Queen’s University
26th Annual Anesthesiology Research Day

Scientific Program Coordinators:

Ian Gilron, MD, MSc, FRCPC

Elizabeth Vandenkerkhof, RN, MSc, DrPH

Scientific Adjudicators:

Khem Jhamandas, PhD  Joel Parlow, MD, MSc, FRCPC  François Donati, MD, PhD, FRCPC (Guest)

Queen’s Anesthesiology Residency Program Director:

Melanie Jaeger, MD, FRCPC

Queen’s Anesthesiology Department Head:

John Cain, MD, FRCPC

Postgraduate Medical Secretary:

Mrs. Kim Asselstine

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Queen’s University 26th Annual Anesthesiology Research Day

SCIENTIFIC PROGRAMME

0900 – 0910 Opening Remarks - Dr. John Cain

0910 – 0920 Introduction - Dr. Ian Gilron

0920 – 1000 Dr. Jacalyn Duffin, Hannah Chair, History of Medicine, Queen’s University
“How historical research parallels (and enhances) biomedical research”

1000 – 1015 Dr. Bethann Meunier, PGY-5
“Personal protective system (PPS) and endotracheal intubation: ‘It’s about time’” (research update)

1015 – 1030 Dr. Mark Odrcich, PGY-4
“Chronobiological characteristics of neuropathic pain: Diurnal pain variation and effects of analgesic therapy” (data presentation)

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

1100 – 1115 Ms. Noufissa Kabli, BSc, MSc Candidate (Pharmacology & Toxicology)
“Behavioural and Molecular Approaches to Study Peripheral Delta Opioid Receptors in a Model of Neuropathic Pain” (data presentation)

1115 – 1130 Dr. Jack McGugan, PGY-4
"Development of an electronic data entry tool for transesophageal echocardiography" (research update)

1130 – 1145 Dr. Cara Reimer, PGY-2
“Alpha-2-delta calcium channel subunit expression in rat spinal cord after administration of opiates” (research proposal)

1145 – 1200 Dr. Jay Ross, PGY-4
“Resident and Staff Perceptions of Changing from a 24 Hour to a 14-16 Hour Call Schedule” (research update)

1200 – 1300 ** Lunch (provided) **

1300 – 1315 Dr. Robert Tanzola, PGY-4
“Novel use of an uncuffed endotracheal tube in Obstetrics” (case report)

1315 – 1330 Dr. Angela Northey, PGY-3
"Correlation of Pre-operative Warfarin Treatment and Bleeding Tendencies: a Retrospective Review in Cardiac Surgery Patients" (research update)

1330 – 1345 Ms. Sarah Holdridge, BSc, MSc candidate, (Pharmacology & Toxicology)
"The central role of the delta opioid receptor in neuropathic allodynia” (data presentation)

1345 – 1400 Dr. Gillian Ramsey, PGY-4
"The effects of intraperitoneal ketorolac on postoperative pain following laparoscopic cholecystectomy” (research update)

1400 – 1430 ** Poster presentations** (see list below) and coffee break **
1430 - 1445  Dr. Jason Erb, PGY-2
"The relationship between evoked versus spontaneous pain and peak expiratory flow after laparoscopic cholecystectomy" (research proposal)

1445 - 1500  Ms. Kelly Smith, BA, MA Candidate (Psychology)
“The relationships of men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/ CPPS): A multiperspective approach” (research update)

1500 - 1515  Dr. Sean Hall, PhD, Postdoctoral Fellow (Physiology)
“Reserpine Prevents Cardiac Dysfunction after Intracranial Hypertension in Rats” (data presentation)

1515 - 1530  Mr. Maneesh Deshpande, MSc, MD Candidate (Queen’s Medicine)
“Impact of therapy on quality of life and mood in neuropathic pain: What is the effect of pain reduction?” (data presentation)

1530 - 1545  Dr. Sumit Sharan, PGY-3
"Cervical spine movement during laryngoscopy: objective assessment and comparisons of indirect fiberoptic and prismatic laryngoscopes” (research update)

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

The Judges will be:
Dr. François Donati, Director of Research, Department of Anesthesia, Université de Montréal
Dr. Khem Jhamandas, Professor, Queen’s Depts. of Anesthesiology and Pharmacology & Toxicology
Dr. Joel Parlow, Associate Professor, Queen’s Depts. of Anesthesiology and Pharmacology & Toxicology

1545 * * * Guest Speaker: Dr. François Donati, Director of Research, Department of Anesthesia, Université de Montréal
“So, you want to publish?”

1830 Cocktails and Dinner (River Mill Restaurant)
* * * Presentation of awards following dinner * * *

Poster Presentations

Mr. James Jeong, BSc, MSc Candidate (Pharmacology & Toxicology)
"A Behavioral and Biochemical Analysis using Ultra Low Doses of Naltrexone in a model of Neuropathic Pain”

Ms. Amanda Green, BA (Psychology)
“The Role of Catastrophizing in Pain Communication and Empathy: Exploring the links between rating accuracy & internal representation of pain”

Ms. Shannon Parker, V.T., Research Assistant. (Pharmacology & Toxicology)
“The effects of chronic morphine and methadone on mu- and delta-mediated antinociception”

Ms. Glory Prupas, BSc, MSc Candidate (Pharmacology & Toxicology)
"Blockade of Spinal Morphine Tolerance with Ultra-low Doses of Opioid Receptor Antagonists: Behavioural and Biochemical Studies”

Ms. Anna Taylor, BSc Candidate (Pharmacology & Toxicology)
“Enhanced delta opioid receptor-mediated antinociception following prolonged morphine: The role of spinal glial activation”
Personal protective systems (PPS) and endotracheal intubation: “It’s about time”.

B.D. Meunier, J. Murdoch, L. Patterson, J.E. Zamora

Background: The global outbreak of severe acute respiratory syndrome (SARS) in 2003 has resulted in more stringent infection precautions for health care workers (HCW)- the “New Normal”. The SARS associated coronavirus (SARS-CoV) has been found to spread via droplet and direct contact, infecting hosts primarily via respiratory and ocular mucosa. The virus may remain infectious outside of the body for up to 48-72 hours.1 The “New Normal” for intubating a low-risk patient includes eye protection, gloves, and N95 mask (gown if anticipate exposure to body fluids). Intubation of patients diagnosed with severe respiratory illness (SRI), has been identified as a high-risk intervention requiring additional precautions. A full personal protective system (PPS) consisting of a N95 mask, eye protection, gloves, complete coverage suit and respirator, is required during intubation of these patients.2,3 A subjective note of lengthy time to don full PPS, subsequent difficulty with movement, visualization and communication were noted by staff involved with the Toronto outbreak of SARS I as well as during training sessions held at the Kingston General Hospital. To date there are no published studies specifically evaluating intubating conditions/abilities while wearing full medical grade PPS.

Methods: Ten volunteers from the department anesthesiology (staff and residents with prior PPS training) will intubate a Laerdal intubating mannequin twice: once while wearing the low-risk (“New Normal”) precautions and once wearing full PPS as for a SRI patient. Volunteers will be randomly assigned as to which intubation they will complete first. Data collected will include total time to intubation (inclusive of time to don respective protective equipment); timing of intubation process only; number of intubation attempts and incidence of endobronchial intubations. Subjective documentation of Laryngeal grading, ease of intubation, fit of protective equipment as well as perceived effects on ease of intubation will also be collected. Intubation times will be compared for the two types of simulated patients. Subjective data will be also analysed for correlation with objective findings (timings and intubation success).

Status: The volunteer consent form has been approved by Research Ethics. The Department of Respiratory Therapy has agreed to assist in running the simulation and has provided all required personal protective equipment. The study has been coordinated with another study in the department involving the protective equipment and is scheduled to commence at the conclusion of the current protective equipment training sessions.

References:
Chronobiological Characteristics Of Neuropathic Pain: Diurnal Pain Variation And Effects Of Analgesic Therapy

Mark J. Odrcich, Joan M. Bailey, Ian Gilron

Aim of Investigation: Clinical impressions suggest that neuropathic pain is often worse at night and significantly impairs sleep. However, the temporal pattern of neuropathic pain during waking hours has not been clearly characterized. Using clinical trial data, we have evaluated the diurnal variation of pain intensity before and during analgesic treatment in patients with diabetic neuropathy (DN) and postherpetic neuralgia (PHN).

Methods: Pain intensity (0-10) measures throughout the day (8:00, 16:00, 20:00) from a placebo-controlled trial of around-the-clock administration of gabapentin (G), morphine (M) and a gabapentin-morphine combination (C) in patients with neuropathic pain were examined.

