The role of Lamotrigine in Reducing Psychologic Side-Effect of Perioperative Ketamine Use

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Summary of changes in red

- **Page 5 – added "Planned surgery duration 3-6 hours" in inclusion criteria**
- **Page 5 - added "history of lamotrigine use" in the exclusion criteria**
- **Page 6 – added** BPRS assessment "within 90 minutes of PACU arrival and the following morning"
- Summary of changes in blue
- **Pages 2, 3, 4, 5,and 6 There are some language and word flow changes throughout the paper**

1. Introduction

Opioid medications are the mainstay in the multimodal perioperative pain management and widely used in the United States.[1,2] Ketamine can play a role in perioperative pain management by lowering opioid utilizations and minimizing the opioid related side-effects.[3]

1.1 Ketamine

Ketamine is a well-known general anesthetic functioning by N-methyl-D-aspartate (NMDA)-receptor antagonism. Additionally, ketamine has diverse molecular targets and neurophysiological properties which can help in the management of acute and chronic pain, depression, posttraumatic stress disorders, and schizophrenia.[4]

1.1.1 Role of ketamine for anesthesia and analgesia

Ketamine can be used for induction of anesthesia, analgesia and for prevention of inflammation and persistent pain. The drug's analgesic and anti-inflammatory effects are particularly useful in perioperative pain management because it reduces opioid requirements.[5] The analgesic effect is mediated through NMDA receptors[6], voltage-gated sodium channels[7,8], BK channels[9], opioid receptors (mu , delta)[10,11] and gamma-aminobutyric acid (GABA) receptors[12] (Table 1). Unsurprisingly, analgesia requires lower concentrations than general anesthesia.[13,14] A range of systemic inflammatory response is set in motion by surgical trauma, eliciting complex interaction with numerous inflammatory biomarkers.[15] Ketamine anti-inflammatory potential is elucidated by the reduction of biomarker interleukin-6 (IL-6) in early postoperative period.[16] Ketamine also play an important role in depression management.[17]

Ostensibly ketamine should be used widely for improving postoperative pain and outcomes. However this is not the case. The psychologic side-effects are one of the main reasons for its limited use. Emergence reactions are in reported in 10-20% of the patients. Consequentially opioid medications are the commonly used medications in perioperative pain management.

Ketamine may play role in reducing perioperative hypotension which has been associated with increased perioperative morbidity and mortality.[18,19] Usually hypotension is noted as an unavoidable side-effect of general anesthetics induction drugs like propofol.[20,21] Inhaled anesthetics and opioids also contribute to hypotension. Etomidate is an alternative induction agent which does not cause hypotension but its use is limited due to assumed adrenal suppression. [22,23] Ketamine preserves hemodynamics better than commonly used anesthetic induction drug propofol and does not cause adrenal suppression like etomidate. Thus Ketamine seems to be a good induction agent, but again the psychologic side-effects again prevents its common use.

In summary, ketamine is a useful drug for anesthesia and analgesia in surgical patients. Common reasons for use in induction and maintenance of anesthesia is the opioid sparing effects and hemodynamic stability. And the most important reason not to use is the psychologic effects.

1.1.2 Psychologic side-effects of ketamine

The use ketamine in perioperative period may lead to psychologic side-effects. But the extent of side-effects from low dose ketamine is not fully characterized. Most information of side-effects comes from chronic pain and psychiatry literature where the dosage and duration of ketamine treatment is much higher. In chronic pain management the use of ketamine is associated with dose-dependent side effects including psychedelic symptoms (hallucinations, memory defects, panic attacks), nausea/vomiting, somnolence, cardiovascular stimulation and, in a minority of patients, hepatoxicity. [24] Usually the dose used is 30 mg/hour for 4-14 days. Blagrove et al reported an increase in dream unpleasantness over the three nights after ketamine use.[25] Browdle et al reported dose-related psychedelic effects in healthy volunteers with the use of ketamine.[26] However no amnestic medications were given which are routine in perioperative of setting.

