Randomized, double-blind, placebo controlled study on the effect of a single postoperative administration of low dose ketamine after gastric bypass and gastrectomy surgeries

Primary Investigator: Jing Wang, M.D. Ph.D.

New York University Langone Medical Center, Department of Anesthesiology

Study Number: S13-00719

Background

Bariatric surgeries for the treatment of obesity and type II diabetes represent one of the most common abdominal operations, with over 300,000 cases performed in 2011.[1] Postoperative care is a critical component for outcome from these procedures. Optimal postoperative pain management, however, can be difficult to achieve. While many incisions are small, a significant proportion of patients who undergo bypass or sleeve gastrectomy still stay in the hospital for more than two to three days, and patients can suffer from a combination of incisional and visceral pain. Pain control currently is achieved through a combination of opioids, Acetaminophen, and NSAIDs. Opioids are the most powerful analgesic in this group. Opioids, however, are well known to cause sedation and respiratory depression, which can significantly impact respiratory status of bariatric patients, many of whom already suffer from respiratory compromise due to obesity and obstructive sleep apnea. NSAIDs, meanwhile, may increase the rate of bleeding complications. Thus, additional analgesics are needed to achieve optimal pain control.

A key component of postoperative pain experience is depressed mood, which further complicates functional recovery.[2,3] Bariatric patients, in particular, have a high co-morbidity of depression, which can be worsened by postoperative pain.[4-6] Optimal pain control, on the other hand, has been shown to improve patient satisfaction, elevate mood, and allow early participation in physical rehabilitation such as early mobility, all of which contribute to better surgical outcome. Studies are needed, however, to examine additional postoperative measures that can enhance functional recovery in bariatric patients.

Ketamine is a well-known analgesic that has been frequently used pre-, intra-, and post-operatively. The analgesic property of ketamine is dose dependent, but it is generally believed to be short lived, as the medication is metabolized within an hour.[7] Although ketamine has been shown in animal studies to block central sensitization to mediate long-acting analgesia,[8] this remains to be proven in clinical practices.[9] Low dose ketamine (<0.5mg/kg/hr) is used routinely and safely for inpatient pain management[10] and outpatient management of certain chronic neuropathic pain conditions such as complex regional pain syndrome.[11]

Meanwhile, in the last ten years or so, a number of studies have provided exciting evidence that ketamine has rapid-onset antidepressant effects that may last up to seven days.[12-14,15,16] Several mechanisms have been proposed to explain this mood elevating effect of ketamine including increased glutamate transmission[17,18] and increased brain derived neurotrophic factor expression.[19] Animal studies have confirmed that ketamine, given as an analgesic, has rapid and

enduring mood elevating effects in postoperative pain states.[20] Despite its wide use in the postoperative setting as an analgesic, however, few clinical studies have examined the effect of ketamine on mood and functional status in the postoperative patients. Currently, there is only one study on peri-operative use of ketamine in bariatric patients,[21] which showed that pre-inductive use of ketamine leads to early extubation and decreased total use of opioids. No study, in contrast, has examined the effects on mood and functional recovery with the use of ketamine postoperatively for pain control.

A number of pro- and anti-inflammatory cytokines (interleukin IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, and tissue necrosis factor, TNF-α) have been linked with stress and mood regulation.[22] Some of these cytokines, particularly IL-1, IL-6 and TNF-α, have also been implicated in pain states as well. In addition, reduced serum levels of brain derived neurotrophic factor (BDNF) have been described to correlate with pain as well as depressed mood, and ketamine has been hypothesized to increase BDNF levels.[23] However, there has been limited study in postoperative pain on the involvement of cytokines and neurotrophic factors as potential markers for assessing pain and predicting analgesia.

Study Rationale

Ketamine, given for postoperative pain control, can be hypothesized to have long lasting analgesic effects as well as effects on improving mood and function in the postoperative period. Ketamine can be administered as a single dose in the post-anesthetic care unit (PACU), where patients are closely monitored for potential side effects. We hypothesize that postoperative use of ketamine should lead to improvement in pain indices including visual analog scale (VAS), a decrease in opioid requirement, mood improvements as measured by psychometric indices, and finally improvements in functional measures including early mobility and faster discharge from the hospital. In addition, we will assess serum levels of IL-1, 6, TNF-α, and BDNF to see if alterations in levels of cytokines and neurotrophic factors occur with postoperative pain and how ketamine treatment may influence the levels of these biomarkers.

