Pain ($\beta=.26$, $p=.003$) and depression ($\beta=.30$, $p<.000$) were the lone predictors of voluntary disability, whereas depression was the only predictor of obligatory disability ($\beta=.34$, $p<.000$). Follow-up analyses examined the unique effects of the depression subscales on disability (i.e., interpersonal, somatic scales). Somatic depression was the only predictor in both voluntary ($\beta=.54$, $p<.000$) and obligatory disability ($\beta=.38$, $p<.000$). A more conservative model was then run including education, IC/PBS symptoms and problems, pain and the somatic depression subscale. In this final model, sensory pain ($\beta=.31$, $p<.000$) and somatic depression ($\beta=.38$, $p<.000$) were predictors of voluntary disability, and somatic depression alone predicted obligatory disability ($\beta=.37$, $p<.000$).

Conclusions: Depression is a robust predictor of disability in women suffering from IC/PBS, over and above the effects of pain, disease-specific symptoms and all other psychosocial variables examined. These novel results show that appropriate depression screening and medical follow-up are warranted in IC/PBS. Further, the biopsychosocial perspective in IC/PBS suggests that managing depression symptoms may be associated with decreased patient-rated disability.

Critical Appraisal Essay

By: **Jessica Collings,** MD, PGY-1, Queen's Anesthesiology

Title of the Publication: ***"Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients"***

Authors: ***Plaud B, Meretoja O, Hofmockel R, Raft J, Stoddart PA, van Kuijk JH, Hermens Y, Mirakhur RK.***

Anesthesiology 2009;110(2):284-94.

General

This study was published in the Feb 2009 edition of Anesthesiology by Plaud et al. The paper presents research conducted by the Department of Anesthesiology and University of Caen Basse-Normandie, Centre Hospitalier Universitaire de Cote-de-Nacre, Caen, France; the Department of Anesthesia, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland; Klinik und Poliklinik for Anasthesiologie und Intensivtherapie, Rostock, Germany; Hoˆpital Brabois, Vandoeuvre les Nancy, France; Bristol Royal Hospital for Children, Bristol, United Kingdom; The Queen's University of Belfast, Belfast, United Kingdom; and Schering-Plough.

Introduction

With the widespread use of neuromuscular blocking agents (NMBAs) in peri-operative medicine, reversal agents such neostigmine or edrophonium are frequently used to hasten the reversal of neuromuscular blockade (NMB) and reduce the risk of any residual block. However, acetylcholinesterase inhibitors are not capable of reversing a profound block and their use has been associated with residual blockade. The reversal agent sugammadex is a water-soluble modified gamma cyclodextrin that selectively encapsulates steroidal NMBAs at a 1:1 ratio, preventing them from binding to nicotinic receptors and removing them from the neuromuscular junction (NMJ) (1). Sugammadex is biologically inactive, and has no interaction with plasma proteins or acetylcholinesterase. In addition, it does not bind to muscarinic receptors, thus avoiding the adverse effects that are seen with the use of acetylcholinesterase inhibitors and the necessary administration of anticholinergics.

Previous studies revealed sugammadex to be capable of rapidly reversing profound rocuronium-induced NMB. When sugammadex was used in doses greater than or equal to 2.0 mg/kg with a shallow blockade, recovery to a train-of-four (TOF) ratio of 0.9 was achieved in approximately 2 min (2-8). However, these phase II studies were carried out in adults and not the pediatric population. This is a phase IIIA study investigating the efficacy and safety of sugammadex in both the adult and pediatric population, with infants aged 28 days to 23 months, children aged 2 to 11 years, adolescents aged 12-17 years and adults aged 18 to 65 years. The goal of the study was to determine a dose-response relationship of sugammadex (administered once the second twitch (T2) could be generated with a TOF stimulus) and reversal of NMB via rocuronium.

Methodology

This parallel-group, blinded, randomized, dose-finding, safety-assessor, multi-centre study was conducted at multiple centers throughout Europe. Ethics approval was granted by the Independent Ethics Committee at each research centre. The subjects were humans, and the study protocol followed the International Conference on Harmonization guidelines, the Declaration of Helsinki and Good Clinical Practice. Inclusion criteria for the study were as follows: between the ages of 28 days and 65 years inclusive; ASA class 1 or 2; scheduled for a general anesthetic expected to last at least 60 min with a single dose of rocuronium; undergoing a surgery in the supine position that allowed for adequate monitoring of NMB. Although this population is routinely seen in the OR, the study neglected to investigate sugammadex in neonates and the elderly. The following additional exclusion criteria were used: patients with known or suspected neuromuscular disorders, significant renal dysfunction or a family history of malignant hypothermia; patients who had taken part in any other trial during the 30 days preceding the current study; the use of any medications that interact with rocuronium; an allergy to general anesthetic medications; and patients who were pregnant, breast-feeding, or not using an effective contraceptive.

In order to determine adequate sample sizes, the authors simulated trials using SAS version 8.2 and the previous recovery times to a TOF of 0.9 observed in the adult studies.

The simulations, using n=5000, estimated that four subjects per dose group were necessary for a minimum power of 95% (i.e. a sufficient dose-response relationship could be observed in at least 95% of the 5000 simulations). With an estimate that 25% of participants would discontinue the study, each of the four age groups in each of the five dose groups would begin with 6 patients, bringing the total to 120. The actual number of patients in the all-subjects-treated group was 91, with 8 infants, 24 children, 31 adolescents and 28 adults. Due to protocol violations, only 85 patients were in the per-protocol group.