1.2 The role of Lamotrigine

The mechanism of psychologic effects of subanesthetic ketamine remains unclear. Increased dopamine release, effect on the γ-aminobutyric acid (GABA) system, and modulation of the serotonergic system have been suggested as possible mechanisms.[27] Lamotrigine, an anticonvulsant which decreases presynaptic glutamate release and widely used for neuropsychiatric illness.[28] Lamotrigine augmentation of serotonin reuptake inhibitors is well tolerated in treatment-resistant obsessive–compulsive disorder. [29] Lamotrigine may play a role in treating ketamine use disorder.[30]

A key study was reported at the Society of Neuroscience meeting in 1997 and later published in the Archives of General Psychiatry. It reported that in healthy subjects, 300 mg oral lamotrigine significantly decreased ketamine-induced perceptual abnormalities as assessed by the Clinician-Administered Dissociative States Scale (P<.001).[31] Furthermore lamotrigine increased the immediate mood-elevating effects of ketamine (P<.05). The authors concluded that glutamate release-inhibiting drugs may reduce the hyperglutamatergic consequences of NMDA receptor dysfunction which may be implicated in the pathophysiologic processes of neuropsychiatric illnesses.

In an another experiment designed to identify the sites of action of ketamine in inducing symptoms and to determine the role of increased glutamate release using the glutamate release inhibitor lamotrigine, the authors concluded that lamotrigine pretreatment prevented many of the signal changes and the symptoms associated with ketamine use.. The results of this clinical study were confirmed in a laboratory study published in Science 1998 –"Reversal of Phencyclidine Effects by a Group II Metabotropic Glutamate Receptor Agonist in Rats".[32] The authors noted that "*Group II metabotropic glutamate receptors were targeted to normalize glutamatergic disruptions associated with an animal model of schizophrenia, the phencyclidine model. An agonist of this group of receptors, at a dose that was without effects on spontaneous activity and corticolimbic dopamine neurotransmission, attenuated the disruptive effects of phencyclidine on working memory, stereotypy, locomotion, and cortical glutamate efflux. This behavioral reversal occurred in spite of sustained dopamine hyperactivity*."

Available evidence therefore supports use of lamotrigine for reducing undesirable psychologic effects of low dose ketamine in perioperative period. If it in fact does, lamotrigine might broaden use of ketamine for anesthesia and pain management.

2. Specific Aim and Hypothesis

Aim – The aim of this pilot trial is to determine whether lamotrigine reduces psychologic side-effects consequent to low-dose ketamine in surgical patients. This pilot study will confirm the feasibility of a subsequent hypothesis testing study, and provide data to strengthen a sample-size estimate.

Hypothesis - Preoperative treatment with 300 mg lamotrigine reduces psychologic side-effects (measured by four key items of Brief Psychiatric Rating Scale: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) in adults given ketamine for non-cardiac surgery.

3. Significance

Ketamine has multiple properties of an ideal anesthetic induction and maintenance agent. The analgesic effects has desirable opioid sparing effects, and the anti-inflammatory properties may help improve outcomes. But its use in perioperative setting is limited, primarily, due to concerns of the psychologic side effect. Lamotrigine can help reduce the undesirable psychologic side-effects of ketamine.

4. Plan of investigation

4.1 Outcomes

1.1.1 Primary outcome
1. Psychologic side-effects measured in PACU (up to 90 minutes after ketamine infusion) by four key items of Brief Psychiatric Rating Scale (BPRS) corresponding to positive symptoms of schizophrenia: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content. Each symptom is rated 1-7 (1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe), and, therefore, the total score based on four key items of BPRS will be between 4 (best score) and 28 (worst score).