Study Objective

Specific aim 1: examine the effect of a single, subanesthetic dose (0.4mg/kg) of ketamine vs. saline control on mood and postoperative function in patients who have undergone gastric bypass and sleeve gastrectomies.

Pain relief and changes in postoperative mood and function will be assessed using both patient report, in the forms of a series of questionnaires, and medical chart review. The questionnaires we use will be Beck Depression Inventory (BDI), Visual Analog Scale (VAS), McGill's short form, QoR-15 form and the Montgomery-Asberg Depression Rating Scale (MADRS). Please see below for a detailed discussion of these forms. In addition, from the chart review we will monitor length of stay during hospitalization, opioid usage per hour during the PACU stay before and after ketamine infusion, total opioid usage per day throughout the hospital stay, time to out of bed to chair, and spirometry use after ketamine infusion.

Specific aim 2: examine the effect of a single, subanesthetic dose (0.4mg/kg) of ketamine vs. saline control on inflammatory cytokines and neurotrophic factors in the postoperative period.

We will examine the effect of ketamine on proinflammatory markers and neurotrophic factors known to be linked with pain. We will examine levels of interleukin factor 1 and 6 (IL-1, IL-6), TNF-α, and BDNF. This aim will provide potential mechanism of action for ketamine.

Overall study design and plan

This is a randomized, double-blind, placebo-controlled, two-arm parallel, single-center study. One hundred subjects (50 in each arm) will be enrolled. Subjects, between the ages 18 and 65, undergoing laparoscopic gastric bypass or sleeve gastrectomy under general anesthesia will be screened for eligibility to participate in the study. Subjects will be screened, recruited and consented during the preadmission visit prior to surgery. Eligible subjects will be randomized to one of the two treatment group in a 1:1 ratio to receive either IV ketamine (0.4mg/kg) or matching placebo. Both men and women will be recruited, and there is no limitation as to racial and ethnic origin.

Participation in the study will not alter the patient's surgical or anesthetic are, post-anesthetic care, or care on the floor. In the PACU, patients, if deemed medically stable by the study physician, will receive either 0.4mg/kg IV ketamine or placebo. All patients will also receive standard post-anesthetic monitoring and care, as well as routine care after transfer out of the PACU. There is no restriction on the use of other analgesics throughout the hospital stay. Patients are followed until the date of discharge, and endpoints (see below) are collected from patient reports as well as from medical charts. During their hospital stay (and once after their discharge from the hospital), patients will fill out five questionnaires which provide estimates of their postoperative pain control, mood and function, and quality of postsurgical recovery.

Patients will be randomized using a block randomization code for assigning 100 subjects to two groups. In Excel we generated 100 random numbers. In the next column we inserted multiple copies of the sequence PCPC where p= "placebo" and c = "control", forming 25 blocks. Then we sorted the random numbers in each 4 subject block, including the assignment letters (P, C) in the sort. The remaining list of Ps and Cs is the randomization.

To check the balance, we then did running counts of the cumulative repeats of "p" and "c" and "p – c". The tally for each totaled 50 and the two groups were always within 2 counts of being perfectly balanced, which met our goal. The list can be extended at will to accommodate screening failures.

Randomization lists will be sent to the pharmacy who will then be able to distribute the study drug/placebo as patients are enrolled and undergoing surgery, and the remainder of the study staff will be blinded.

An additional component of the study, which is entirely optional, is to obtain patient serum samples (about two teaspoons) in the operating room and 15 minutes and 4 hours after ketamine infusion. We will use these samples to assess levels of IL-1, IL-6, TNF-α, and BDNF, which are markers for pain. In addition, with patient consent, we will also store serum samples for future research use to measure other cytokines and neurotrophic factors and molecular markers associated with pain and depression.

