82927 - RCT OF CESAMET® (NABILONE) FOR PREVENTION OF PONV IN ELECTIVE SURGERY

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Introduction: Postoperative nausea, vomiting, or both (PONV) continues to be an important clinical problem. Untreated, one third of patients undergoing general anesthesia will have PONV\(^1\). PONV frequently delays discharge, and is the leading cause of unexpected hospital admission after planned ambulatory surgery\(^2\). Nabilone is a synthetic cannabinoid and a potent CB1 agonist\(^3\) which has been shown to be effective in preventing nausea and vomiting in patients receiving chemotherapy\(^4\). Given the past success translating treatments for chemotherapy-induced nausea and vomiting (ie. 5-HT receptor agonists) for use in the perioperative environment, we hypothesized that preoperative administration of nabilone would reduce the rate of PONV in the PACU.

Methods: With prior REB and Health Canada approval, informed patient consent and trial registration, we conducted a double-blind, randomized, placebo-controlled, single center, trial of Cesamet® (nabilone) for the prevention of PONV. A priori sample size calculation indicated the need to treat a total of 330 patients to detect a 25% reduction in PONV when selecting patients with a high pre-operative risk of developing PONV (based on the presence of at least 3 of 4 Apfel risk factors\(^1\)) scheduled for elective surgery under general anesthesia. Patients were randomized to receive either nabilone (0.5 mg) or placebo by mouth 1 to 3 hours pre-operation and were followed until discharge from the PACU. The primary outcome is nausea or vomiting in PACU and secondary outcomes include the total number and dose of rescue medications, nausea scores, rates of medication side effects, time to discharge from PACU, rates of admission due to PONV, pain scores and adverse events.

Results: Target enrollment (n=330) was completed just prior to abstract submission deadline so datalock and unblinding have not yet occurred. Preliminary demographic data showed mean age of 50 (range;18-84 SD;15) and all female subjects. The categories of surgery are: Intra- or retro-peritoneal 16%; Head-and-neck surgery – 14%; Urologic or gynecologic – 41%; Orthopedic – 14%; Breast – 16%. Overall, 31% of patients reported PONV and/or were given antiemetic therapy prior to discharge from the PACU. After unblinding and primary and secondary outcome analysis, we will
perform a multivariate analysis to stratify outcomes based on preoperative risk of PONV, type of surgery and the number and types of antiemetics given prophylactically at the anesthesiologist’s discretion. Categorical data will be analyzed using a chi-square test, continuous data using a student’s t-test or ANOVA, and survival analysis will be performed using Cox regression, with a level of significance set as P < 0.05.

**Discussion:** This is the largest trial of nabilone for PONV to date. This study was designed to be pragmatic and generalizable, including patients for a wide range of surgeries and simple single dosing regimen taken just prior to surgery. If this trial shows nabilone to be efficacious for this application it could provide a new option with no known prolongation of QT interval to prevent PONV in patients at high risk for this adverse outcome.

**References:**


FUNCTIONAL CONNECTIVITY IS PRESERVED UNDER SEVOFLURANE ANESTHESIA.

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Background: Anesthetic agents dependably and reversibly abolish conscious perception, an event for which the ultimate mechanism remains elusive. Advances in brain imaging technology have allowed us a peek into this enigma. Defined regions of the brain are interconnected into networks that allow for complex processing of stimuli. These functional connectivity maps can be seen as fluctuations in blood-oxygen level, correlated to changing levels of brain activity, on MRI scans (BOLD-fMRI). Functional connectivity studies have shown that there are number of resting state networks that are reproducible at the individual level. The objective of this study is to look at the changes in resting state functional connectivity under 1 MAC sevoflurane anesthesia in mechanically ventilated patients.

Methods: After REB approval and informed consent, adults scheduled for MRI of the brain under general anesthesia were recruited for the study. Routine standard preparation of the patient for general anesthesia for MRI was carried out in all patients. Resting state fMRI scans were acquired in all patients on a 3 Tesla scanner at 1 MAC of sevoflurane concentration. During the study period, ETCO\textsubscript{2} and the blood pressure were maintained at baseline value. Spontaneous BOLD fluctuations are measured, and a seed-voxel analysis done to identify the resting state networks. Five networks were investigated, the default mode network (DMN), executive control network (ECN) as well as the auditory, visual and sensorimotor networks. For each seed taken separately, Pearson’s correlation r-values were calculated between the seed time-course and the time-courses at each grey matter voxel. The r-values were transformed into Fisher z values.