Results: Baseline data in untreated patients revealed no effect of day of week but a significant effect of time of day in both DN (p<0.001) and PHN (p<0.001) such that pain intensity progressively increases throughout the day. This temporal pattern is essentially preserved during treatment with G, M, C.

Conclusions: Neuropathic pain intensity progressively increases throughout the day and this temporal profile appears to be unaffected by treatment with gabapentin and/or morphine. Advancing our understanding of the chronobiology of neuropathic pain may shed new light on various neurohormonal and neurophysiologic influences and lead to the identification of novel therapeutic targets. Furthermore, recognizing diurnal pain patterns may guide treatment strategies such as the targeted timing of analgesic therapies.

Acknowledgements: This work was supported by CIHR Grant # MCT-38149
Behavioural and Molecular Approaches to Study Peripheral Delta Opioid Receptors in a Model of Neuropathic Pain

Noufissa Kabli, Catherine M. Cahill

Animal and human studies continue to demonstrate the analgesic effects of peripherally-restricted opioid agonists in chronic pain conditions that have an inflammatory etiology. In the peripheral nervous system, exogenous opioid ligands applied locally exert antinociception by activating peripheral opioid receptors on cutaneous free nerve endings. In this study, we investigate the anti-allodynic efficacy of peripherally-acting delta opioid receptors (DOR) agonists in a rat model of neuropathic pain. Peripheral nerve injury (PNI) produced a significant decrease in mechanical withdrawal thresholds on days 7, 14, and 21 following sciatic nerve constriction, as assessed with von Frey filaments. Subcutaneous administration of Deltorphin II (a selective DOR2 agonist), but not vehicle, into the hindpaw ipsilateral (ipsi) to nerve injury, significantly and dose-dependently increased mechanical withdrawal thresholds on days 7, 14, and 21 following PNI. To examine systemic effects of the agonist, Deltorphin II was administered into the contralateral (contra) paw and testing was performed ipsi to PNI. Using this protocol, Deltorphin II had no effect on mechanical withdrawal thresholds indicating that the effects of the agonist were indeed local. Naltrindole, a DOR antagonist, blocked the anti-allodynic effects of Deltorphin II demonstrating that the effects were mediated via activation of DORs. Morphine also significantly increased the mechanical withdrawal thresholds at days 7 and 14, but lost its anti-allodynic effects by later time points. Interestingly, DPDPE (a DOR1 agonist) did not significantly alter the mechanical withdrawal thresholds of neuropathic animals. Using Western blotting techniques, we show no change in DOR protein levels in the L4-L6 DRG ipsi versus contra to the site of nerve injury on day 14 following PNI. However, an up-regulation of DOR protein was found in neuropathic ipsi DRG compared to sham ipsi DRG, suggesting that there may be a bi-lateral increase in the expression of DOR following PNI. Taken together, our findings suggest that drugs that activate peripheral DORs may be an attractive therapeutic target in the treatment of neuropathic pain. (Supported by the Canadian Institutes of Health Research, the Ontario Innovation Trust, and the Canada Foundation for Innovation).
Development of an electronic data entry tool for transesophageal echocardiography

Jack McGugan, Mohamed Ali

Introduction: Canadian Guidelines for Training in Adult Perioperative Echocardiography, to be published soon, stipulates that all relevant quantitative and qualitative information derived from TEE examination should form part of a TEE report. There is currently no Canadian standardized and accepted perioperative TEE report available in an electronic format.

Purpose: We decided to develop a Windows-based standardized TEE report for KGH that may used by all Canadian centers engaged in perioperative TEE.

Methods: Using Microsoft Visual Basic 6, a 348 kB executable file was produced that permits entry of TEE data and subsequent reporting to a paper record on any computer running Windows 98/ME or NT/2000/XP. An electronic record of the report is also saved to an encrypted, password-protected database. The program and database are stored on a hospital network-mapped hard drive. In addition to TEE data, the time required to enter the data is also captured.

Results: The latest version of the program will be demonstrated briefly on resident research day.

Future Considerations: Once developed we will assess the acceptance and applicability of the TEE reporting tool at KGH. In future we will assess its applicability nationally as a standard reporting tool.

At the time of this writing, the TEE reporting tool is in late alpha/early beta stage of testing. We expect to move the site of data entry from hospital terminals to a dedicated computer physically attached to the echo machine and at that time we will examine the times required to enter the data. Ideally, electronic entry of the report will be faster than pen and paper and we will work to achieve this. Even in the absence of substantial time savings, this mode of reporting will still serve the additional purpose of providing a standardized, legible report that will be electronically available to the TEE department for quality control and as a research tool.

There is also opportunity here to capture the TEE video within the same program and save this with the TEE report adding to its potential utility as a research tool.
Alpha-2-delta Calcium channel subunit expression in rat spinal cord after administration of opiates

Cara Reimer, Ian Gilron, Khem Jhamandas, Catherine Cahill

Chronic pain is a challenging aspect of anesthetic practice commonly requiring opiate therapy. A major undesirable side effect of chronic opioid use is tolerance. In recent years gabapentin (GBP) has been used as an adjunct in chronic pain. Recent evidence demonstrates that GBP has a potential role in blocking and reversing chronic opioid tolerance. It has also been shown that when administered with morphine, GBP decreases opioid requirements and may have a synergistic or additive effect. A potential mechanism for these observations may be GBP’s binding to the alpha-2-delta Calcium channel subunit. It has been shown that this subunit is upregulated in the DRG and dorsal spinal cord of rats with neuropathic pain.

The proposed research study asks the following question: Is there upregulation of alpha-2-delta Calcium channel subunit in the rat spinal cord after induction of morphine tolerance? And, if indeed this is the case, is GBP binding at the subunit a mechanism of tolerance-reversal?

References:


Resident and Staff Perceptions of Changing from a 24 Hour to a 14-16 Hour Call Schedule

Jay Ross, Brian Milne, Elizabeth VanDenKerkhof

Background: In July, 2004, the Department of Anaesthesia at Queen’s University took a bold step with their call scheduling of residents. Instead of the 24 hour call shift, which had been in place for years, residents would now have both pre and post call days off, in effect working a 14 to 16 hour shift.

This new call schedule is consistent with changes made to almost half the Anaesthesia programs in Canada, and reflects emerging opinions in the medical community regarding safety issues during prolonged shifts. The medical literature, including the Anaesthesia literature, suggests deleterious effects of sleep deprivation on patient care, on physicians’ health, and on job satisfaction, to name a few. North America has not kept pace with the European Union, New Zealand, and others by implementing changes in call schedules to combat the negative effects of sleep deprivation.

The purpose of this study was to assess the perception and attitudes of the residents and staff after the implementation of a new call schedule that attempts to deal with the issues of sleep deprivation and prolonged shifts.

Methods: A questionnaire was sent out to the Anaesthesia residents, and a modified version to the Anaesthesia staff at Kingston General Hospital, approximately 4 to 5 months after implementing the new call schedule. People were asked to compare the new schedule with the older one, and to rank their answers on a 5-point scale. Additional comments were requested and welcomed.

Results: The response rate was 80% for residents and 52% for staff. The majority of respondents felt that the new schedule has had a positive impact on their mental and technical abilities. Data is currently being further analyzed and will be discussed on Resident Research Day.

Discussion: This survey will serve to pilot-test our questionnaire while providing a short-term snapshot of the attitudes and perceptions of the Queen’s University Anaesthesia residents and staff in regards to the new call schedule utilizing shorter shifts.
Correlation of Pre-operative Warfarin Treatment and Bleeding Tendencies: a Retrospective Review in Cardiac Surgery Patients

Angela Northey, David Mark, Elizabeth VanDenKerkhof

Introduction: More than 2 million patients in North America are on warfarin. Although preoperatively cardiac surgery patients are commonly on this medication, there is a paucity of data on the appropriate time to discontinue this medication and its effects postoperatively. In accepted practice warfarin is stopped 3-5 days before surgery. However this practice is based on the time needed to normalize the INR and does not account for the fact that only 30% of clotting factors need to be functioning to have a normal INR. It has been noted after receiving IV fluid that patients’ post operative INRs are higher than the initial values. Intuitively a higher INR would lead to more bleeding postoperatively, but this has never been shown in the literature. Of course clinicians strive to reach a balance between bleeding complications and thrombotic complications and surprisingly there is little clinical data to guide warfarin use peri-operatively.

Hypothesis: Warfarin use will increase bleeding risk after cardiac surgery.