Study site: Tisch Hospital

Outcome measures

Primary outcome measure: scores on the following questionnaires: 1) The Beck Depression Inventory (BDI); 2) Visual Analog Scale (VAS) score; 3) McGill's short form; 4) QoR-15 form; and 5) Montgomery-Asberg Depression Rating Scale (MADRS). The BDI and MADRS provide assessments for mood and function, VAS and McGill's assess pain, and QoR-15 assesses patient's overall satisfaction with postoperative recovery.

After consent is achieved in the pre-admission clinic prior to surgery, patients will be asked to fill out BDI, MADRS and QoR-15 forms to establish baseline scores. The BDI, MADRS will be filled out on postoperative days (POD) 0 after the infusion of ketamine, and BDI, MADRS and QoR-15 forms will be repeated on POD1, 2 and 7. McGill's short form will be filled out prior to discharge from the PACU and on POD 1, 2 and 7. VAS will be filled prior to PACU discharge, and every day while patient is in the hospital and on POD 7. VAS is a routine part of hospital care and will be administered daily whether a patient is enrolled in the study or not. If a patient has been discharged prior to POD2 or 7 (patients typically are discharged on POD2 or 3 in our practice), then a member of the study team will contact the patient by telephone to fill out these questionnaires.

Secondary outcome measures: 1) length of stay during hospitalization; 2) opioid usage per hour during the PACU stay before and after ketamine infusion; 3) opioid usage per day throughout the hospital stay; 4) time to out of bed to chair (OOB); 5) spirometry use 4 hours after the termination of ketamine infusion; 5) anti-emetic use in the PACU.

Length of stay, opioid usage, and anti-emetic use will be recorded from electronic medical chart. Patient will be asked to record and report the time to OOB. Spirometry use will be assessed by a study team member to determine whether the patient is meeting the goal set by the surgical team 4 hours after ketamine infusion.

Exploratory secondary outcome measures: changes in serum levels of IL-1, IL6, TNF-α, and BDNF, which will be collected at baseline (in the OR preoperatively), and 15 min and 4 hours after the termination of ketamine infusion.

Study population

Inclusion criteria:

1. Adults, >18 years, <65 years, who will undergo gastric bypass or sleeve gastrectomy.
2. Subject is non-lactating and is either:
   a. Not of childbearing potential; or
   b. Of childbearing potential but is not pregnant at time of baseline as determined by pre-operative pregnancy testing.
3. Subject is ASA physical status 1, 2, or 3.
4. Subject who is deemed medically stable

Exclusion criteria:

1. <18 years of age; >65 years of age
2. Pregnant or breastfeeding
3. Does not speak or understand English (the study forms used are copy-right in English)
4. Cognitively impairment (by history) or clinical signs of altered mental status
5. History of misuse or abuse of ketamine
6. History of chest pain or chest pain in the PACU
7. Use of a medication that interferes with metabolism of ketamine within the last 24 hours
8. A diagnosis of schizophrenia and/ or a history of chronic antipsychotic medication use
9. History of head trauma
10. History of intracranial mass or hemorrhage
11. History of stroke
12. History of cardiac arrhythmia
13. Subject for whom ketamine is contraindicated
14. Unwillingness to give informed consent according to HIC guidelines

Entry into Study

Flyers will be designed and posted in the bariatric clinic as well as the pre-admissions testing (PAT) clinic to inform patients about this study. Patients will be recruited from the bariatric clinic during their visit with the pre-surgical clinic visit with their surgeons, from the PAT during their preadmission visit, or from the holding area on the day of surgery. Researchers will hold a general discussion with interested patients regarding the study. The patient may have family included, if he/she prefers. We will be approaching all subjects (male and female) who are undergoing laparoscopic gastric bypass or sleeve gastrectomy.

Pre-Study Screening

Potential subjects will have an initial pre-study screening, conducted by a member of the research team, to determine eligibility for the study. Potential subjects who are non-English speaking will be automatically excluded, because the questionnaires are copyrighted in English only. Subjects who do not have the capacity to consent will not be recruited. All other subjects will be recruited. For any patient who might be illiterate, consents will be read to him or her and witnessed by available staff or family member.