4.1.2 Secondary outcomes
1. Opioid use in PACU – total IV morphine equivalents
2. Pain score in PACU – numeric rating scale (0-10)
3. Binary outcome postoperative nausea vomiting (PONV) in PACU
4. Postoperative Nursing Progress Record (NPR) records nausea vomiting severity as: 0=none, 1= mild, 2=moderate, 3= severe; analysis will compare two study groups on moderate and severe nausea / vomiting (0 or 1 *vs*. 2 or 3) in the PACU.

4.1.3 Exploratory outcomes
1. Sedation agitation scale[33] (RASS score) at the time of admission in PACU.
2. Average daily opioid utilization during hospitalization (morphine equivalents).

3. Opioid related side-effects, using the opioid related symptom distress scale (ORSDS) on the first and second postoperative days.[34,35]

4.2 Trial design
Double blind, randomized (1:1), pilot study.

4.3 Sample size

This pilot study will enroll 50 patients, with 25 randomized to lamotrigine or placebo.

With 50 total patients we will be able to estimate a treatment effect with 95% confidence interval. Variability and treatment effect estimates observed in this pilot study will be used for planning larger trials powered for binary outcomes.

Although not the focus, assuming standard deviation of 2 units (Anand and others, Attention of the Neuropsychiatric effects of Ketamine with Lamotrigine reported the mean ± SD of 1.5± 2 for BPRS outcome), the sample size of N=25 patients per group (N=50 patients total) will provide about 90% power at the 0.05 significance level to detect the difference of 1.9 or larger in units drop between two study groups.

5. Eligibility criteria
Patient undergoing elective abdominal surgery. Specifically, we will enroll surgical inpatients 18-65 yr having noncardiac surgery who require a general anesthesia. We will exclude patients in whom ICU admission is planned preoperatively.

5.1 Inclusion criteria
- 18-65 years of age
- Planned overnight hospital stay
- Planned surgery duration 3-6 hours

5.2 Exclusion criteria
- Pediatric and pregnant patients
- History of seizure
- History of Schizophrenia
- History of unstable angina
- Antiepileptic medications
- History of lamotrigine use

6. Training for rating scales:

a. BPRS ratings: will be conducted by anesthesia fellows. All fellows will be trained on how to do the ratings by co-investigator, Dr. Amit Anand (Vice-chair of Research, Center for Behavioral Health). Raters

will also have to pass a quiz used in a large ketamine study being conducted at the Cleveland Clinic to assess understanding regarding the ratings.

6. Protocol

6.1 Patient recruitment

From anesthesia preoperative clinic.

6.2 Randomization and blinding

1:1 randomization without stratification use web-based software (Redcap) before surgery. Allocation will be concealed from the patient, the nurse, the operating room team. Both patient and the operating room team will be blinded to the treatment allocation (double blind).

6.3 Preoperative care

Standard preoperative care as per anesthesia care team. Patient will receive lamotrigine vs. placebo with small sips of water. Lamotrigine reaches peak level 1-4 hours after oral administration. Single dose lamotrigine is safe and is not associated with rash.[36]

6.4 Intraoperative care

Standard intraoperative care as per the anesthesia care team. All patients will receive Ketamine 1 mg/kg at induction. Ketamine 5mcg/kg/min will be started at induction and stopped at the end of surgery.

6.5 Postoperative care

Standard postoperative care as per PACU team. The psychologic side-effects will be measured using Brief Psychiatric Rating Scale (BPRS)[37,38] using an online tool(http://farmacologiaclinica.info/scales/BPRS/), within 90 minutes of PACU arrival and following morning.

Research fellow will receive standardized training in administering BPRS from Dr Amit Anand using structured material. Dr Anand has used this training for other current research projects.

7. Data analysis

The analysis and reporting of the results will follow the CONSORT guidelines (www.consort-statement.org). The process of patient selection and flow throughout the study will be summarized using a flow-diagram.