Methods: A Retrospective matched case-control study using cardiac surgery data base and chart review. The patients will be matched for age, sex and type of surgery. The time frame will be from 2000 to present. Approximately 200 charts will be reviewed. The primary outcome will be transfusion exposure. Other outcomes to be assessed will be INR pre and post operatively; amount of bleeding, length of hospital stay and mortality.

Progress: A list of patients preoperatively on warfarin has been generated. Pending Research Ethics Board approval 20 initial charts will be reviewed and assessed for feasibility of data extraction. Then the cases will be matched with similar controls and all the charts will be reviewed for the variables of interest.
The central role of the delta opioid receptor in neuropathic allodynia

Sarah Holdridge, Catherine Cahill

Pharmacological evidence supports the involvement of the delta opioid receptor (dOR) in antinociception; however its potential role in the treatment of neuropathic (NP) pain remains largely unknown. In the present study, we examined the anti-allodynic effectiveness of the selective dOR ligand, Deltorphin, following peripheral nerve injury (PNI) by means of chronic constriction of the sciatic nerve in rats. Mechanical allodynia was assessed using calibrated von Frey filaments prior to and on Day 14 following PNI. Neuropathic animals showed significantly lower mechanical thresholds in the ipsilateral hind paw as compared with presurgical baselines, indicating the development of allodynia. No contralateral effects were present. Intrathecal administration of Deltorphin dose-dependently reversed the allodynic behaviour and these effects were blocked by the dOR-selective antagonist, Naltrindole, as well as by the mOR-selective antagonist, CTOP. Western blotting experiments revealed increased total dOR protein levels in the dorsal lumbar spinal cords of neuropathic animals as compared with controls. Next, the involvement of various sensory fiber types in the development of allodynia was examined using administration of capsaicin, a compound shown to inhibit the development of nociceptive primary afferents when given neonatally. Capsaicin-treated rats developed significant allodynia following PNI, which was reversed by intrathecal administration of Deltorphin. These results suggest that the development of allodynia following nerve injury does not involve nociceptive primary afferents but rather involves sensory fibers normally responsible for transmitting innocuous tactile information. Furthermore, these data support a therapeutic role of the dOR in treating neuropathic allodynia and provide insight into the synaptic plasticity of sensory transmission that likely underlies neuropathic pain.
The effects of intraperitoneal ketorolac on postoperative pain following laparoscopic cholecystectomy.

G. Ramsey, J. Murdoch, Y. Borshch, T. Saha, D. Tod, B. Orr

**Background:** Delay in discharge from day surgery is frequently secondary to postoperative pain.¹ Some of the pain following laparoscopic procedures has been attributed to the rapid distension of the peritoneum causing traction and tearing of blood vessels and nerves, and release of inflammatory mediators. The amount of pain after laparoscopy may be related to the concentration of these locally induced mediators, including prostaglandins. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit inflammatory mediator release through the inhibition of cyclooxygenase synthetase. NSAIDs, administered by various routes, have been shown to be more effective in reducing postoperative pain in laparoscopic surgery when compared to placebo or acetaminophen. Prior work has suggested that intraperitoneal installation of the NSAID tenoxicam, combined with lidocaine, significantly reduces postoperative pain following laparoscopic cholecystectomy relative to placebo.²

**Aim:** The aim of this study is to determine the analgesic effectiveness of intraperitoneal ketorolac for postoperative analgesia following laparoscopic cholecystectomy and to compare this route with intravenous administration. Secondary analysis will include incidence of nausea and vomiting and overall patient satisfaction.

**Methods:** One hundred and twenty (120) patients ASA I-III, aged 18-65 years old undergoing elective day case laparoscopic cholecystectomy will be recruited following Ethics Board approval and informed consent, and they will be randomized to 3 treatment groups. Group 1 will receive intravenous (IV) saline 1ml, intraperitoneal (IP) saline 250ml. Group 2 will receive IV ketorolac 30mg, IP saline 250ml. Group 3 will receive IV saline 1ml, IP ketorolac 30mg in 250ml saline. All investigators and the subjects will be blinded to the contents of the solutions administered. All patients will receive 975mg PO acetaminophen 1 hour prior to surgery and all incision sites will be infiltrated with 0.25% bupivacaine. A standard anaesthetic protocol will be followed for all subjects. Visual Analog Pain (VAS) scores at rest and with movement will be recorded in the recovery by a blinded observer at 30min, 1 hour, and 2 hours post injection and prior to discharge. Follow up will be made at 24 hours post surgery with a telephone questionnaire. Further follow up will be done 14 days post-operatively. Time to first request for analgesia, total analgesic requirement, incidence of shoulder tip pain, side effects, incidence of nausea and vomiting, and patient satisfaction will also be recorded.

**Progress:** The research proposal was submitted to the Research Ethics Board (REB) in January, 2004 and final approval of the study by REB was given in July, 2004. Since that time, unfortunately only 32 patients have been enrolled in the study. This makes it too early for any significant preliminary analysis of the data.

**References:**
The relationship between evoked versus spontaneous pain and peak expiratory flow after laparoscopic cholecystectomy

Jason Erb, Ian Gilron

This study is proposing to look at the relationship between evoked versus spontaneous pain and pulmonary function measurements after upper abdominal surgery, in particular laparoscopic cholecystectomy. It is well known that postoperatively there are changes in pulmonary function. In particular, changes are seen in functional residual capacity, vital capacity, and inspiratory capacity. There are several contributors to this phenomenon. Several previous studies have found that pain contributes to inspiratory muscle dysfunction and pulmonary function.

Pain can be described as two components, spontaneous and evoked pain. A patient who has undergone a procedure will have a baseline pain level referred to as spontaneous pain. Activity such as movement or coughing generally results in a pain level that is in excess of the patient’s spontaneous pain and can be described as evoked pain. Deep breathing, coughing, incentive spirometry are all means that can trigger this evoked pain. However, these maneuvers are necessary for patient rehabilitation and prevention of thromboembolic phenomenon and atelectasis that can lead to pneumonia.

This study proposes to look at measures of pulmonary function FEV1, PEF, and FVC postoperatively and the concurrent levels of spontaneous and evoked pain. The study would examine the strength of the correlation between pain scores and pulmonary function changes from baseline. The three hypotheses to be tested for upper abdominal surgery are:

A. Movement evoked pain is more severe than pain at rest.
B. Post operative pain is significantly correlated with post operative lung function.
C. Movement evoked pain is more significantly correlated than rest pain

Study design will consist of ASA 1 or 2 patients undergoing elective laparoscopic cholecystectomy. Expected correlation coefficient value (r) of 0.6 with two tailed alpha = .05 and beta = 0.2 which will give an estimated sample size of 25. Preoperative care will be routine with exception of baseline pulmonary function measurements and teaching in use of spirometer. Anesthetic plan will be flexible except fentanyl will be the only opioid used. Postoperative pain will be managed by IV fentanyl.

Data will be collected at 20, 40, 60, 80, 100, and 120 minutes time points. Measurements will include baseline pain at rest, pain on sitting, and cough pain. Visual analog scale will be used to assess pain intensity. Spirometry measurements will include PEF, FEV1, and FVC. Pain score for performing these maneuvers will be recorded. Patients are to be discharged home from PAR.

Values of pulmonary function will be plotted as a percentage of baseline value against time. Pain scores will be plotted as a function of time. The pain scores will be correlated with the pulmonary function of each patient to estimate the magnitude and statistical significance of correlation coefficients. Correlation analysis will be used to look at the relationship between pain and pulmonary function, both spontaneous and evoked.
The relationships of men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS):
A multiperspective approach.

Smith KB, Soryal AK, Simms DC, Nickel JC, Pukall CF, Tripp DA

Introduction: Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is a condition in men that involves pain in the external genitalia, perineal, pelvic, or suprapubic area, and concomitant voiding difficulties, erectile dysfunction, and ejaculatory problems. Unfortunately, the etiology of CP/CPPS is poorly understood and efforts to treat this syndrome are largely unsuccessful. Consequently, men with CP/CPPS may endure recurrent and painful physical and sexual symptoms for several months or years at a time. Likewise, men with CP/CPPS may also experience interpersonal problems; for example, initial evidence indicates that men with CP/Chronic Pelvic Pain Syndrome (CPPS) experience relationship difficulties and reduced psychosocial functioning. However, these relationships of men with this syndrome have not been rigorously studied and previous research has neglected to gain the perspective of the partner when examining such relationships.