Informed Consent

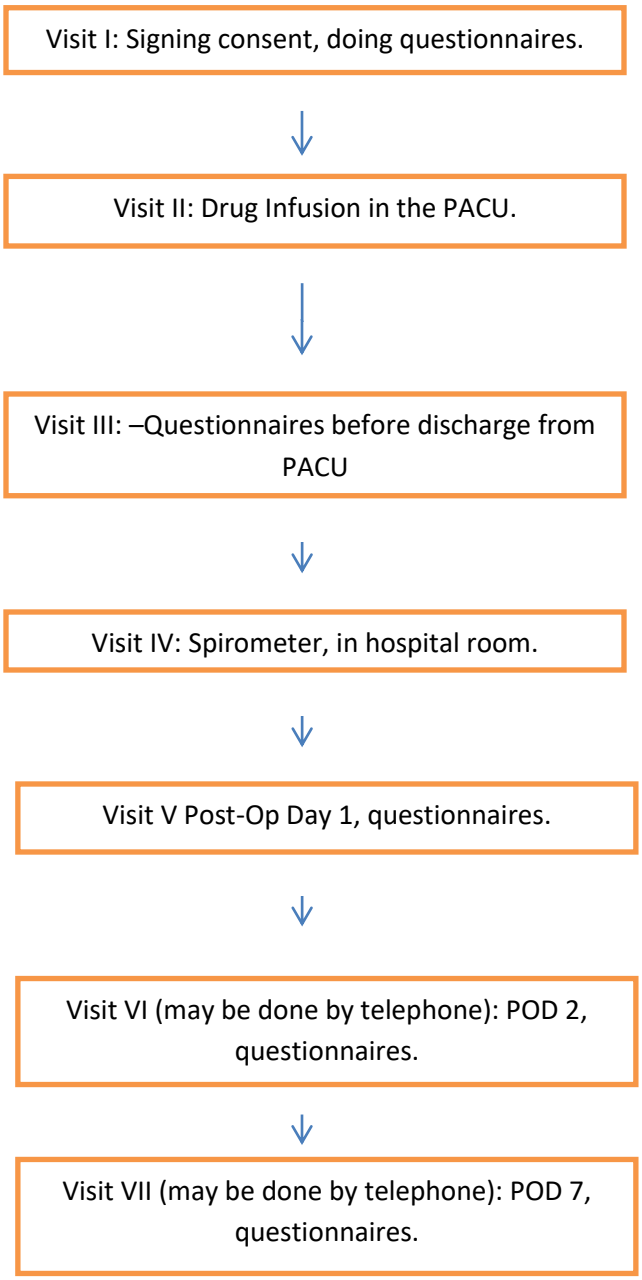
Eligible patients will be assessed for capacity to give informed consent by a study team member. Medical clearance/status/stability will be addressed by members of the research team. Eligible patients will be invited to participate in the study. A verbal explanation of the study will be given followed by a written consent form. Study staff members are experienced at consenting patients for anesthesiology studies, and they include physicians as well as research associates.

Intervention Administration

Ketamine bolus doses of 0.4 mg/kg (by ideal body weight) will be prepared and stored by the Pharmacy staff at Tisch Hospital and will be delivered to the PACU on an on-call basis when required for a study subject. The study drug will be administered in accordance to best practices. Ketamine will be given via intravenous infusion through an IV line established in the PACU. All patients will have an IV line in the PACU as per standard postoperative care protocol after bariatric surgery. If necessary, an additional IV line will be placed by the study team for the infusion of the study drug. The study drug or control will be administered over <60 minutes. The dose for ketamine will be fixed at 0.4 mg/kg (ideal body weight). The staff administering the infusion will have no knowledge whether the agent is drug or saline control. The patient will be monitored in the PACU according to the standard PACU protocol. In addition, the patient will be monitored for any potential side effects of the medication, which include hypertension, tachycardia, nystagmus, perceptual disturbances, confusion, sedation, euphoria, dysphoria, and dizziness. These side effects are uncommon, and a majority of these side effects are expected to resolve shortly after infusion.[13] Side effects will be documented and treated if necessary as per standard PACU protocol.