We will analyze patients in the treatment group to which they are allocated, according to the intention-to-treat principle. Any patients lost to follow-up will be censored at the time they are lost to follow-up.

7.1 Statistical plan

First, we compared two randomized groups (lamotrigine vs. placebo) for balance on potentially confounding patients' demographic, baseline and surgical characteristics using univariable summary statistics (mean and standard deviation, median and quartiles, or proportions, as

appropriate) and using absolute standardized difference scores (ASDs). ASDs are defined as the absolute value of the difference between means, mean rankings, or proportions divided by a combined estimate of standard deviation; thus the ASD roughly represents the number of standard deviations the two study groups are apart from one another.

The exploratory outcomes will be summarized by two randomized groups using descriptive summary measures: expressed as mean (standard deviation) or median (interquartile range) for continuous variables and number (percent) for categorical variables. No formal statistical test will be conducted for the exploratory outcomes.

Primary analysis

As for primary analysis, two randomized groups will be compared on the continuous total score based on BPRS four items ranging between 4 (best score) and 28 (worst score). We will estimate the effect of Lamotrigine on reduction psychological side-effects of ketamine infusion using the two-sample Wilcoxon rank sum test and Hodges Lehmann estimation of location shift (along with 95% confidence interval). This method is appropriate since we expect that the outcome will exhibit a skewed distribution. If the incidence of any psychologic effects is very low, meaning that vast majority of the patients will have a score of four (corresponding to no symptoms), we will treat the outcome as binary (no symptoms vs. any symptoms). I this case the chi-square test will be used to compare two randomized groups; the odds ratio along with 95% confidence interval will be reported.

The Type I error for the primary analysis will be kept at 5% level with significance criterion of $P<0.05$.

Secondary analysis

Assuming log-normal distribution of PACU opioid consumption (in IV morphine equivalent), we will evaluate the percent difference in geometric mean IV morphine equivalent dose between the two randomized groups using t-test on the log-transformed data. To evaluate the difference in mean PACU pain scores (in VRS scale) we will first summarize the pain scores (in VRS scale) by computing PACU time weighted average (TWA) pain score for each patient. Then we will use a t-test to assess the exposure effect on the TWA pain scores. Binary PONV outcome will be compared between two study groups using chi-square test.

We used the Bonferroni adjustment for multiple analyses to preserve Type I error at 5% level for the secondary analysis with the significance criterion of 0.017 for each of the secondary outcome (i.e., 0.05 / 3).

7.2 Data management

Redcap software will be used for storing patient level information for this study. Or paper case report form will be used and stored in secure location at Outcomes Research department.

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Table -1 Ketamine receptors

Antagonism/Inhibition

NMDA receptors	• Dissociative anesthesia, amnesia (Oye et al., 1992) • Inhibited sensory perception (Oye et al., 1992) • Analgesia (Oye et al., 1992)
HCN channels	• Hypnosis (Chen et al., 2009; Zhou C. et al., 2013)
Calcium channels (L-type voltage-dependent)	• Negative cardiac inotropy (Baum and Tecson, 1991) • Airway smooth muscle relaxation (Yamakage et al., 1995)
Voltage-gated sodium channels	• Decreased parasympathetic activity (Irnaten et al., 2002) • Local anesthetic effect (Frenkel and Urban, 1992; Haeseler et al., 2003)
BK channels	• Analgesic effects on neuropathic pain (Hayashi et al., 2011)

Agonism/Activation

Opioid receptors (particularly μ, δ)	• Central antinociception (Finck and Ngai, 1982; Pacheco Dda et al., 2014)
AMPA receptors	• Rapid antidepressant effects (Zanos et al., 2016)
GABA$_A$ receptors	• Anesthetic properties (Irifune et al., 2000)

NMDA, N-methyl-D-aspartate; HCN, Hyperpolarization-activated cyclic nucleotide; BK, Large-conductance potassium channels; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA$_A$R, γ-aminobutyric acid A receptor.