Purpose: This presentation will outline recent research examining sexual and marital functioning among patients with CP/CPPS and their partners, couples’ interactions when the patient has pain, and partner's psychological health. This research is part of an ongoing, longitudinal study examining pain, sexual & marital functioning among patients with CP/CPPS and their partners; initial results (time 1) of the study will be outlined.

Methods: All participants completed questionnaires assessing pain, sexual functioning and satisfaction, and relationship quality. Participants were 25 patients with CP/CPPS (M=50.68 years of age; SD=8.53) and their female partners and 25 males without chronic pain or illness (M=47.76 years of age; SD=6.67) and their female partners. All participants were married or in a cohabiting relationship of at least one year duration.

Results: Preliminary analyses indicate that men with CP/CPPS and their partners experience several aspects of reduced sexual functioning compared to control couples. No differences in relationship quality exist between patient couples and control couples. Furthermore, partners of men with CP/CPPS experience decreased psychological and physical functioning in comparison to female controls.

Discussion: The initial results of this study are consistent with previous literature suggesting impaired intimate relationships & reduced sexual functioning among men with CP/CPPS. This study improves upon previous research by gaining partner data and perspective. The implications of this study and directions for future research will be discussed.

This presentation will outline recent research examining sexual and marital functioning among patients with CPPS and their partners, couples’ interactions when the patient has pain, and partner's psychological health.
Reserpine Prevents Cardiac Dysfunction after Intracranial Hypertension in Rats

Sean Hall, Louie Wang, Brian Milne, Murray Hong

Introduction: Various catastrophic cerebral events that induce intracranial hypertension, such as severe head trauma or spontaneous intracerebral hemorrhage, often lead to profound alterations in cardiac rhythm, hemodynamic function and pulmonary edema. The cardiac consequences are believed to result from a pathological imbalance in central autonomic tone favouring an exaggerated release of endogenous catecholamines together with synaptic denervation. To examine these issues, myocardial norepinephrine stores were depleted with reserpine prior to intracranial hypertension and the integrity of the nerve terminal was assessed following a bolus infusion of the indirect acting sympathomimetic tyramine in a rat model.

Methods: Male Sprague-Dawley rats (300-350 g) were injected daily with reserpine (1.0 mg•kg\(^{-1}\)•day\(^{-1}\) ip) or vehicle for 3 days. In halothane anesthetized animals, intracranial hypertension was induced following a rapid inflation of a subdural balloon catheter acutely elevating ICP. Hemodynamic function, plasma catecholamines and ECG changes were recorded. To investigate the functional integrity of the cardiac sympathetic nerve terminal, 60 minutes after subdural balloon inflation, rats were given pargyline (10 mg/kg, i.v.) and after an additional 10 minutes, tyramine (16 µg, i.v.). The peak hemodynamic response was recorded.

Results: There was an increase in circulating levels of norepinephrine (356±176 % of pre-inflation levels, P < 0.01) and epinephrine (1042±272% of pre-inflation levels, P < 0.001) during the period of raised intracranial pressure in vehicle-treated rats and cardiac dysrhythmias were observed. Shortly following the induction of intracranial hypertension, hemodynamic function was depressed. Tyramine administered to vehicle-treated rats 60 minutes after the induction of intracranial hypertension resulted in an exaggerated increase in hemodynamic function (HR 141%, LVP 184%, LVDP 191% and LV dP/dtmax 239% above 60 minute levels), and the recurrence of cardiac dysrhythmias. The hemodynamic and ECG changes corresponded with an excessive rise in circulating norepinephrine (448% above 60 minute levels), in the absence of an associated increase in epinephrine. Reserpinization caused virtually complete depletion of myocardial norepinephrine stores. The increase in plasma catecholamines (norepinephrine 68±33% of pre-inflation levels and epinephrine 117±68% of pre-inflation levels, P = NS) was attenuated and ECG changes were blocked (P < 0.05) during raised intracranial pressure. At the end of 60 minutes, hemodynamic function was not different from baseline. Moreover, reserpinization led to a greatly modified hemodynamic response to tyramine, which was similar to sham-operated rats. There were no cardiac dysrhythmias and the rise in plasma norepinephrine was attenuated (175±57% of 60 minute levels, P < 0.05).

Conclusions: The results of the present study provide evidence for the central pathogenic role that intramyocardial release of endogenous norepinephrine plays in the deterioration in cardiac function associated with intracranial hypertension. Secondly, an inability of the cardiac adrenergic efferent postganglionic nerve endings to release norepinephrine as a cause for cardiac dysfunction after intracranial hypertension can be ruled out. The precise myocardial changes that contribute cardiac dysfunction resulting from sympathetic hyperactivity require further study.

April 15, 2005
Impact of therapy on quality of life and mood in neuropathic pain: What is the effect of pain reduction?

Maneesh A. Deshpande, Ronald R. Holden, Ian Gilron

**Background:** Quality of life (QOL) and mood outcomes vary widely in neuropathic pain trials. This may be explained by variability in pain reduction and other beneficial or adverse treatment-related effects. This study specifically evaluates the relationship between pain intensity reduction and mood/QOL in neuropathic pain.

**Methods:** Pain, side effects, QOL and mood outcomes from a placebo-controlled trial of gabapentin, morphine and a morphine-gabapentin combination in non-depressed patients with diabetic neuropathy or postherpetic neuralgia were examined.

**Results:** Baseline QOL was impaired according to aggregate Short Form Health Survey (SF-36) scores. Baseline mood, according to aggregate Profile of Mood States scores, was comparable to that of a non-depressed population. Pain reduction with any of the three treatments was significantly correlated with improvement in QOL. Pain reduction with gabapentin or morphine was significantly correlated with improvement in mood. Pain reduction with a morphine-gabapentin combination was significantly correlated with improvement in only one of several domains (anger-hostility) of the Profile of Mood States. Severity of sedation, constipation and dry mouth during any treatment did not significantly correlate with changes in mood or QOL.

**Conclusions:** These results can be interpreted to imply that larger analgesic treatment effect sizes lead to more substantial improvements in QOL and/or mood. However, other beneficial or adverse treatment-related side effects may also impact on mood/QOL. Therefore, future studies are needed to also evaluate the impact of treatment-related side effects on QOL and mood in analgesic trials.
Cervical Spine Movement during Laryngoscopy: Objective Assessment and Comparisons of Indirect Fiberoptic and Prismatic Laryngoscopes

S. Sharan, J. E. Zamora, K. Sullivan

**Background:** Direct laryngoscopy requires cervical spine movement. The GlideScope is a video laryngoscope that is inserted conventionally. The physician can monitor the passage of the laryngoscope tip down to the epiglottis area. The Viewmax laryngoscope blade is a prismatic modification of the Macintosh laryngoscope blade that allows the user a more anterior view of the larynx.

In a suspected cervical spine injury, the goal of the anesthesiologist is to secure the airway without worsening the patient's neurological condition. Routine intubation requires direct laryngoscopy that involves extension of the head at the occipito-atlanto-axial complex and flexion of the lower cervical vertebrae. In cervical spine trauma patients, there is a conflict between minimizing this movement and allowing sufficient laryngeal exposure to allow tracheal intubation. The Bullard laryngoscope is an indirect fiberoptic laryngoscope. Several studies have shown that it decreases cervical spine movement during intubation when compared to more conventional laryngoscopes such as the Macintosh and Miller blades. One of the claimed advantages of the GlideScope is less neck movement resulting in less trauma to the patient. Currently there is a single correspondence that shows an improvement in laryngeal view when comparing the GlideScope with the Macintosh laryngoscope.

At the present time, no publications exist mentioning the Viewmax laryngoscope. The aim of this study is to compare cervical spine movement in cadavers (measured radiologically) and laryngeal view obtained with the GlideScope, Viewmax, Bullard, and Macintosh laryngoscopes.

**Research Question:** Do the GlideScope and Viewmax reduce cervical spine movement, improve laryngeal view and reduce the number of attempts during intubation when compared with other laryngoscopes?

**Study Design:** The study is a randomized, controlled, crossover trial.

**Methods:** 20 fresh cadavers will be used as subjects. Each cadaver will act as its own control. Cadavers with oropharyngeal or cervical spine pathology, decreased range of head or neck movement, and those less than 18 years of age will be excluded from the study. Each cadaver will undergo intubation by the same anesthesiologist in a standardized fashion using manual in-line stabilization. During the course of intubation lateral x-rays will be taken in the neutral position and at the time of intubation. Each cadaver will undergo intubation using each of the laryngoscopes.