Results: Total of 21 patients were recruited for the study and data from 13 patients were included in the final analysis (7 men and 6 women, mean age 39 years). Under 1 MAC sevoflurane anesthesia, resting state functional connectivity is preserved in all the five networks. For the DMN we identified connectivity in the posterior cingulate cortex/precuneus (z=9.5), medial prefrontal cortex, middle temporal and parahippocampal gyrus. For the ECN, dorsolateral prefrontal cortex showed highest connectivity (z=8.6). For the auditory, visual and motor networks, insula (z=8.8), cuneous (z=8.2) and pre-central gyrus (z=8.5) showed increased connectivity respectively.
Discussion: To our knowledge this is the first study to show the persistence of resting state networks under surgical anesthesia (1 MAC Sevoflurane). Our results suggest that there is a continued activity within the DMN under 1 MAC sevoflurane anesthesia. DMN plays a role in conscious self-awareness, a property of brain activity thought to be abolished by general anesthesia. This study suggests that some components of consciousness may be preserved even under clinically significant doses of anesthetics. Further studies are needed to confirm these early findings.

References:

Introduction: Ideal perioperative management of pheochromocytomas / paragangliomas (pheo) is a subject of debate and can be highly variable. (1-4) The purpose of this study was to identify potential predictive factors of hemodynamic instability during pheo resection.

Methods: A retrospective review of pheo resections from 1992 to 2013 was done after obtaining ethical approval. Intraoperative hemodynamics, patient demographics, tumor characteristics, and perioperative management were examined. Post-operative intensive care admission, myocardial infarction, stroke and 30-day mortality were reviewed. Linear regression was used to analyze factors influencing intraoperative hemodynamics.

Results: During the 20-year study period, 100 patients underwent pheo resection. Postoperative morbidity and mortality was significantly reduced (p = 0.003) in the last ten years of practice. There was a trend towards greater morbidity and mortality with intraoperative hemodynamic instability (p = 0.06). The preoperative dose of phenoxybenzamine and number of laparoscopic procedures increased in the last decade (59 mg (95% CI 32, 108) to 106 mg (95% CI 91, 124) p = 0.008 and 27 vs 54%, p=0.05, respectively). Increased preoperative phenoxybenzamine dose was a significant predictor of improved intraoperative hemodynamic stability (p=0.01). Lack of intraoperative magnesium use resulted in greater hemodynamic instability as preoperative SBP increased (p=0.002).

Discussion: Post-operative outcomes following pheo resection have improved over the last two decades. Preoperative alpha-blockade plays a significant role in improving intraoperative hemodynamics and post-op outcomes. Increased doses of phenoxybenzamine and utilization of laparoscopic approaches have likely contributed to improved outcomes in the last decade. Intraoperative magnesium use may provide protection against hemodynamic instability and warrants further study.

References:


85112 - GLUTAMATE RECEPTOR CHANGES IN EXPERIMENTAL SUBARACHNOID HEMORRHAGE

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Introduction: Understanding the subcellular processes which contribute to cellular injury during stroke and traumatic brain injury may guide appropriate use of neuroprotective anesthetics during periods of neuron vulnerability. Glutamate is important in the pathogenesis of brain damage after cerebral ischemia, including subarachnoid hemorrhage (SAH). Notably, brain extracellular and cerebrospinal fluid (CSF) as well as blood glutamate concentrations increase after experimental and clinical SAH [1,2]. While neurons are one potential source of glutamate, platelets also release glutamate as part of their recruitment [3] and might mediate neuronal damage. This study investigates the hypothesis that platelet microthromboemboli release glutamate that mediates excitotoxic brain injury and neuron dysfunction after subarachnoid hemorrhage (SAH).

Methods: Ethics approval was received from the institutional committee on animal care. We used two models, primary neuronal cultures exposed to activated platelets, as well as a whole animal subarachnoid hemorrhage preparation. Propidium iodide was used to evaluate neuronal viability, and surface glutamate receptor staining was used to evaluate the phenotype of platelet exposed neurons.

Results: We demonstrate that thrombin-activated platelet-rich plasma releases glutamate, which exceeds concentrations of 300 micromolar. When applied to neuronal cultures, this activated plasma is neurotoxic, and attenuated in part by glutamate receptor antagonism. We also demonstrate that exposure to thrombin-activated platelets induces a marked downregulation of the surface glutamate receptor GluR2, a marker of excitotoxicity exposure and a possible mechanism of neuron dysfunction. Linear regression demonstrated that seven days following SAH in the animal there was a strong correlation between proximity to microthrombi and reduction of surface glutamate receptors.