Study drug storage
The Pharmacy at Tisch Hospital will randomize and prepare samples (study medication or saline control). Study medications and placebo will be kept by the Pharmacy staff at Tisch Hospital until use.

Main Study


Visit I: Signing consent, doing questionnaires.
Visit II: Drug Infusion in the PACU.
Visit III: –Questionnaires before discharge from PACU
Visit IV: Spirometer, in hospital room.
Visit V Post-Op Day 1, questionnaires.
Visit VI (may be done by telephone): POD 2, questionnaires.
Visit VII (may be done by telephone): POD 7, questionnaires.

Pharmacologic profile of study drug

Ketamine [(+/-)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone] is a white, crystalline powder or clear liquid. It is a schedule III substance and is classified as a dissociative anesthetic. Ketamine is available as a racemic mixture with the S-(+)- isomer being more potent than the R-(-)- isomer. It is commercially supplied as the hydrochloride salt in 0.5 mg/mL and 5 mg/mL ketamine base equivalents. Clinically, it is commonly used as an anesthetic induction agent for diagnostic and surgical procedures prior to the administration of general anesthetics. It is also used as a low dose infusion for analgesia. For induction of 5-10 minutes surgical anesthesia, a dose of 1.0-4.5 mg/kg is intravenously administered; 6.5-13 mg/kg is given intramuscularly for 12-25 minutes of surgical anesthesia. As an analgesic, it is infused at a rate of 0.1 - 0.5 mg/kg/hr, with or without a loading dose.

The risks for ketamine are well studied. In general, ketamine is a well-tolerated medication. However, the following risks have been reported.

Pharmacokinetics: Bioavailability following an intramuscular dose is 93%, intranasal dose 25-50%, and oral dose 20±7%. Ketamine is rapidly distributed into brain and other highly perfused tissues, and is 12% bound in plasma. The plasma half-life is 2.3 ± 0.5 hours. Oral administration produces lower peak concentrations of ketamine, but increased amounts of the metabolites norketamine and dehydronorketamine. Ketamine and its metabolites undergo hydroxylation and conjugation. Norketamine produces effects similar to those of ketamine. There are no significant differences between the pharmacokinetic properties of the S-(+) and R-(-)-isomers.

Pharmacodynamics: Analgesia, anesthetic and sympathomimetic effects of ketamine are mediated by different sites of action. Non-competitive NMDA receptor antagonism is associated with the analgesic effects; opiate receptors may contribute to analgesia and dysphoric reactions; and sympathomimetic properties may result from enhanced central and peripheral monoaminergic transmission. Ketamine blocks dopamine uptake and therefore elevates synaptic dopamine levels. Inhibition of central and peripheral cholinergic transmission could contribute to induction of the anesthetic state.

Molecular Interaction / Receptor Chemistry: Cytochrome P450 3A4 is the principal enzyme responsible for ketamine N-demethylation to norketamine, with minor contributions from CYP2B6 and CYP2C9 isoforms. Potential inhibitors of these isoenzymes could decrease the rate of ketamine elimination if administered concurrently, while potential inducers could increase the rate of elimination

Psychological Effects: Decreased awareness of general environment, sedation, dream-like state, vivid dreams, feelings of invulnerability, increased distractibility, disorientation, and subjects are generally uncommunicative. Hallucinations, impaired thought processes, delirium, out-of-body experiences, and changes in perception about body, surroundings, time and sounds can occur at higher doses. Delirium and hallucinations can be experienced after awakening from full anesthetic doses of ketamine.

Physiological: Anesthesia, cataplexy, immobility, tachycardia, increased blood pressure, nystagmus, hypersalivation, increased urinary output, profound insensitivity to pain, amnesia, slurred speech, and lack of coordination.

Cardiovascular: Cardiovascular side effects have included elevated blood pressure and pulse rate following administration of ketamine alone. However, hypotension and bradycardia have been observed. Arrhythmia has also been reported.

Respiratory: Respiratory side effects have included stimulated respiration, although severe depression of respiration or apnea may occur following rapid intravenous administration of ketamine. Laryngospasms and other forms of airway obstruction have occurred during ketamine anesthesia.