**Analysis:** Changes in angle between each cervical vertebra will be determined and the mean will be calculated for each laryngoscope. If the data is normally distributed, repeated measures ANOVA will be used for comparative analysis. If data is not normally distributed, Friedman analysis will be performed. Cormack and Lehane grade and number of attempts will be analyzed using the Chi-square test using frequencies or percentages. Time to intubation will be measured in seconds and the mean time will be analyzed using repeated measures ANOVA.

**Project Timeline:** Recruiting 20 fresh cadavers will require approximately 1 year.

**Progress:** Funding obtained through PSI Foundation Resident Research Award. Study has been completed on one cadaver.
Critical Appraisal Essay

By: Ryan Endersby, MD, PGY-1

Title of the Publication: “Simulation Study of Rested Versus Sleep-deprived Anesthesiologists.”

Authors: Howard SK, Gaba DM, Smith BE, Weinger MB, Herdon C, Keshavacharya S, Rosekind MR

Anesthesiology 2003; 98:1345-55

General

The issue of sleep deprivation and medicine is not a new one. However, only recently has the literature started to address the impact of sleep deprivation on both the patient and the practitioner. Part of this likely stems from the fact that hospitals and doctors are looking for new ways to improve patient safety and reduce medical errors. Unfortunately due to the nature of medicine, doctors are forced to work beyond standard work hours, providing care around the clock. In the specialty of anesthesia this is no different and due to the nature of some of the high acuity cases, being available at all hours of the day is more of a harsh reality in this specialty as compared with others. Hence Anesthesiologists often work long shifts which result in sleep deprivation (1-2). Further this sleep deprivation is not only apparent in the postcall period but recent studies have shown anesthesia residents to have a level of daytime sleepiness equivalent to that of patients with severe sleep disorders such as narcolepsy and sleep apnea (2). These effects could be reversed with periods of additional sleep. These issues appear to be the impetus for the paper “Simulation Study Of Rested Versus Sleep-Deprived Anesthesiologists” by Steven K. Howard, David M. Gaba, Brian E. Smith, Matthew B. Weinger, Christopher Herrdon, Shanthaia Keshavacharya and Mark R. Rosekind of Patient Safety Center of Inquiry and Stanford University in Palo Alto, California, USA.

Introduction

This study entitled “Simulation Study Of Rested Versus Sleep-Deprived Anesthesiologists” attempts to address the important issue of how sleep deprivation affects job performance of anesthesia residents. There have been a number of studies which try to determine the effects of chronic sleep deprivation on performance in physician populations, but the results have been mixed (3-8). Up until the publication of this study only a handful of studies have addressed how sleep deprivation affects the field of anesthesia specifically (9-13). Further this is the first published study to use the novel concept of anesthesia patient simulator to study the effect of sleep deprivation on actual clinical performance. The hypothesis being tested in this case is that the patterns and adequacy of performance (psychomotor and clinical) during a long anesthetic would be different for residents who were sleep deprived relative to the patterns and adequacy of performance seen when the residents were well rested. Further, they also hypothesized that acute sleep deprivation would result in an increased propensity of residents to fall asleep even when conducting simulated patient care. Therefore the authors through the anesthesia patient care simulator are able to address the problem of whether sleep deprivation would affect psychomotor and clinical performance in anesthesia residents.

Methodology

The study was set up as a prospective randomized crossover study, which was experimental in nature as a patient simulator was used. In the study, 12 anesthesia residents having previous experience with the patient simulator were either randomized to the sleep deprived condition (DEP), in which residents were kept awake for at least 25 hours before the case or the sleep extended condition (EXT) in which residents were instructed to maximize their sleep for 4 consecutive nights before the case. Two different, yet similarly challenging cases were formulated and after having rotated through one in either the DEP or EXT condition, residents rotated through the other scenario in the other sleep condition, hence acting as there own controls. Residents obviously could not be blinded as to which sleep condition they were in, however independent observers who graded their performance on their clinical performance, vigilance, task analysis, assessment of behavioral alertness and psychomotor testing were blinded. As well the crossover design allowed for the residents themselves to act as their own controls.

The population under study in this case was the anesthesia resident population and cases again were performed on an anesthesia patient simulator. There were several reasons for this approach. First, this caused no risk to real patients if errors were made in either situation, hence making the study quite ethically sound. Second, the cases could be presented reproducibly to each test subject. Third, the nature of the anesthesia patient simulator allows residents to be monitored extensively. Fourth, the key independent variables (e.g. sleep deprivation vs. sleep extension) can be manipulated more easily. Fifth, Performance probes and abnormal clinical events can be presented at predetermined times under controlled conditions. Finally this set-up also allows itself to be very similar to anesthesiologist own clinical practice when compared with other studies, which instead of using a anesthesia patient simulator use other methods to measure the effects of sleep deprivation such as a driving simulator (12).

The sample size for the study seemed to be slightly small, being only 12 residents, however the crossover design increased their sample size to 24 subjects. As well, the
experimenters attempted to get around the small sample size in some of their experiments by performing numerous tests or measurements, such as in the psychomotor test battery, which was performed on three separate occasions during each test and involved 90-100 different reaction time measurements during each session. The task analysis and assessment of behavioral alertness were also significantly powered because they involved analysis of videotape, which yielded multiple measurements. However, some tests such as the vigilance probes, abnormal clinical events, clinical management of preoperative conditions, and check of an anesthesia machine with known faults seemed underpowered because they were only performed 3, 2, 1 and 1 times respectively per case.

In the study there was no mention of any groups that were excluded. However, the study was a voluntary one of residents in the anesthesia program at Stanford University School of Medicine. There was an equal number of females and males (six and six) and they had an average age of 31.8 ± 3.1 years and 18 ± 11 months of clinical experience. No staff anesthetists participated in the study. Residents were appropriately randomized either to start in the DEP or the EXT sleep condition. Since all of the residents had previous simulator training there wasn’t any effect from having to learn how to interact with the simulator.

The study appears to be designed to test the hypothesis that psychomotor and clinical performance would be different between a group of sleep deprived and well rested residents. In the study they had tests to measure psychomotor performance such as the psychomotor test battery, which consisted of the Psychomotor Vigilance Task, Probed Recall Memory, Profile of Mood States and Stanford Sleepiness Score. In order to measure clinical performance, the experimenters looked at how the residents checked anesthesia equipment with known faults, managed preoperative medical conditions, maintained vigilance and reacted to abnormal clinical events. Additionally, the sessions were also videotaped and evaluated by a blinded independent observer for task analysis (essentially what tasks the resident was completing, including sleeping) and behavioral alertness, which are also somewhat indirect measures of clinical performance. Finally, a Postsimulation questionnaire was also filled out to assess the cases perceived realism, clinical difficulty and similarity to each other.

All these methods of assessment had been performed in numerous other papers and were detailed enough in the paper that they could be reproduced in a subsequent trial. The equipment used in the experiment was also detailed, with them using a MedSim/Eagle Patient Simulator, Madulus II Plus anesthesia machine, a AS3 physiologic monitor with Capnomic Ultima respiratory gas analyzer (all Datex-Ohmeda products) and a fully stocked anesthesia supply cart in addition to a standard OR table and surgical light. One of the investigators also played the role of the surgeon during a laparoscopic procedure and another retired OR nurse played the role of the circulating nurse.

Data collection was only from these simulated scenarios and analysis was done using a variety of software including Microsoft Excel 98, Statview 4.1, SuperANOVA and STATISTICA MAC 4.1. The experiment generally used nested repeated – measures design in which subjects were their own controls for the two sleep conditions and various measures were repeated throughout the simulated and on-call night and the simulation sessions. Nested repeated-measures analysis of variance using SuperANOVA, with significance levels corrected for sphericity by Greenhouse-Gesser epsilon were used for comparisons between equivalent endpoints in the simulation sessions when possible. Nonparametric analysis was used to for ordinal data and proportions. In the study Vigilance probe response time deviated substantially from a normal distribution and hence was analyzed nonparametrically as well. Nominal data (e.g. such as the detection of clinical events) was analyzed using chi-square tests. A P<0.05 was considered the level for statistical significance in the study. This statistical analysis used in the study on careful review seems appropriate.

The primary endpoint of the study was the completion of the two simulated scenarios by the 12 residents in each of the sleep conditions. These scenarios were of similar difficulty and only differed in the residents sleep condition. As well these scenarios by their descriptions in the journal article seemed to be similar to what would be encountered in a real clinical environment.