Discussion: We conclude that platelet-mediated microthrombosis contributes to neuronal glutamate receptor dysfunction and might therefore influence clinical outcome following subarachnoid hemorrhage. Accordingly, we are hoping to begin a pilot trial on the use of ketamine for neuroprotection following SAH, which may confer neuroprotection through its anti-glutamatergic activities. This work was published in the
Dec 2014 issue of the Journal of Neurosurgery.

References:

Introduction: Wada test is a diagnostic test performed to determine the language and memory lateralization prior to temporal lobectomy in patients with epilepsy\textsuperscript{1,2} The procedure involved intra carotid administration of etomidate to anesthetize one cerebral hemispheres and assessing the language and memory functions of awake contralateral hemispheres\textsuperscript{3}. During the test, electroencephalogram (EEG) recordings are used to confirm the anesthetic effect. Currently we don’t know how etomidate injection affects the EEG and neurophysiological functions. Unilateral etomidate injection has been shown to increase not only the slow activity but also the faster activity, in some case even bilaterally.\textsuperscript{4} The aim of our study is to determine if the clinical effects of etomidate can be explained by a functional de-synchronization of EEG activity from the relevant targeted regions of the anesthetized hemisphere.

Methods: After IRB approval, we retrospectively analyzed the EEG data from 15 patients who underwent etomidate Wada test in our institution from August 2010 to December 2014. The EEG data from 3 time periods (before the etomidate injection, during the clinical effect and at least three minutes after the end of the clinical effect) were analyzed. Four electrodes (2 anterior (F3, F4) and 2 posterior (P3, P4)) out of 24 were analyzed. Samples were re-referenced to A1. We analyzed two frequency bands – alpha (7-13 Hz) for posterior electrodes (P3, P4), delta (1-4Hz) for anterior electrodes (F3, F4). After artifact rejection, we measured the anterior (delta) and posterior (alpha) inter-hemispheric connectivity before, during and after the drug effect using Matlab correlation function (http://www.mathworks.com/help/matlab/ref/corrcoef.html). The statistical analysis were done using paired t-test, where P value < 0.05 was considered statistically significant.

Results: Eleven out of 15 patients had left hemispheric injection of etomidate and the rest right-sided injection. EEG analysis showed increase in delta and alpha activity both in the injected side and the contra-lateral side (Figure 1-A). Connectivity analysis showed that 13/15 patients had significant de-synchronization between the hemispheres in the anterior delta frequency band. (Figure 1-B). Interestingly, de-synchronization of delta frequency recovered to higher synchronization level after
etomidate cessation, when comparing to the synchronization before the Wada test. Similar phenomenon was not consistently observed for the posterior alpha band (Figure 1C).

**Discussion:** Our study shows that intra-arterial etomidate injection results in anterior inter-hemispheric de-synchronization of frontal slow wave activity (delta). Frontal slow wave activity (delta) has been shown to be associated with attention/working memory and these frontal processes probably play a major role in memory tasks.⁵,⁶ Hence the frontal de-synchronization of EEG activity probably affect the memory task and this could possibly explain the clinical effects during etomidate WADA test. Further studies are needed to validate this effect.

**References:**

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Background: Despite tremendous advancements in the management of liver transplantation (LT), there is no precise method to assess the function of transplanted organ. Transplant organs come from either Deceased Donors (DD) or Living Donors (LD). The metabolic activity of the donor organ depends on the size of the donor organ and the amount of donor organ damage as a result of cold or warm ischemia. In the case of DD and LD, their influences on liver function are quite different. Our objective was to investigate whether pharmacokinetic (PK) of two anesthesia drugs routinely used during LT [i.e. Rocuronium (ROC) and Tranexamic acid (TXA)] could serve as a marker to evaluate the function of transplanted livers. ROC was considered because it is metabolized partially by the liver, and TXA was chosen since it is eliminated exclusively by the kidney.