Ocular: Ocular side effects have included diplopia, nystagmus, and a slight elevation in intraocular pressure.

Oral: Hypersalivation can occur but is rare.

Gastrointestinal: Gastrointestinal side effects have included anorexia, nausea, and vomiting.

Musculoskeletal: Musculoskeletal side effects have included enhanced skeletal muscle tone manifested by tonic and clinic movements sometimes resembling seizures.

Local: Local side effects have included pain and exanthema at the injection site.

Dermatologic: Dermatologic side effects have included transient erythema and/or morbilliform rash.

Psychiatric: Psychiatric side effects have included anxiety, euphoria, dysphoria, illusions, hallucinations, flashbacks, blunted affect, catatonia and psychotic episodes.

Neurologic: Impaired attention/memory/judgment, disorientation, delirium, diplopia, blurred vision.

Urinary: Increased urinary output; rarely cystitis.

Duration of Effects: Onset of effects is within seconds if smoked, 1-5 minutes if injected, 5-10 minutes if snorted and 15-20 minutes if orally administered. Effects generally last 30-45 minutes if injected, 45-60 minutes if snorted, and 1-2 hours following oral ingestion.

Tolerance, Dependence and Withdrawal Effects: In long-term exposure, high tolerance, drug craving, and flashbacks are described. Little evidence of a physiological withdrawal syndrome unless abrupt discontinuation in chronic users.

Drug Interactions: Lorazepam may decrease ketamine-associated emotional distress but does not decrease cognitive or behavioral effects of ketamine. Acute administration of diazepam increases

the half-life of ketamine. Lamotrigine significantly decreases ketamine-induced perceptual abnormalities, but increases the mood elevating effects. Haloperidol may decrease impairment by ketamine in executive control functions, but does not affect psychosis, perceptual changes, negative schizophrenic-like symptoms, or euphoria. Alfentanil is additive to ketamine in decreasing pain and increasing cognitive impairment. Physostigmine and 4-aminopyridine can antagonize some pharmacodynamic effects of ketamine.

Absolute contraindications to IV ketamine are age <3 months and schizophrenia. Relative contraindications include increased ICP, glaucoma, or acute globe injury. Caution is suggested in patients with cardiovascular illness, porphyria, or thyroid disorder.

Human subject

This study will be carried out under the guidelines of the New York University School of Medicine, Institutional Review Board (IRB), the NYU-HHC CTSI, and in accordance with the Guide for the Care and the Use of Laboratory Subjects as adopted and promulgated by the US National Institutes of Health.

Protection of Human Subjects: Patients who will undergo bariatric surgery who meet entry criteria will be presented the option of enrolling in proposed studies. If they decide to participate, they will be asked to provide written informed consent prior to participation in this study. They will review an IRB-approved research consent with study personnel. This consent form will describe the purpose of the study and how long it will last, the procedures to be used, any expected discomfort or inconvenience, the expected risks and benefits, alternative treatment plans, use of research results, and any special circumstances. The consent form will be read and signed in the presence of a member of the research team. Study subjects will be given the opportunity to ask questions at the time of signing consent and throughout the course of the study. They will also be informed of their rights as study participants, that they are free to choose not to participate and can withdraw at any time. A copy of the consent will be given to all study participants. If they have questions or concerns at a later time, they may use the phone numbers listed on the consent form to contact the investigator or other study associates.

Institutional Review Boards: The principal investigator will ensure that a duly constituted Institutional Review Board (IRB) complying with all Federal regulations will review all protocols and informed consent forms. The investigator will promptly report to the IRB all changes in research activity and all serious adverse events or unanticipated problems involving risks to human subjects or others. No changes will be made to protocols without IRB approval, except where necessary to eliminate immediate hazards to human subjects. If an emergency change is necessary, the IRB will be notified within 24 working hours. The NYU School of Medicine IRB operates under OHRP Federal-Wide Assurance of compliance number FWA00004952.