Results

The groups used in the study were most certainly comparable because of the nature of the crossover design of the study. In such a design the experimental group is also used as control group. Since the nature of the effect that the experimenters were trying to measure, namely the effect of sleep deprivation on psychomotor and clinical performance, was reversible this study design was excellent for this study.

The only data that was eliminated from the study was that of the first subject for the behavior alertness assessment part of the study. The reason for this was that the rater for the assessment of Behavioral Alertness was trained on alertness scale using data from the first subjects case, hence his data was eliminated from this particular part of the experiment and the subsequent analysis was made using data from the remaining 11 subjects.

In analyzing the results of the study there seems to be a paucity of graphs and figures. Much of the information of the study was not displayed in graph or table format. Further the results in the tables and graphs were at times difficult to interpret and took substantial amount of time to decipher. Hence the study could have been enhanced if more clear graphs and figures would have been used.

Discussion

There are three main findings of the study. First, many of the subjects showed sleepy behaviors when sleep-deprived and approximately one third fell asleep. These findings did not occur in the sleep extended setting. Secondly, the performance of the subjects on laboratory tests of psychomotor vigilance, memory and mood testing showed progressive impairment during and after a night of sleep deprivation. There was also significant impairment the day after the night of sleep deprivation. The nadir of the sleep deprivation subjects on these test was around 06:00-08:00hrs, which is later than the expected circadian nadir of 02:00-04:00. Thirdly, the performance on clinically relevant tasks and probes during
simulated cases showed only modest, if any, impairment between subjects who were sleep deprived and those in the sleep extended condition. Subjects in both groups made clinically relevant errors, with a trend towards more errors in the sleep deprived group, however this trend was not statistically significant.

The results of the study seem to support the conclusions drawn by the study. However, it should be noted that the statistical power of the final experiment on clinical performance was underpowered. The reason for this is the experimenters didn’t realize the true variability of clinical performance between individuals, assuming near perfect performance of rested individuals on clinical tasks and hence having a smaller number of trials as a result. This unfortunately wasn’t true in this experiment and even the well rested individuals made clinical errors in their performance. Thus because this last experiment was underpowered the authors didn’t fully address one of the main purposes of their experiment, which was to see if sleep deprivation affected clinical performance. They did address the other issues of whether sleep deprivation affects psychomotor performance and propensity for sleepy behaviors during a simulated anesthetic.

The authors didn’t devote a lot of time to discussing the results of the psychomotor testing which has been investigated and evaluated in numerous other studies. They however focused on the clinical performance aspect of the study. The author’s sited the fact that one of the reasons why they were unable to show statistical significance between the two groups in terms of clinical behavior was because their study was underpowered. Further the reason why their study was underpowered was because they were expecting less variability between subjects, in particular those in the sleep extended group, whom they were expecting nearly perfect clinical performance from. Thus the authors sited a number of reasons for this high variability, including some individuals being less susceptible to sleep deprivation, clinical performance being more complex and difficult to measure than psychomotor performance and sleep deprived individuals rapidly and frequently cycling in and out of reduced alertness. In addition some compensatory behaviors such as focused attention were sometimes used to maintain performance and the simulation tests were conducted during a relative circadian “upswing” of alertness. The simulations were not the same as real cases and possibly these somewhat artificial situations may result in either artificially increased or decreased attention. Finally the authors also sited the fact that because individuals in the sleep deprived group only assisted with call duties the night before call, they may not have been as fatigued as a resident who had actually completed a full night of call.

An additional interpretation to the data might include the viewpoint that because the subjects were residents, with only an average of 18 ± 11 months of anesthesia training experience and in different years of residency, that a high degree of variability could be expected in there clinical performance even without sleep deprivation. Perhaps staff anesthesiologists might have been a better group of subjects to study because this may have eliminated some of the variability that is inherent with the initial phases of residency training.

The results of the study appear not to be as clinically and statistically relevant as one might have hoped for at the outset of the study. This again stems from the fact that the last and possibly the most important part of the study, the clinical performance study was underpowered and hence doesn’t tell us a lot. This is unfortunate because this is the most clinically significant part of the study. The aspects of the study dealing with psychomotor testing, sleepy behaviors and task allocation, which were significantly powered, did produce meaningful results, however these results are only abstractly applied to a clinical setting. Thus again it is unfortunate that clinical performance portion of the study was fundamentally flawed in this paper.

Unfortunately, the results of this study are very similar to previous studies and add very little to the existing literature. Other studies have demonstrated that sleep deprivation negatively impacts on psychomotor tasks and increases the propensity to fall asleep (14-17). As well, with the clinical performance aspect of the study being underpowered, this too doesn’t produce results which suggest anything more than a trend to more sleep related errors. This aspect of the study would have been the one that could have added new information to the existing literature. However that being said, in the study the researchers did note that there was no difference between task patterns in the two groups. This was different than in previous studies which noted that task patterns differed between rested and sleep deprived subjects (18-20). Perhaps the biggest reason for this difference was the fact that the researchers in the anesthesia simulation study had a relatively simplistic approach to task analysis when compared with these other studies. Those issues aside however this study does have a unique approach to studying sleep deprivation and that is the use of the anesthesia simulator. The simulator does make it easier and safer to study the effects of sleep deprivation on clinical performance. Thus this study does serve as a pilot study for future studies on sleep deprivation and clinical performance.

The major limitation of the study was that the study was again that the clinical performance study was underpowered as previously mentioned. A further limitation of the study was that it was conducted in a simulated patient, therefore it wasn’t as realistic as with a genuine patient. Further responses and results of the study could have been somewhat different if the subjects had been performing the experiment with a real patient. However this approach does provide greater patient safety as well as greater standardization between subjects.

The unanswered questions to take away from this paper is the one that has been surfacing and resurfacing and that is if the study was significantly powered would the researchers have been able to show a statistical difference in clinical performance between the sleep deprived subjects and the sleep extended subjects? The researchers in the paper admit this and state that this study should be taken as more of a pilot project for future studies looking at sleep deprivation and clinical performance. Another unanswered question that arises out of this study is if sleep deprivation does negatively impact on clinical performance, as it does on psychomotor testing, then what can be done about it. Anesthesiologists by the nature of their job are forced to be on call at all hours of the day and cannot avoid working at night and hence running the risk of becoming sleep deprived. This issue wasn’t really addressed in the paper, but perhaps working shorter on call shifts such as only 16 hour call shifts may avoid some of the negative effects of extended sleep deprivation. Such a study taking a look at the effect of reducing call shifts to 16 hours was recently published in the
New England Journal of Medicine. It found subjects in the 16 hour call group slept 5.8 hours more a week and had half the rate of attentional failures that those did in the 24 or more hour call group. Thus perhaps implementing schedules such this might be a acceptable solution to the potential problem of decreased clinical performance with sleep deprivation (21).

Applicability of the Paper

This paper had several important points in it. First it detailed an new way of conducting clinical experiments in sleep deprivation in a reproducible and safe environment using the anesthesia patient simulator. As well, it also illustrated the need to determine the number of individuals needed for a study to be significantly powered to observe a difference between groups, before the outset of the study. Further, it also demonstrated that there is significant variability between different residents in regards to their clinical performance even in sleep extended circumstances. This last point translates into a larger group of subjects needed in order to make a call on whether specific variables such as sleep deprivation affect clinical performance. Finally, the paper also served to reinforce the fact that sleep deprivation does cause deficits in psychomotor performance and the propensity to fall asleep, which has been illustrated before in numerous other studies (14-17).

The results of this study have impressed upon me the importance of getting an adequate amount of sleep and the potential need to adjust the way physicians approach sleep. Sleep deprivation I think is far too common in clinical practice in regards to their clinical performance even in sleep extended circumstances. This last point translates into a larger group of subjects needed in order to make a call on whether specific variables such as sleep deprivation affect clinical performance. Finally, the paper also served to reinforce the fact that sleep deprivation does cause deficits in psychomotor performance and the propensity to fall asleep. This study also suggests that there may be the potential for detrimental effects of sleep deprivation on clinical performance. Thus I will try to get more sleep, not only for my own health but perhaps for the health of my patients as well.

References

Critical Appraisal Essay

By: Samia Ali, MD PGY-1

Title of Publication: Pain During Injection of Propofol: The Effect of Prior Administration of Butorphanol

Authors: Anil Agarwal, M.D., Mehdi Raza, M.D., Sanjay Dhiraaj, M.D., Ravinder Panday, M.D., Devendra Gupta, M.D., Chandra Kant Pandey, M.D., Prahab K Singh, M.D., and Uttam Singh, PhD.