Methods: Following REB approval and written informed consent, 22 consecutive patients scheduled for LT were recruited. Patients were divided into two groups: DD (n=13, assuming 1500 g liver) received cadaveric livers, and LD (n=9, 672±89 g liver) received living livers. Immediately prior to reperfusion of the transplant organ, all patients were given 0.6 mg·kg⁻¹ of rocuronium (ROC). Tranexamic acid (TXA) was given as 1 g bolus at the beginning of LT followed by 10 mg·kg⁻¹·h⁻¹ for 2 h. Blood samples for PK analysis were collected at baseline and at 5, 30, 60, 180, 300, 420 and 540 min post TXA bolus, at 15, 120, 240, 360 min and 24 h after discontinuation of TXA infusion, and at 5, 30, 60, 90, 120, 180, 240, 300 and 450 min post ROC bolus. The plasma concentrations of TXA and ROC were measured by solid phase microextraction (SPME)-based extraction and liquid chromatography mass spectroscopic (LCMS) analysis as described previously. PK analysis was conducted using a PKPD modeling software, ADAPTS® (BMSR version 5, USC).
**Results:** After bolus of ROC, biexponential decay profiles fit a two-compartmental model, revealed a significant difference in ROC clearance (CL). Patients from DD transplant group had a significantly lower CL ($0.157 \pm 0.050 \text{ mL-min}^{-1} \cdot \text{g}^{-1} \text{ liver}$) compared to those from LD transplant group ($0.265 \pm 0.148 \text{ mL-min}^{-1} \cdot \text{g}^{-1} \text{ liver}$), values comparable to those ($0.21 - 0.31 \text{ mL-min}^{-1} \cdot \text{g}^{-1} \text{ liver}$) in healthy subjects$^3$. By contrast, there was no difference in TXA CL ($1.05 \pm 0.50$ vs. $0.965 \pm 0.38 \text{ mL-min}^{-1} \cdot \text{kg}^{-1}$; $P > .05$) or distribution volume ($503 \pm 71$ vs. $467 \pm 57 \text{ mL-kg}^{-1}$; $P > .05$) between two groups. Baseline creatinine concentrations ($81.8 \pm 46.7$ vs. $89.6 \pm 19.7 \text{ μM}$) and creatinine clearance ($103.6 \pm 34.7$ vs. $83.2 \pm 20.0 \text{ mL-min}^{-1}$) for LD and DD transplants were not significantly different ($P > .05$), suggesting normal renal function in both groups.

**Conclusions:** ROC CL was lower in DD than in LD transplant group which may indicate differences in the metabolic capacity of the donor organ immediately after reperfusion. In contrast, there was no difference in TXA metabolism which suggests there is no difference in renal function between the groups. Differences in the ROC metabolism may be used to assess immediate liver function.

**References:**

Introduction: Oxycodone is among the most commonly used opioid for postoperative pain control. Studies have demonstrated marked variation in the pharmacokinetics (PK) of oxycodone among pediatric population. The principal metabolic pathway of oxycodone is N-demethylation via enzyme Cytochrome P450 3A4 (CYP3A4) to generate inactive noroxycodone. However, 11% is O-demethylated by CYP2D6 to become oxymorphone, the active and potent metabolite that exhibits about 40 times the affinity and 8 times the potency on μ-opioid receptors compared to the mother substance. Frequencies of cytochrome P450 2D6 (CYP2D6) enzyme phenotypes for the Caucasian population are: poor metabolizers 5–10%, intermediate metabolizers 65–90%, and ultra-rapid metabolizers 5–10%. Ultra-rapid metabolizers may be at risk for serious side effects in the commonly prescribed dose. Understanding oral oxycodone pharmacokinetics and pharmacogenomics favors safe and effective use of this analgesic in a wide variety of pediatric surgical patients. There is little information of oral oxycodone pharmacogenomics and its metabolites in pediatrics. The aim of this study is to characterize the population PK of oxycodone and its metabolites (oxymorphine, noroxymorphine and noroxycodone) with specific respect to the pharmacogenomics.

Methods: This prospective cohort, single-center trial is approved by the hospital investigational review board. A total of 40 opioid-naive children, aged 0-6 years, scheduled for in-patient surgery, will be consented. Blood samples will be collected for the assay oxycodone and its main metabolites at specific time intervals and for CYP3A4 and CYP2D6 genotype. Oxycodone, oxymorphone, noroxymorphone and noroxycodonel levels at 10 time points will be assayed using LCMS (liquid chromatography- mass spectrometry) and single-dose Pharmacokinetics (PK) metric determined. CYP2D6 genotype will be determined to identify the ultra-rapid metabolizers.

Results: The preliminary analysis of 10 patients reveals an interpatient variability similar to that previously reported (1,2) (Figure 1). Some patients have a very short onset of
absorption with Cmax up to 10ng/mL, while others exhibit a lag time for absorption of at least 4h with peak concentrations under 4ng/mL. Although so far all these patients exhibit similar CYP3A4 expression, these differences in oxycodone plasma concentrations seem to agree with their CYP2D6 expression differences. Plasma concentrations using 250 mL of whole blood were analysed with state-of-the-art pharmacokinetics software.

**Discussions**: These preliminary results strongly suggest the paramount role of CYP metabolism in the systemic concentrations of oxycodone, and hence the need for its consideration in the dosing optimization of the drug.

Figure 1: Differences in onset of absorption and magnitude of oxycodone concentrations relative to CYPs 3A4 and 2D6 expression

**References:**