The experimental protocol was designed to test the hypothesis that a dose-response relationship exists between the administration of sugammadex and recovery of NMB caused by rocuronium. Anesthesia was provided with propofol and opioids, with caudal analgesia given to one child and all infants. The only inhaled anesthetic use was in children, if necessary for IV insertion. If a volatile was used, there was a mandatory 10 min washout period prior to giving rocuronium to prevent any neuromuscular blockade from the volatile. Following anesthetic induction, acceleromyography using the TOF-Watch SX system was used to monitor adductor pollicis activity. Acceleromyography was chosen because of its use in previous studies investigating sugammadex (2-8). An adequately detailed description of the default settings used and the stabilization procedure is provided in the paper. TOF stimulation was applied every 15 s with the data recorded onto a monitoring program. Neuromuscular monitoring continued for at least 30 min following the dose of sugammadex or placebo and ceased once anesthesia ended, or until a TOF ratio of at least 0.9 was attained. Additional monitoring included checking for inadequate reversal or reversal of blockade; oxygen saturation and pulse oximetry were also monitored for a minimum of 7 hours. However, clinical signs of neuromuscular function were not consistently checked in the PACU. Patients were randomized through a central randomization system to one dose of sugammadex at 0.5, 1.0, 2.0, or 4.0 mg/kg or placebo following the reappearance of T2 after 0.6mg/kg of rocuronium. The randomization was grouped by age with a fixed block size of five and was available online. The authors do not mention what was used as the placebo, but they do note how all agents were administered.

The primary efficacy endpoint for this study was the first time point of three consecutive TOF ratios of at least 0.9 following the administration of sugammadex or placebo. This TOF ratio was chosen as the endpoint as it is widely used as the minimum for return of normal muscle function. The time points to reach TOF ratios of 0.7 and 0.8 were also measured as secondary efficacy variables. A stable recovery was defined as a plateau following a TOF ratio of 0.8 or higher. In addition to efficacy, safety was also monitored using lab values, urinalysis, vitals, intra-operative ECG, and post-anesthetic physical exam. Adverse events were reported at the discretion of the investigator, who determined whether they were clinically relevant. Plasma samples were collected at 2 min following rocuronium, at the reappearance of T2, and at 2, 5, 15 and 60 min (or the end of surgery) following the dose of sugammadex or placebo. In order to investigate the pharmacokinetics of sugammadex and rocuronium, total plasma concentrations were subjected to validated liquid chromatographic assay methods using mass spectrometric detection.

Statistical analysis evaluated the data for both safety and efficacy. Safety was investigated using descriptive statistics for the "all-subjects-treated" group, which included all treated patients that were randomized to either sugammadex or placebo. Efficacy was explored in the "intent-to-treat" group (treated patients with a minimum of one post-baseline efficacy measurement) and the "per-protocol" group (intent-to-treat patients without any protocol violations). Weighted linear regression was used to interpret the efficacy data, which was broken down by dose and age groups, in order to explore the dose-response relationship of sugammadex. The following equation was used: "Estimated time to recovery of the TOF ratio to 0.9 = a + b.exp (c.dose)." a was the average subject's most rapid recovery time, b was the time difference between mean spontaneous recovery following placebo administration and mean recovery following an "infinitely large dose of sugammadex," and c was the degree of change in recovery time seen with sugammadex.

Results

The efficacy results from the adults, adolescents and children revealed a dose-response relationship in which the median time to a TOF ratio of 0.9 decreased as the dose of sugammadex increased. The data from the infant group was not sufficient to allow for interpretation. When sugammadex was given at 2.0 mg/kg, a minimum TOF ratio of 0.9 was reached in a median time under 2 min in all age groups, with shorter times seen in children and adolescents than adults, as predicted. Although it is stated that similar trends were seen with TOF ratios of 0.7 and 0.8, this data is not represented in table or graph form.

The safety data discusses adverse events, differentiating those attributable to surgery from those thought to be related to sugammadex. However, it is unclear how this distinction was made, as only one child out of the 9 who vomited after receiving sugammadex was included in the "possibly related to the study drug" category. In addition, the authors label certain adverse events as moderate or severe intensity, but they do not explain the rationale for these designations. In a table, an episode of bradycardia in an infant is classified as a "procedural complication,"

while in the text, it is considered to be possibly related to the placebo.

The data for the plasma levels of sugammadex and rocuronium is shown in graph form, revealing similar levels of sugammadex across all three age groups. One possible flaw is a variability of sampling time points for plasma rocuronium concentrations, with a caution from the authors that the values not be interpreted as absolute concentrations. This section of the paper concludes with an admission that data from this study is "sparse" and that it was added to data from other trials for further pharmacokinetic-pharmacodynamic investigation. However, the names of the other trials are not mentioned.

Discussion

This study revealed that in adults, adolescents and children, there exists a dose-response relationship between sugammadex administration at T2 and the reversal of rocuronium NMB. Although the results address the stated hypothesis and support this relationship, the authors admit that the limited sample sizes do not allow for any "firm conclusions" to be made. The small sample sizes also led to the use of median instead of mean values for recovery times to a TOF ratio of 0.90, in an attempt to reduce outliers. Despite these limiations, the results of this study are similar to those from two other phase II studies in adults (2,3). Although this is the first study to investigate safety and efficacy in the pediatric population, unfortunately the small sample sizes were too small due to sugammadex expiration dates. Therefore, no concrete dose-response relationship could be established in infants (n=1 or 2 for each dose group). Unfortunately, the small sample sizes in this study also limited the authors' ability to state any firm conclusions regarding the safety of sugammadex. They do, however, interpret the numerous adverse events to be unrelated to sugammadex, while one might argue differently. It seems that among patients with similar symptoms, some were attributed to sugammadex while others were explained by anesthesia or expected procedural side effects.

When the plasma (complexed plus free) concentration of rocuronium was measured up to 1 h following a dose of sugammadex, an increase was seen. This was not the case when placebo was administered, which is consistent with previous studies (2,9,10). The authors explain this increase in rocuronium plasma concentration by suggesting, as others do (9,10), that rocuronium shifts from the tissue compartment and NMJ to the plasma, where it complexes with sugammadex. This raises rocuronium's total plasma concentration while also establishing a diffusion gradient, leading to the creation of more plasma complexes and reversal of the NMB. However, an additional limitation lies in the methodology: while the half-life of sugammadex is about 100 min, blood samples were only taken up until 1 h, thus negating the possibility of a pharmacokinetic analysis.