Anesthesia Analgesia 2004; 99:117-9

INTRODUCTION

There have been numerous studies conducted over the years looking at ways to combat pain associated with injection of Propofol. The fact that pain after injection of Propofol occurs in 28-90% of patients (1) and that Propofol is so widely used in clinical practice certainly warrants looking at different drugs and techniques to minimize patients’ discomfort. In fact some of the same authors of this study had previously conducted a study assessing the effect of pretreatment with Pentothal for prevention of Propofol associated pain. (2)

Interestingly, this study suggests IV pretreatment with Butorphanol 2mg for attenuation of pain associated with Propofol. The investigators compared the efficacy of Butorphanol and Lidocaine for prevention of Propofol induced pain and came to the conclusion that while both drugs reduced the incidence and severity of pain, Butorphanol was more effective (P<0.05). (3) However, during my limited experience in Anaesthesiology I have heard no mention of Butorphanol being used as suggested by the study. Moreover, Butorphanol, though still available on the market is not available in our hospital formulary.

Butorphanol is an agonist antagonist opioid. It is an agonist at kappa receptors and its activity at “mu” receptors is either antagonistic or partially agonistic. Side effects of Butorphanol include drowsiness, sweating, nausea and CNS stimulation. (4)

METHODOLOGY

The study was a prospective randomized double blind clinical trial. 150 ASA I-II adults between the ages of 18-50 undergoing elective surgery were randomly assigned into 3 groups of 50 each.

Exclusion criteria were, in my opinion distinctly lacking. Only patients having difficulty in communication or with history of allergy to the study drugs were excluded. While communication was a vital attribute in participants since the outcome of the study was highly dependant on the ability to communicate their experience, other factors needed to be considered. In a similar study looking at prevention of Propofol-associated pain, Nathanson et al 1 also excluded patients with a history of chronic pain syndromes, thrombophlebitis and neurological diseases. I believe the results of this study would have been more valid if these factors had been taken into consideration.

All patients received pretreatment solutions one minute before the induction of anaesthesia with Propofol depending on the group to which they belonged. Group I was the control group where patients received Normal Saline. Group II patients received Lidocaine 2% (40mg) and group III patients received Butorphanol 2mg. Patients were assigned to one of the 3 groups with the help of a computer generated table of random numbers. (3) This method of randomization is quite reasonable.

Prior to the surgery the patients were premedicated with Lorazepam 2mg and Ranitidine 150mg the night before surgery as well as two hours before induction of anaesthesia. (3) No mention was made regarding the patients’ affect and level of consciousness prior to receiving the pretreatment drugs.

The authors then described in adequate detail the manner in which the study drugs were prepared and administered by independent blinded anaesthesiologists.

While Propofol was being injected, patients were observed for vocal response, facial grimacing, arm withdrawal or tears suggesting severe pain. If these signs and symptoms were absent patients were questioned every 5-10 seconds during injection regarding the presence of pain or discomfort. A four-point scale was used to grade pain:

0 = no pain, 1 = mild pain (pain reported only in response to questioning without any behavioral signs), 2 = moderate pain (pain reported only in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning) and 3 = severe pain (i.e., strong vocal response or response accompanied facial grimacing, arm withdrawal, or tears). (3)
The authors do not mention who the observers were and whether they were male or female. They also do not mention whether the patients received any treatment for pain if in fact they did experience it.

Analyses of the results was done using the Z test and Fisher’s exact test where appropriate. SPSS was used for statistical analysis. These are acceptable and widely used statistical methods.

The primary end points of the study were incidence and severity of pain. While the injection site was checked for pain or an inflammatory response by a blinded anaesthesiologist within 24 hours of the surgery, rather than being an end point this would serve as a means of looking for adverse effects of the drugs under investigation.

RESULTS

In terms of demographic data, the groups were in fact comparable, and this is clearly displayed in table form. No subjects were eliminated from the study. But, breakdown of pain assessment by age and gender was not done. In my opinion these two factors may have significantly affected the reporting of pain.

It was found that 78% of patients receiving normal saline experienced pain during Propofol injection as compared with 42% and 20% in the Lidocaine and Butorphanol groups respectively. There is a clear discrepancy however between the text and tabulated intergroup comparison: while the text states that Butorphanol decreased the frequency but not severity of Propofol pain when compared with Lidocaine (p<0.05), a table displaying this comparison shows in fact that both the incidence and severity of pain was less in the Butorphanol group. Later on, in their discussion the authors clearly stated that Butorphanol pretreatment was most effective in attenuating pain, both in terms of incidence and severity. (p<0.05). (3)

DISCUSSION

The main conclusion of the study was that while pretreatment with either Butorphanol 2mg or Lidocaine 40mg reduced the incidence and severity of pain associated with Propofol injection, Butorphanol pretreatment was most affecting in attenuating incidence and severity of pain. While the results of the study do in fact support this conclusion, certain limitations in the study would discourage me from accepting the superiority of Butorphanol based on this study.

These limitations are:

- Exclusion criteria: Failure to take into consideration and exclude from the study patients with previous or ongoing painful conditions, which may alter their perception of Propofol-induced pain.
- Premedication with a Benzodiazepine: The sedative and anxiolytic effect of Lorazepam would likely alter the perception and affective component of pain.
- Assessment of patients’ pain: Gender differences in the observers may lead to bias in interpreting patients’ response to Propofol. Also, the scales used to interpret pain seem quite subjective. If the investigators had used a more standardized scale such as the McGill pain questionnaire the results would have been more valid.
- Reporting pain: Gender differences in patients may affect how readily patients report pain. Women may admit to feeling pain more readily than men. This very important difference was not taken into account in the analysis.
- Frequent questioning regarding pain while injecting Propofol: Patients were questioned every 5-10 seconds about pain while the Propofol was being injected. This anticipation of pain may in itself have led patients to believe that they were actually experiencing pain when they were not.

If all the above factors had been taken into consideration when designing the study, the question that would still remain answered would be precisely determining the site of action of Butorphanol. The authors state that Butorphanol may act centrally through opioid receptors and as a local anaesthetic. This central action may lead to inaccurate assessment of Propofol induced pain.

At this stage, my clinical practice would not be influenced by this study until further evaluation. While the study does in fact address a very common problem and open a new avenue for intervention it would be premature to accept the authors’ hypothesis at this stage.

REFERENCES


April 15, 2005
Critical Appraisal Essay

By: Kara Gibson, MD, PGY-1

Title of Publication: “Prophylaxis of Postoperative Nausea and Vomiting with Oral, Long-Acting Dimenhydrinate in Gynecological Outpatient Laparoscopy.”

Authors: Kim E. Turner, MD, Joel L. Parlow, MD, Nicole D. Avery, MSc, Deborah A. Tod, RN, and Andrew G. Day, Msc.


The study by Turner et al was conducted in our own institution, Kingston General Hospital. This poses a unique opportunity for an internal review of our own department, which is good practice for any institution.

Introduction

The problem addressed in this study is common in anesthesia – postoperative nausea and vomiting (PONV). The authors propose that dimenhydrinate, either alone or in combination with droperidol, would be more effective in treating PONV than droperidol alone in outpatient gynecological laparoscopy. This issue is especially relevant in the population in question – gynecological outpatients. Currently, there are many adequate pharmacological choices to manage PONV; nausea, however, remains a challenge to treat. Certainly, PONV is a significant and frequent symptom for patients, but rarely a serious or prolonged event. Prevalence alone may be the best reason to justify the need for this study. This study will examine a particular pharmacological choice that is familiar and inexpensive, and, while not the primary intent of the study, may also contribute to the body of literature on PONV regarding timing of administration and multireceptor targeting with combination drug treatment.

Methodology

The study is well designed. It is a prospective, experimental, randomized, double-blinded study on humans. The control for the study is historical, using an estimate of 35% complete treatment failure of PONV with droperidol in our PACU as a comparison. There is no placebo arm as the standard of practice and the literature dictate treatment of such a high-risk group with active drug. The sample size is correctly set at 40 per group to power the study at 80%.

Ethically, the study is sound. There is no placebo arm, given the reasons stated above; all treatments used are effective. Sample size was carefully chosen with enrollment of only slightly more patients to allow for potential protocol violations and dropouts, ensuring patients are not exposed to an unknown regimen needlessly in an under- or over-powered study. Ethics approval was obtained. No sponsors are listed. Informed consent was obtained.