Patient Confidentiality: To maintain patient confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number only, and HIPAA guidelines will be followed. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the NYU IRB. Subjects will be

informed of these exceptions in the informed consent document

The research material obtained from human subjects in this proposed study is to be collected solely for research purposes. It will include the following:

a. *Research information* obtained by medical history, research questionnaires and patient interviews.

b. *Clinical information* obtained from chart review of the subject's hospital records to help in clarifying diagnostic and concurrent treatment information.

c. *Serum levels of inflammatory cytokines and neurotrophic factors* will be obtained three times during the course of study.

d. *Pregnancy*: Subjects currently pregnant will not be eligible for study participation. Female subjects of child bearing age must agree to use acceptable contraception throughout the study. As these subjects are inpatients admitted for surgery, there is minimal likelihood that they should be pregnant or become pregnant during our study.

Confidentiality and Study Assessments: To safeguard confidentiality, all information will be stored on locked files which can be accessed only by members of the research staff for this project. No names or other identifying information will be used in publications which stem from this research. The study data will be stored in a locked drawer within a locked office space at NYU School of Medicine and The Alexandria Center. Only study staff will have access to the study data. All electronic data will be accessible only to authorized personnel.

Risk/benefit Ratio of the Study: The risks involved in this study are justified by the anticipated benefits. There is a potential benefit gained to study subjects for better postoperative analgesia, mood elevation as well as faster recovery from surgery. In addition, there is benefit in society for better understanding of the postoperative analgesic and mood elevating strategies. The risks for engaging in this procedure are primarily related to brief acute ketamine effects as addressed above.

Costs to the subject: Patients will not receive payment for participation in the study. The cost of ketamine and its preparation will be paid by research funds from the PI of the study and the Department of Anesthesiology.

Statistical Analysis

Sample Size Justification: Previous studies on the antidepressant effects of ketamine on depressed patients typically yield a mean difference in psychometric measures of 40%, with a standard deviation of roughly 40% as well. Power analysis yields n = 50 patients in each arm. This will allow for us to detect a true difference in the mean value of our outcome variable of $\pm$ 22.5% with a probability (power) of 0.8. The type I error probability associated with this test of the null hypothesis that the population means of the ketamine versus control groups are equal is 0.05.

Statistical Analysis: For this study, descriptive statistics will be performed for all data and subgroups as needed:

1) Outcome tests (see above), N (%) for each category, showing absolute values, absolute

and percent differences, stratified by treatment etc.
2) Demographics showing continuous parameters (age, height, weight, etc.) as mean + SD; categorical parameters, as N (%); all also stratified by treatment.

Analysis of variance (ANOVA) test with repeated measures will be performed to determine within-patient effects (time) and between patient effects (treatment) on outcome measures. Pearson correlation will be used to assess relationships between continuous variables, and Spearman's Rho will be used for ranked data. For non-normally distributed, the Kruskall-Wallis test will be used for global significance, and Mann Whitney for subsequent pairwise comparisons.

Exploratory analysis will fit continuous (VAS score, length of stay in the hospital) and categorical (ordinal outcome data) to a Logistic Regression model which predicts the treatment bivariate (IV ketamine or placebo).

Interim Data analysis: An interim data analysis will be performed after a total of 50 patients have completed the study. An analysis of primary and secondary endpoints will be analyzed, and if the primary endpoints are met, we will opt to terminate the study.

DATA SAFETY AND MONITORING PLAN

Timeline

1) Estimated start date: Sept 1, 2013
2) Estimated time for start-up: 2 months
3) Time allotted for enrollment: 2 years
4) Estimated study end date: August 30, 2015

Data acquisition and management

The research material obtained from human subjects in this proposed study will be collected solely for research purposes. It will be as follows:
a. *Clinical information* obtained by medical history, questionnaires and interviews.
b. *Clinical information* obtained from chart review of the subjects' hospital records
c. *Serum samples* will be obtained.

All research data will be collected in Case Report Forms (CRFs). Clinical safety data, routine labs, screening information, informed consent, and progress notes will also be collected in Source Documents.