Applicability

In the future, further studies are required to establish the safety and efficacy of sugammadex in the pediatric and elderly population. The efficacy of this drug in the context of profound NMB also calls for further investigations. However, as a newcomer to anesthesia, I was previously unaware of sugammadex and thus found this study to be a very informative introduction to a drug that has the potential to revolutionize future use of NMB reversal agents.

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Critical Appraisal Essay

By: **Tricia Doyle,** MD, PGY-1, Queen's Anesthesiology

Title of the Publication: ***"Effects of age and gender on intravenous midazolam premedication: a randomized double-blind study."***

Authors: ***Sun, G., Hsu, M., Chia, Y., Chen, P. & Shaw, F.***

British Journal of Anaesthesia 2008; 101: 632-639.

Introduction

Midazolam is a benzodiazepine medication commonly used in anesthesiology practice for its sedative, amnesic, and anxiolytic properties.1 Originally designed for perioperative use, midazolam in the intravenous (i.v.) form has the advantages of a relatively short half-life, quick onset and with little hemodynamic change or respiratory depression.1,2,3 It is effective as a preoperative anxiolytic, which favourably influences anesthetic induction, recovery from surgery and overall patient satisfaction of the surgical experience.4 Age and gender often have clinically relevant effects on the pharmacokinetics and pharmacodynamics of drugs and may be important considerations in midazolam administration. This paper offers a critical appraisal of a journal article by Sun et al.,5 who address the influence of age and gender on i.v. midazolam premedication. Reference information for the article is as follows:

Sun, G., Hsu, M., Chia, Y., Chen, P. & Shaw, F. (2008). Effects of age and gender on intravenous midazolam premedication: a randomized double-blind study. British Journal of Anesthesiology. 101: 632-639.

The institutions involved in the study are: Department of Anaesthesiology, Yuli Veterans Hospital; Institute of Neuroscience, Tzu Chi University; Department of Nursing, I-Shou University; Department of Anaesthesiology, Kaoshiung Veterans Hospital and Institute of Cognitive Science, National Cheng Kung University; all which are located in Taiwan, Republic of China.

Sun et al. identify excessive preoperative anxiety and the lack of knowledge on the potentially important effects of age and gender on midazolam premedication as the two problems that were incentive for their study. Similar to the journal title, the question asked is, "Do age and gender alter anxiety, sedation, and cardiorespiratory outcomes when administering two different doses of i.v. midazolam in the preoperative period of elective surgeries?" They hypothesize that age and gender will alter anxiety, sedation, and cardiorespiratory outcomes in midazolam premedication and that a lower dose of midazolam will be clinically effective without the side effects experienced at higher doses.

Background

Midazolam is a short-acting, water-soluble benzodiazepine medication that was first formulated in 1976 and whose pharmacology is relatively well understood compared to other anesthetic agents.6 Midazolam has an affinity for benzodiazepine receptors, which act as specific binding sites for gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Midazolam is commonly administered in the injectable form (intravenous or intramuscular),7 however use of oral midazolam has come into favour recently, particularly in the pediatric population.8 Midazolam has an onset of action in the i.v. form of 1.5-5 min and a half-life of 1-4 hours.7 Metabolism is through the CYP3A4 oxidation pathway in the liver and elimination is mostly through urine.7 In the central nervous system, midazolam reduces cerebral blood flow and cerebral metabolic rate.9,10 It produces dose-related central respiratory system depression,11 and minimal hemodynamic effects, mostly through a reduction in arterial blood pressure due to decreased systemic vascular resistance.[3] The labeled indications for midazolam are as a perioperative medication and in ICU sedation.7,12 The suggested i.v. dose for adults for preoperative sedation is 0.02-0.04 mg/kg; which can be repeated every 5 minutes as needed to a desired effect or up to 0.1-0.2 mg/kg.12 It is already recognized that particular caution should be exercised when dosing midazolam in the elderly population.

Though the pharmacology of midazolam has been thoroughly studied, Sun et al. found only a few published studies that investigated parts of their question. Bell et al13 were not able to identify those at risk for hypoxia according to age, gender and midazolam dose during premedication for upper gastrointestinal endoscopy. Fredman et al.14 found that i.v. midazolam in geriatric

patients undergoing transurethral procedures did not adversely affect mental and psychomotor recovery, though it did increase the incidence of having an SpO2 of less than 94%. Avram et al. 15 studied midazolam kinetics in two age groups of women and found little difference between the groups. Chen et al.16 investigated for sex differences in CYP3A activity, and though women showed significantly greater hepatic and intestinal activity, there was only a minor difference in the area under the curve analysis, which was felt to be clinically irrelevant. Klotz17 found no significant differences in the pharmacokinetics of midazolam between young and old patients, but did note that the elderly population demonstrated a significantly higher CNS sensitivity to midazolam.

To further the background search, a PubMed MeSH search was done using various combinations of the terms "midazolam [MeSH]," "preanesthetic medication [MeSH]," "age factors [MeSH]" and "sex[MeSH]." There was one article related to the question by Servin et al.18 who studied the pharmacokinetics of midazolam (though used as an induction agent in this case), in elderly and comparison groups and found that distribution volume was significantly increased in elderly compared to young subjects, total body clearance was significantly reduced in elderly compared to younger men, though not for women, and that midazolam plasma protein binding was not influenced by age.

The background search continued using the "related articles" function in PubMed, which, only returned one applicable study by Parlak et. al.19 who compared midazolam versus propofol for cardioversion sedation in two different age groups and found that older participants required less medication to acquire the same sedation level of the younger group.

From this search, we have some evidence of that there is an influence of age and gender on the pharmacology of midazolam, however, I agree with the authors that this information is sparse, inconclusive and that it is difficult to determine how clinically relevant the information is. There appears to be more data on the effects of age and gender on intramuscular midazolam premedication, in particular, a study by Nishiyama et al.,20 who had a similar study design to Sun et al., but who used the intramuscular form of midazolam. In this study, they found that age, but not gender, affected the i.m. dose for midazolam premedication.