Patient selection is from the operating room list for gynecological laparoscopic outpatient surgery at KGH. Exclusion criteria are explicitly quoted in the paper. However, it is not clear if every patient on the OR list was approached, nor how many, and who may have refused to be part of the study. Exclusion criteria seemed reasonable and relevant comparing other PONV studies. These included BMI > 35, presumably because of increased risk from vomiting secondary to difficult airway management, treatment with drugs with similar effects, pregnancy, nausea or vomiting (N/V) in last 24h to avoid confounding with N/V of a different etiology, and inability to swallow the medication. The only unclear exclusion criteria is pre-existing GI disease requiring management. Perhaps this is because they may be more likely to have N/V, because the management may be an antihistamine, or because the protocol used indomethacin. Patients are randomized by a computer-generated table and stratified by history of PONV.

The experimental protocol was concise and focused on testing the hypothesis. The details are almost completely described in the paper and could easily be reproduced. Strengths of the study design are its simplicity and conformity to routine OR and PACU practice, excepting the choice of drugs. This gives it clinical relevance and likely contributes to the complete absence of protocol deviation, dropouts and loss to follow up. The surgical procedure and anesthetic drug doses including induction agents, opioids, neuromuscular blockade and reversal, analgesics and fluids are clearly recorded in the paper. There is a noticeable paucity of details largely regarding the surgical management of the patients, such as insufflation pressures, difficulty of procedure, excessive bleeding, and complications. From an anesthetic perspective, it would be interesting to note if there was prolonged mask ventilation, decompression with a nasogastric tube or a clerk or PGY-1 was inducing! Another notable omission is the specific criteria used in the PACU to administer ‘rescue medication’, a very important point as this decision may have moved patients from CTF (for nausea only) to TFV (vomiting, retching, or rescue medication). The paper states only that rescue medication was given on patient request or “if deemed necessary by PACU staff”. Additionally, the scales used to assess nausea were not validated. The researchers compared the severity of the nausea with an unnamed test and determined there was no difference, so nausea was dichotomized into presence and absence. Frequency of vomiting is not recorded. No validated scales were used to assess pain, ability to return to ADLs, drowsiness etc but these results were not used in the primary or secondary conclusions of the study.

Endpoints of the study are primarily CTF, defined as any of N/V/retching/rescue medication and secondarily TFV, defined as any of V/retching/rescue medication. Data were
successfully collected by PACU staff and by study personnel who interviewed patients over the phone who were keeping patient diaries. There were no dropouts, none lost to follow up and rescue medication was analyzed as both CTF and TFV.

Statistically the correct tests were applied – ANOVA to continuous data and Fisher’s exact test to a small sample of nominal data. The sample size was set at N=40 per group, with a=0.05 for a two-tailed test of significance, for power of 80%. The authors decided they would consider an absolute risk reduction of 25% in CTF to be clinically significant, which would translate to a reduction from the estimated 35% CTF to 10%. As noted above, p<0.05 is statistically significant. The software is named in the analysis.

Graphs constructed to display data were on the most part clear and useful. The demographic, surgical and anesthetic data, Table 1 is quite standard. The cumulative bar graphs for CTF and TFV are exceptional, showing concisely that a significant portion of symptoms occur after discharge. Table 2 summarizing numerical results, CI, p-value etc for each group is somewhat cumbersome and difficult to read.

Conclusions

The study failed to show any clinically significant difference between any treatment groups, although the combination group fell just below clinical significance with 24% reduction in TFV. The only statistically significant difference is in this same combination group for a reduction in TFV with a p=0.007. It should be noted that dimenhydrinate tends to be more effective, in combination or alone, compared to droperidol on all accounts but failed to reach levels of significance.

Discussion

In regard to experimental methodology, there is a small potential for confounding in the study. Comparison between groups shows no differences in how groups were treated, specifically in regard to what each received as part of their management. The only difference between initial groups was found to be in BMI, with the combination group having a larger BMI (26 vs 24). However, not many comorbidities were addressed as inclusion/exclusion criteria or to compare patient groups initially. It is difficult, logically, to implicate a greater BMI as contributing to the positive result found in this group (decreased vomiting). It might be proposed that obese patients are more easily nauseated, although I cannot say this is proven. It might also be reasoned that a patient with a greater BMI may make the laparoscopic procedure more difficult, requiring higher insufflation pressure, resulting in more N/V. All of these would suggest there should be a greater incidence of PONV in this group not a lesser incidence. It is probable that rather than invalidating the study’s findings, this difference in patient groups would be more likely to mask a potentially greater treatment effect than what is seen.

Furthermore, there is potential for bias in the study secondary to deconstruction of the blind. Observer bias may be introduced if side effects of the preoperative dimenhydrinate, such as drowsiness, become evident before the patient is called to the surgical suite, especially if cases were delayed. It is unlikely that pre-induction administration of droperidol had a clinically noticeable effect.

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Lastly, concerning bias, it should be noted that the type of data and means of data collection is successfully designed to limit reporter and observer bias. When assessing the quality of data presented in this study by Turner et al, the choice for categorical data - presence or absence of nausea, vomiting, retching - gives more reliable data than subjective scores of severity. However, it does seem that frequency of vomiting would be easily obtained nominal data that would have clinical significance. The addition of this parameter would add utility to this study if it were included.

A potential concern of the experimental protocol may be the dose of droperidol used (0.625 mg IV). Work by Henzi et al (1) on the efficacy and dose-response of droperidol specifically for PONV reports that there is no dose-response for the antinauseant effect and low doses may be adequate (0.5 mg IV), but there is a dose-response for the antiemetic effect, the most efficacious dose being 1.5-2.5 mg IV. This could potentially change the results of the study to show that droperidol is in fact superior to dimenhydrinate alone for TFV when droperidol is used in therapeutic doses. It should not change the results on CTF as the dose for the antinauseant would be correct at 0.625 mg. It should be mentioned, however, that the droperidol dose of 0.625 mg IV was a commonly used dose in this institution at the time of the study and is also found throughout the literature in PONV studies. Similar data on dose-response and efficacy for dimenhydrinate are not yet established but the doses used here are quite common.

Worth mentioning is the remarkably high incidence of CTF in this study, especially compared to the authors’ pre-study estimate. It is quite reasonable to explain this, as the authors have done in their paper, as being related to a very high risk group of young women undergoing gynecological procedures, an outpatient group who would be traveling, use of opioids in the anesthetic, use of cholinesterase inhibitors for neuromuscular blockade reversal, and most importantly the addition of incidents occurring after discharge, which are numerous as we see in figures 1 and 2. More than half of the nausea for all groups occurred at home.

From this study it is obvious that nausea is the more common and more difficult symptom to treat. For our purposes CTF can be thought of as ‘at least nausea’; any more symptoms also put the patient into the TFV category. The two categories are not exclusive. Only one patient who vomited did not also have nausea in this study. Similar separation of nausea and vomiting in response to treatment is seen in other studies. In a meta-analysis by Kranke et al (2) of dimenhydrinate for PONV, dimenhydrinate is shown to be effective against vomiting but no better than placebo for nausea! It is a personal perception that perhaps nausea may be a more important clinical complaint than vomiting, especially when vomiting has been suppressed. Reassuringly, a study by Scuderi et al (4) of patient satisfaction of PONV management suggests that nausea is not the most important factor in patient satisfaction. Briefly, in this study treatment groups received a multimodal approach with triple-prophylaxis with Ondansetron, droperidol and dexamethasone and a low risk anesthetic, versus a standard anesthetic with Ondansetron versus a standard anesthetic with placebo. There was no significant difference in vomiting; the incidence of vomiting was very low overall. There was a significant difference in incidence and severity of nausea across groups. Satisfaction was assessed on a 0-10 pt scale. The
presence of severe nausea affected the satisfaction score only minimally or not at all. The satisfaction was 92-100% across groups. Perhaps the score has more to do with the personable anesthesia and PACU staff caring for the patients. Perhaps if they had asked the patients while they were nauseated, rather than five days afterward, they would have received poorer scores.

The bottom-line is that this study would not significantly impact my practice but rather makes me aware that nausea is more challenging to treat than vomiting. Unfortunately, it is the choice of drugs studied rather than a lack of positive results that limits the utility and applicability of this study. Since the time of this study the FDA has issued a ‘black box’ warning for droperidol because of risk of cardiac arrhythmias. As stated by Scuderi 2003 (3) the objective estimates of adverse events in droperidol versus Ondansetron, a widely-used and accepted antiemetic, are 0.06% and 0.04% respectively and reasonably, he suggests their use should be weighed in context of risk-benefit. It is a realistic expectation that the legal implications of the use of droperidol after the FDA warning will and have impacted its clinical use; I have not seen this drug used during

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