Methodology

This study recruited 360 patients undergoing elective surgery from one large Taiwanese general hospital, organized them into groups according to their age and gender, and then randomized them to two different doses of midazolam. Outcome measures of anxiety and sedation level, heart rate (HR), respiratory rate (RR), mean blood pressure (MBP) and oxygen saturation (SpO2) were performed prior to and fifteen minutes after the administration of intravenous midazolam. The study design was experimental, randomized and double-blinded, and outlined in enough detail to be reproducible. All of these factors support the validity of the study.

The authors explicitly outlined the independent and dependent (outcome) variables.
All patients in the study were undergoing elective surgery, though the type and distribution of types of surgery across age and gender weren't specified. Height and weight of each patient were determined. The study group was divided into male and female, and then stratified by age (young :20-39, middle-aged: 40-59, and elderly 60-79), creating a total of 6 groups. Sixty patients were chosen for each group and then randomized by computer-generated numbers to doses of either 0.02 or 0.06 mg/kg of i.v. midazolam. Assessments of anxiety were done by a visual analogue scale. Sedation depth was measured using the Observer's Assessment of Alertness/Sedation. The authors note that these scales have been previously validated by other studies. The assessments were performed by a blinded co-investigator in the surgical holding area, who also monitored vital signs (HR, RR, MBP, SpO2) throughout the experiment. An anesthesiologist administered either dose of midazolam to each patient intravenously. The patient was blinded to the dose of midazolam that they were receiving, and each would receive the same volume of solution, diluted appropriately.

Exclusion criteria for the study were patients with the following characteristics: 1. ASA class greater than II, 2. Pregnancy, 3. Psychiatric disorders and/or taking antipsychotics, 4. Using β-blockers or calcium channel blockers, and 5. Hypersensitivity or allergy to midazolam. These exclusion criteria are likely for safety purposes and to prevent confounding the pharmacology of one-time midazolam administration by other medications or comorbidities.

The hospital's ethics committee had approved the study and informed patient consent was obtained for all participants. The human population study, I believe, was justified due to the longstanding safety record of midazolam and its common use already in anesthesia practice, as well as the investigators attention to safety.

Statistical analysis was performed as follows:

- Sample size was determined using a Cohen's table for medium sized effect for six groups using ANOVA with α=0.05 and a power of 0.80.
- Patient characteristics were compared using independent sample t-tests

- Means, ranges and standard deviations for physiological and neurophysiological data before and after midazolam premedication were calculated and organized into histograms. This allowed for easy visual comparison of for each variable.
- Differences in outcomes of each group and their interactions were measured using ANOVA, appropriate for comparison of a continuous variable across different levels of one or more categorical variables (young, middle-aged, elderly, male and female). This was followed by additional post hoc comparisons.
- Correlation of all independent and dependent variables were determined using Pearson correlation (r), where age and gender were expressed this time as continuous variables, assigning gender classification as male, 1 and female, 2.
- Differences in all measures pre-midazolam and post-midazolam were determined by simple subtraction of the post-test score minus the pre-test score.
- Regression analysis was performed between age and all outcome measures.
- Scatterplots were created to show the changes in the correlation between heart rate and mean blood pressure by midazolam according to age and gender factors, to determine if they were independent factors.
- A $P<0.05$ was used as the definition for statistical significance, a universally accepted standard.

Results

Sample size:
Sample size using Cohen's table for medium-sized effect for ANOVA with 6 groups was determined to be 210. Consent was obtained from 389 patients, and 29 were excluded according to criteria. The patients were divided into groups of 30 according to age and gender. It is curious that there were 360 patients that ended up being divided equally into groups of 30 according to age and sex, and details are not provided on how this was obtained.

Patient characteristics:
The authors present the patient characteristics in table form for each group. Included are age presented as a mean and range as well as height and weight, presented as mean and standard deviation. The results of the t-test were not presented in the results section, and they did not comment on the similarity of patient characteristics among groups. There are likely other patient characteristics that vary amongst the different age groups, including other medications taken and premorbid conditions, however this would have greatly complicated the analysis. Authors also did not specify the ethnic origin of the participants, nor the type of surgery they were undergoing.

General:

- Almost all patients (98.9%, n=356), suffered from some level of anxiety in the preoperative period.
- Satisfactory sedation was achieved after midazolam administration in 87.5% of patients.
- Anxiety was significantly decreased after midazolam administration in all age groups ($P<0.0001$).
- A reduction in MBP was observed in all age groups with after midazolam administration.
- No correlation was observed in HR changes before and after midazolam administration.
- RR increased after midazolam administration in all groups.
- Decreased SpO2 correlated with increased RR after midazolam administration.
- A compensatory pattern was found between HR and MBP before midazolam administration.

Age relationships:
- All outcome parameters changed with statistically significantly correlation in parallel with age according to regression analysis.
- Younger patients had higher anxiety scores both before and after midazolam administration.
- Deeper sedation levels were found in older compared to younger patients ($P<0.01$).
- HR had a negative correlation with age both before and after midazolam administration ($P<0.01$).
- SpO2 level had a negative correlation with age both before and after midazolam administration ($P<0.01$).

Gender relationships:
- Women had higher anxiety levels before and after midazolam premedication compared to men ($P<0.01$).
- Deeper sedation levels were found in men compared to women ($P<0.01$).
- MBP was significantly lower, and HR significantly higher in women compared to men (P's <0.0001) both before and after midazolam administration.
- RR was significantly higher in women compared to men before midazolam administration ($P<0.05$).
- Women had higher SpO2 levels compared to men before and after midazolam

Dosing relationships:
- No significant differences were found in anxiety levels between the two doses of midazolam ($P>0.05$)
- Sedation was more pronounced in the group receiving 0.06 mg/kg compared to 0.02 mg/kg.
- MBP decreases significantly with increased midazolam dose ($P<0.01$)
- HR was not significantly affected by dose ($P=0.66$).
- RR showed a significant increase with increased midazolam dose ($P<0.01$).

- SpO2 was negatively affected by increased midazolam dose (P=0.05).
- There was a higher incidence of apnoea in the 0.06 mg/kg group

Discussion

The authors conclude that age and gender have clinically relevant effects on neuropsychological and physiological parameters in midazolam premedication. They claim that they are providing new and valuable information and that their results support their original hypothesis. I am mostly satisfied with this conclusion as they indeed showed statistically significant differences in many categories: higher anxiety levels overall amongst the young and females, lower MBP before and after midazolam in the female group, higher SpO2 values before and after midazolam in women and the young, and higher RR in women before midazolam. The results obtained are mostly consistent with previous studies looking at age effects,14,17,18,19,20 with the exception of the study by Bell et al.;13 but not necessarily consistent with studies examining gender effects.15,16,20 According to the results by Sun et al., it is difficult to appreciate whether the gender and age influences are from innate physiology differences amongst the groups, or from differences in the pharmacokinetics and pharmacodynamics of midazolam.

The authors postulate that age differences may be due to an increased sensitivity to midazolam in older patients, producing a deep sedation effect and worsening MBP and SpO2. They also note the likely contribution of age-related decreases in baroreceptor sensitivity, age-dependent changes in basal sympathetic nerve activity, and a decrease in systemic vascular responsiveness to the age differences. The authors thought that the gender differences they observed may have been due in part to the endogenous activity of hormones in females, particularly estrogen and progesterone, which could possibly influence GABA receptors. Though these are all possible reasons for differences among gender and age, these cannot be verified with this study, and prior evidence for these explanations are unclear.

The authors were successful in confirming previously studied concepts: that midazolam produces a significant decrease in anxiety levels, adequate sedation, dose-dependent decreases in MBP and SpO2 and dose-dependent increases in RR.1,2,3,4

I am satisfied with the validity of the study, as it is a double-blinded, randomized control trial with well-defined independent and outcome variables. It would be easily reproducible, could potentially be done in a regular clinical setting, and has an adequate sample size. The study design is compatible with the pharmacology of midazolam. The validity could be improved with a larger sample size and if it were a multi-centre trial and amongst different races, to decrease the chances of selection bias. A comparison with a placebo medication as well as intermediate dosages may also have been helpful. The results of this study may be generalized only to patients aged 20-79 undergoing elective surgery, therefore the study would not be applicable to a large portion of the population in the <20 and >79 age range, and those undergoing more emergent surgery.

This study also claims that it provides evidence for the advantages of a smaller dose of midazolam for premedication, where midazolam at 0.02 mg/kg produced sufficient anxiolytic and sedative effect without the risk of apnea and excessive sedation that they observed at 0.06 mg/kg. The ill-effects of higher doses of benzodiazepines had been previously determined.7,12

Applying the premedication routine described by Sun et al. to centres in this area would be difficult, as patients often do not have i.v. access until immediately before their surgery, and may not have appropriate monitoring, especially for the elderly, prior to their surgery. Often, in this centre, benzodiazepines will be given in the oral as opposed to the i.v. form for premedication. The study by Sun et al. would allow our centre to have a greater appreciation for the influence of age and gender on i.v. midazolam premedication, but does not provide further guidance on how midazolam dosing should be adjusted according to these factors. Clarification of dosing recommendations as well as comparison of the gender and age influences with different routes of administration of midazolam are both areas for future work surrounding this question.

Conclusion

Sun et al. have conducted a randomized, double-blind study that provides statistically significant evidence confirming the hypothesis that age and gender produce differences in neuropsychological and physiological responses after i.v. midazolam premedication. They also confirm that a dose of 0.02 mg/kg of midazolam achieves adequate anxiolysis and sedation in the preoperative period. The information that they provide allows for a greater appreciation of the influence of age and gender on benzodiazepine premedication. It remains to be determined how we can adjust anesthesiology practice to allow for the influence of these factors.

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Critical Appraisal Essay

By: **Yasser M. Hayat,** MD, PGY-1, Queen's Anesthesiology

Title of the Publication: ***"Early Goal-Directed Therapy In The Treatment Of Severe Sepsis And Septic Shock"***

Authors: ***Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group.***

N Engl J Med. 2001 Nov 8;345(19):1368-77.

I will review the article that was published in The New England Journal of Medicine, November 8, 2001, Volume 345, Number 19, titled, "EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK" by Rivers et al. I will use following broad questions as a framework to carry out the critical appraisal of this article:[1]

1. Are the results of the study valid?
2. What are the results?
3. Are the results applicable in the day to day clinical practice?

Are the results of the study valid?

In this study the authors wish to examine "whether early goal-directed therapy before admission to the intensive care unit effectively reduces the incidence of multi-organ dysfunction, mortality, and the use of health care resources among patients with severe sepsis or septic shock."[2]

First step in determining the validity of the study is to assess if the study identifies a clear issue that needs to be addressed. The authors of this study clearly state their objective as to evaluate the efficacy of early goal-directed therapy in patients presenting with severe sepsis or septic shock. They specifically mention that the reduction in mortality is their primary efficacy outcome. Secondary outcomes include the resuscitation end points, organ-dysfunction scores, coagulation-related variables, administered treatments and the consumption of health care resources. Their population of interest is the patients presenting with severe sepsis or septic shock. The authors state that the study has been conducted under the auspices of an independent safety, efficacy and data monitoring committee.

The authors discuss the findings of their literature search while looking for an answer to their questions. Some studies have based their therapeutic targets on pathogenic changes in patients as they transition from systemic inflammatory response syndrome (SIRS) to severe sepsis and septic shock, with several hours delay in the interventions. Some other studies have focused on goal directed hemodynamic optimization, but have failed to offer significant benefits in terms of outcome.[3] The authors identify that the transition from SIRS to severe illness and shock occurs in critical "golden hours". This is the critical period that is the focus of their intervention protocol.

This study states the inclusion criteria appropriately - the fulfillment of two of four criteria for the systemic inflammatory response syndrome (SIRS) and, a systolic blood pressure no higher than 90 mm Hg or a blood lactate concentration of 4 mmols per liter or more. All adult patients presenting to a tertiary care hospital with sepsis syndrome, severe sepsis or septic shock during March 1997 through to March 2000 were assessed for possible enrollment in the study. The exclusion criteria include age of less than 18 years, pregnancy, the presence of an acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhytmias (as a primary diagnosis), contraindication to central venous catheterization, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, a requirement for immediate surgery, uncured cancer, immuno-supperssion (organ transplantation or systemic disease), do not resuscitate status, or advanced directives restricting the implementation of the study protocol. The review of the exclusion criteria makes me think that the confounding is highly unlikely.

Randomization is another important element that needs to be present in a study as it eliminates bias in the participant assignment. In determining the validity of a study, a review of the randomization process is required. The study under review is prospective randomized study that was approved by the institutional review board. Written informed consent of the patients was appropriately obtained and patients were assigned to early goal-directed therapy or to standard (control) therapy through computer generated randomization process.

This study also meets the criteria of a blind study as the patients and researchers were not aware of the patient assignments to a particular treatment group. The clinicians who initially assessed the patients were unaware of the patient's treatment assignments. The study group assignments were through randomly assorted envelopes that were opened by a hospital staff member who was not one of the study investigators. Critical care clinicians, who assumed the care of all the patients after initial six hours, were unaware of the patients' group assignments.

For the results of a study to be valid, it is also important that all the participants of the study are accounted for. By assuming a rate of refusal or exclusion of 10 percent, a two-sided type I error rate of 5 percent, and a power of 80 percent, our authors calculated a sample size of 260 patients to be adequate. The study enrolled 263 patients and all were included in the intention to treat analysis. 130 were randomly assigned to early goal directed therapy of which 13 patients did not complete first 6 hours of therapy and 133 patients to standard therapy of which 14 did not complete 6 hours of therapy. The study adequately explains the reasons as to why 27 patients did not complete the initial six hours of the study.

The review of base line characteristics of the patients in two arms of study shows no significant difference between the early goal-directed therapy group and standard therapy (control) group. Adequacy and duration of antibiotic therapy, vital signs, organ-dysfunction scores, and coagulation related variables were similar in the two study groups at the baseline. Patients in both groups had cardiac monitoring, pulse oximetry, urinary catheterization, arterial and central venous catheterization. Patients in standard therapy group (control) were treated with standard treatment protocols to achieve resuscitation end points (CVP ≥ 8-12 mm Hg, MAP ≥ 65 mm Hg and Urine output ≥ 0.5 ml/kg/hr). After blood and urine specimens were obtained for cultures, antibiotics were administered at the discretion of the treating clinicians. The patients assigned to early goal directed therapy group had their central venous oxygen saturation (Scvo2) continuously monitored and included as an additional resuscitation end point in addition to the ones in the standard therapy group. As a part of early goal directed therapy treatment protocol, the patient in this group received a 500 ml bolus of crystalloid every 30 minutes to achieve a CVP of 8 to 12 mm Hg. If the MAP was less than 65 mm Hg, vasopressors were given to maintain a MAP of at least 65 mm Hg. If MAP was greater than 90 mm Hg, vasodilators were given until it was 90 mm Hg or below. If Scvo2 was less than 70 percent, red cells were transfused to achieve a hematocrit of at least 30 percent. After the CVP, MAP and hematocrit were optimized, if the Scvo2 was less than 70 percent, dobutamine was administered at a dose of 2.5 μg/kg/minute, a dose that was increased by 2.5 μg/kg/minute every 30 minutes until the Scvo2 was 70 percent or higher or until a maximum dose of 20 μg/kg/minute was administered. Dobutamine was decreased in dose or discontinued if the MAP was less than 65 mm Hg or if heart rate was above 120 beats per minute. To decrease oxygen consumption, patients in whom hemodynamic optimization could not be achieved received mechanical ventilation and sedatives.[2]

What are the results?

In the above section, I used critical appraisal screening tools to establish that the results of the research by Rivers et al. are likely valid. Before reviewing the actual results, I will carry out a review of their method of data collection and data analysis to determine that if their findings have clinical significance. The study states that the patients' vital signs and resuscitation end points were continuously monitored and recorded for the first 6 hours, and then assessed every 12 hours for 72 hours. Their arterial and venous blood gases values, lactate concentrations, coagulation related and clinical variables were all used in the determination of the Acute Physiology and Chronic Health Evaluation (APACHE II) score (on a scale from 0 to 71), the simplified Acute Physiology Score II (SAPS II, on a scale from 0 to 174), and the Multiple Organ Dysfunction Score (MODS, on a scale from 0 to 24). These scores were obtained at baseline (0 hours) and at 3, 6, 12, 24, 36, 48, 60, and 72 hours. A higher score for each category indicated more severe organ dysfunction.[2] Patients were followed for 60 days or until mortality. I feel that the primary and secondary efficacy outcomes are clearly stated and all the variables that should have been measured were adequately measured and nothing significant was left out.

I also feel that the authors have adequately explained the rationale that to detect a 15 percent reduction in in-hospital mortality requires a sample size of 260. Against which the study actually enrolled 263 patients. Kaplan-Meier estimates of mortality, along with risk ratios and 95 percent confidence intervals, were used to describe the relative risk of death. The two study groups were tested by the use of the appropriate statistical tools such as t-test and chi-square test to determine any differences. Incremental analyses of the area under the curve were performed to quantify differences during the interval from base line to six hours after the start of treatment. An independent, 12 member external safety, efficacy, and data monitoring committee reviewed interim analyses of the data at predetermined intervals and made recommendations for the trial to be continued. The authors appropriately determine a P value of 0.04 or less to indicate statistical significance.[2]

Now that we have established that the data collection and analysis were adequately addressed in this study, next step is to find out if the research provides answer to the question – early goal-directed therapy reduces incidence of mortality, which is this study's primary goal. The secondary aims include reduction in multi-organ dysfunction, meeting resuscitation end points targets and the use of health care resources. In hospital mortality was 30.5 percent in the patients in early-goal directed therapy group as compared with 46.5 percent in the patients assigned to standard therapy (P=0.009), this is significantly lower. The combined hemodynamic goals for central venous pressure, mean arterial pressure, and urine output were achieved in 86.1 percent of the standard therapy group, as compared with 99.2 percent of the early-goal directed therapy group (P<0.001). With in 7 hours to 72 hours interval, the mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal directed therapy than in those assigned to standard therapy (P<0.001). In the patients who survived to hospital discharge, those assigned to standard therapy had stayed a significantly longer time in the hospital than those assigned to early goal directed therapy (18.4±15.0 vs. 14.6±14.5 days, P=0.04).

Are the results applicable in the day to day clinical practice?

Having reviewed the study's results and their validity, the next question is whether the study's results are transferable and can be applied to day to day clinical settings. The significant reduction in mortality in early-goal directed therapy group means better patient out comes and translates into standard of care. I feel that the results of this study are easily transferable to similar patient population elsewhere and with relative ease as the patients presenting with severe sepsis and septic shock share similar characteristics. The reduction in in-hospital stay also means that the early-goal direct therapy optimizes the use of health care resources. The study was conducted in the emergency department of an academic tertiary care hospital and can very easily be implemented in any tertiary care hospital in Canada as the equipment and skills required are quite often already in place.

In general, I feel that the study by Rivers et al. meets the criteria set out in the critical appraisal of the medical research framework. Authors asked a clear question, followed appropriate research protocols in data collection, data analysis was carried out to clearly identify the significance of the results. The treatment protocol supported by their study is easily transferable to clinical setting elsewhere. In fact I had an opportunity to observe the successful use of early-goal directed therapy protocol in the emergency department and later in the intensive care unit of Kingston General Hospital. I will definitely use early-goal directed therapy protocol for the better outcome for my patient during my intensive care rotation or as a clinician down the road.

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Critical Appraisal Essay

By: **Karen Wong,** MD, PGY-1, Queen's Anesthesiology

Title of the Publication: ***"Identification of Patients at Risk for Postoperative Respiratory Complications Using a Preoperative Obstructive Sleep Apnea Screening Tool and Postanesthesia Care Assessment"***

Authors: ***B.Gali, F.X. Whalen, D.Schroeder, P.C. Gay, D.J. Plevak.***

Anesthesiology 2009;110:869-77.

Background:

The purpose of this study is to use a two-phase screening tool perioperatively to identify patients who are at risk for obstructive sleep apnea (OSA). OSA is defined by complete cessation of airflow (apnea) or reduced airflow (hypopnea) for greater than 10 seconds during sleep. Currently, sleep-disordered breathing affects up to 9% of middle-aged women and 24% of middle-aged men1. Despite increased vigilance for diagnosing OSA, only about 15% of men and women with OSA are diagnosed, and many of these undiagnosed patients present for surgery. The gold standard for diagnosing OSA is polysomnography, and patients are assigned an apnea-hypopnea index based on the severity of their disease (AHI 5-15 mild, 15-30 moderate, >30 severe). Patients with OSA not only present with intermittent airway obstruction, which is made worse by anesthetic agents, but they commonly have cardiovascular co-morbidities including coronary artery disease, arrythmias, pulmonary hypertension, stroke and dilated cardiomyopathy. Moreover, airway management is also more difficult in OSA patients than in healthy patients2. A case-control study by Gupta et al. shows that 24% of OSA patient had postoperative complications versus 9% in the control group3.

Despite the prevalence of OSA, its impact on the perioperative course and the fact that many patients are undiagnosed and untreated, there is a deficit in the knowledge of how to identify and manage these patients perioperatively. The practice guidelines by the ASA in 2006 recommend a careful preoperative evaluation of patients at risk for OSA, in addition to minimizing systemic opiods, as well as close monitoring in the postoperative period4. In terms of preoperative screening, many clinical assessment tools for OSA are available, however, their specificities for predicting which patients have increased risk in the post-operative period are poor. Therefore, the authors in this study would like to know whether combining a clinical assessment tool preoperatively, with observation of adverse events in the post-anesthetic unit, can better predict which patients are more likely to experience post-operative adverse events.

Study Design:

This single-center, prospective cohort clinical trial enrolled patients who presented to preoperative evaluation in the Mayo Clinic (Rochester, Minnesota) from October 2005 to September 2007. Inclusion criteria were patients scheduled for surgery requiring at least forty-eight hours hospital stay postoperatively and have not been diagnosed with OSA. 693 patients met criteria and consented to the study. All patients were evaluated with the Flemons criteria preoperatively, which incorporates neck circumference, history of hypertension, snoring, and obstructive symptoms during sleep, to generate a probability of sleep apnea. It is used widely in the outpatient setting, and its sensitivity is 76% with a positive predictive value of 77%, which is comparable to other models. Each patient is associated with a sleep apnea clinical score (SACS), and a score greater than 15 has a posttest probability of 81% for OSA.

On the day of surgery, all clinical care providers were blinded to the patient's SACS, and anesthetic management was under the discretion of the attending anesthesiologist. Postoperatively, patients were monitored continuously in the PACU with data recorded every 30 minutes for 3 periods (total 90 minutes). The patients were assessed for apnea, bradypnea, desaturations and pain-sedation mismatch. The occurrence of more than one event during 2 or more assessment periods would be considered to have recurrent PACU events. Once discharged from the PACU, all patients were monitored for 48 hours with pulse oximetry, and the oxygen desaturation index (ODI), which is the average number of oxygen desaturations of 4% or more below baseline per hour, was recorded. An ODI greater than 10 (ODI>10) is found to have sensitivities of 71-85% and specificities of 90-95% for sleep-related disordered breathing. In this study, ODI is a marker for clinically significant desaturations rather than a diagnostic tool.

One of the primary endpoints of the study is cardiorespiratory complications (including ischemia and

infections) and thus patients were followed during their entire hospital stay to monitor for these adverse events. The other primary endpoint is the ODI, as the authors were also interested in whether their screening tool can identify those patients at risk for significant desaturations. The endpoints were analyzed with multiple logistic regression and analysis of covariance for continuous outcomes with two explanatory variables that were generated from the two-phase screening: SACS (high vs. low) and recurrence of PACU events (yes vs. no). No interactions between these two variables were detected. In addition, patients who experienced intraoperative events leading to prolong ventilation were excluded from final analysis, but all 693 patients were included in the analyses. The study is appropriately powered (80%) to analyze the two explanatory variables and the effect size of 10% difference between the groups is also clinically significant.

Results

The patient characteristics between the SACS groups were compared by the two-sample t test and chi-square test. The high SACS group had significantly higher BMI, neck circumference and blood pressure, which directly correlate with their Flemons score The Flemons score was also analyzed between the two groups, which, as expected, is significantly different. There were more patients in the low SACS group (472 vs. 221), and significantly more males (86% vs 43%) in the high SACS group, which reflects the higher prevalence of OSA in males. Not surprisingly, the high SACS group has a significantly higher proportion of patients in the higher ASA classes, likely secondary to a higher prevalence of other comorbidities. There was no difference in age, type and duration of anesthesia between the groups, which suggests that blinding was effective. Far more patients received a general anesthetic (86%) versus a regional technique (14%) in this study. The association of SACS and events in the PACU were analyzed, which showed a significantly higher proportion of patients had episodes of desaturations in the high versus low SACS group (13% vs. 4%). Surprisingly, the high SACS group did not demonstrate increased epidsodes of hypopnea, apnea, and pain-sedation mismatch, which would correlate with OSA.

Postoperative outcomes, including the mean ODI, ODI>10, cardiac, respiratory and any major hospital events, were compared using SACS and PACU events as independent explanatory variables. The ODI was analyzed over the first 24 hour as well as the entire duration of oximetry monitoring (between 37-39 hours for both groups), presumably because there may be delayed respiratory depression in OSA patients. SACS was found to be significantly associated with higher mean ODI and occurrence of ODI>10 in both the 24 hour and entire observation period. Recurrent PACU events was also associated with higher mean ODI and likelihood of experiencing ODI>10, but not in the first 24 hours. A total of 33 patients had respiratory events, which is a sufficient number to analyze the two explanatory variables, and both were found to be significantly associated (odds ratio were 3.5 and 21.0 for SACS and PACU events, respectively). Any major hospital events were also found to be associated with high SACS and recurrent PACU events, but there was no mention of what these events were and whether they include cardiac and respiratory events, which were already accounted for in the analysis. Cardiac events were not found to be associated with SACS and recurrent PACU events; however, only 13 events were observed in total, which is not enough to determine a statistical correlation.

Incidences of postoperative respiratory complication were compared between four groups based on SACS (high vs. low) and recurrent PACU events (yes or no). This is found to be highest in the groups with recurrent PACU events (high SACS, 33%; low SACS, 11%) than those without (high SACS, 2%; low SACS, 1%). No statistics was performed on this data set and the number of patients per group is disproportionate (52 vs. 91 vs. 169 vs. 381 patients), but the finding that high SACS combined with recurrent PACU events present the biggest risk for respiratory events supports the hypothesis of the study. Furthermore, recurrent PACU events are associated with a higher odds ratio, suggesting that it is a stronger risk factor. This is not unexpected since PACU events in the immediate postoperative period could be the beginning of a spectrum of respiratory complication, or may be the inciting event leading to further complications. Finally, the outcomes were re-analyzed after adjusting for age, BMI and sex. The ODI results were the same as before, however, SACS was no longer associated with postoperative respiratory complication but recurrent PACU events continued to be. The authors made the appropriate observation that the number of respiratory complications was not sufficient to analyze five variables; however, since SACS is also associated with both BMI and sex, this also contributes to the lack of association after adjusting for those variables.

Discussion

The authors conclude that using a clinical sleep apnea score in conjunction with PACU assessment can help identify patients that are at higher risk of post-operative complications and higher ODI, and thus require closer monitoring. The methodology and data analyses of the study appear to be sound, however the data collection for postoperative outcomes is less clear. Specifically, there is no mention whether the in-hospital follow-ups were done in a blinded fashion. Although the study emphasizes that both SACS and recurrent PACU events correlate with post-operative complications, it seems that PACU events alone can be predictive of this, especially

since SACS showed no association with postoperative respiratory events after adjusting for baseline characteristics. In fact, data comparing the four groups showed that recurrent PACU events results in much greater incidence of respiratory complications regardless of SACS. Hence, despite the fact that SACS associates with higher ODI across all analyses, the clinical significance is not apparent in terms of postoperative consequences, which is what the authors were most interested in. It may be worthwhile to determine the relationship between ODI and postoperative complications in future studies, whether having ODI>10 increase the risk of morbidity postoperatively.

Overall, the study does not add to the knowledge of how to best screen for these patients in a preoperative setting so that timely interventions can be made to improve perioperative outcome. In a similar study in 2008, Blake et al also found that patients who are at risk for OSA are also at increased risk for postoperative hypoxemia and recommended that patients suspicious of OSA be monitored closely5. In addition, many models and questionnaires have been developed to aid anesthesiologists in identifying patients who are at risk for increased perioperative morbidity secondary to their undiagnosed OSA6. In particular, the ASA taskforce has developed a checklist composed of predisposing features and symptoms of OSA for clinician to use in their assessments. The sensitivity is found to be as high as 87.2% for patients with an AHI greater than 30. The biggest problem with this study, however, is using PACU assessments as a means of identifying at-risk patients, which seems to be a self-fulfilling prophecy since the patient is already experiencing a postoperative respiratory event. Moreover, the SACS does not seem to predict at-risk patients any better than the sex and BMI of the patient. The study, however, does confirm what is already known about patients with OSA characteristics, that they are more likely to have desaturations, which would warrant closer monitoring, oxygen supplementation, and minimizing narcotics. What this study brings to light is the importance of monitoring patients who have OSA features and have had difficulties in the PACU closely, as they have all the reasons to be at an increased risk for adverse respiratory outcomes.

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