Data Entry: CRFs of all research data will be entered into assessment specific data entry forms with macro programming to organize repeated measures into table format. Data and results from laboratory tests will be entered by study staff directly from the CRFs into secure computer designated for Dr. Wang at NYU-Tisch Hospital. The data are then stored using a secure password. The computer used for this study will be password protected and kept locked in a locked office in the Anesthesia office. Only designated study staff will have access to patient data and these include: the PI of the study Dr. Wang, the Research Coordinator and the Research

Assistant. Hard paper copies of the laboratory results, if necessary, will be stored in a secured area in Dr. Wang's office in Alexandria Center for Life Sciences. Though the information collected in this study may be published, no patient will be identified by name or other personal information.

Adverse events will include events reported by the subject and thought to be associated with the research. Unanticipated problems and adverse events will be gathered by study investigators. Adverse events will be evaluated throughout the hospital stay. Any serious adverse effects will be reported to the IRB according to regulatory requirements.

Quality Assurance: Source Documentation and CRF's collected for the first 5 participants will be reviewed by the PI, Dr. Wang, following completion of testing with each participant. Study procedure consistency, data entry accuracy and completeness, and normative range of values will be checked. Where applicable, consistency between Source Document and CRF will be evaluated. Thereafter, source documentation and CRF's for 1 out of every 5 participants will be selected randomly and reviewed in a similar manner. If an error or errors are discovered, corrective action will be taken to remedy particular errors when discovered.

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Exploratory analysis will fit continuous (VAS score, length of stay in the hospital) and categorical (ordinal outcome data) to a Logistic Regression model which predicts the treatment bivariate (IV ketamine or placebo).

Interim Data analysis
An interim data analysis will be performed after a total of 50 patients have completed the study.

An analysis of primary and secondary endpoints will be analyzed, and if the primary endpoints are met, we will opt to terminate the study.

Data Safety and Monitoring Board (DSMB)

In addition to the PI, Dr. Wang, an independent patient safety DSMB panel will also review study documents and safety data on a routine basis. This board will meet once every three months, and more frequently as needed. In addition, the board will meet with study coordinator and assistant after a total of 50 patients have completed the study to perform an interim analysis. This board will include the additional following members from the department of anesthesiology.

1. Dr. Lisa Doan
2. Dr. Fahad Khan

None of these DSMB panel members has any conflict of interest with this study protocol.

Study safety assurance

Confidentiality and Study Assessments: To safeguard against the loss of confidentiality, all information will be stored on locked files which can be accessed only by members of the research staff for this project. No names or other identifying information will be used in publications which stem from this research. Subjects will be informed of these exceptions in the informed consent document.

Reporting of Adverse Events (AEs): The DSMB Panel will report a study summary and updates on the clinical safety documentation and assessments, as well as the primary outcome measures. Baseline demographics, recruitment rates and reasons of ineligibility, as well as study retention rates, will be summarized. An update of regulatory status and any protocol amendments will be provided. A summary of adverse events (AEs) and serious adverse events (SAEs) that have occurred will be provided.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related or clinically significant**.** A new illness, symptom, sign, or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present (and documented) prior to clinical trial entry and do not worsen are not considered AEs. AEs will be recorded on the AE Form. The AE Form is also used to record follow-up information for unresolved events. Each month, a study investigator and/or study clinician (physician, nurse, or physician's assistant) will review the AE Form completed for the previous month for any events that were reported as continuing, and provide corrective action as needed. Per the IRB of the NYUSOM policies, only those adverse events that are unexpected and related to the study drug, and those events that are harmful, will be submitted to the IRB within five days. All other events will be reviewed by the DSMB.

All adverse events will be collected – whether they are related to study drug or not, and submitted to the IRB or not. Events will be collected by speaking to the patients as well as through the medical record. Data will be kept up to date by patient, and investigator will be notified when something comes up.

The study coordinators will be in charge for the initial monitoring. All data collected by the coordinators, will be reviewed by the PI. In cases where the PI feels there needs to be further review, he will do so. In addition, all data will be formally assessed every three months. The study coordinators will inform the PI immediately when there is any serious adverse event, whether or not it needs to be submitted to the IRB. Unexpected adverse events and harmful events related to the study drug will be reported to the IRB, will be within five days.

Any event that is considered serious and attributable to the study drug will be immediately submitted to the IRB and the PI. The investigator will assess any events that are related and serious and decide whether or not to continue with this study.

The IRB will be kept apprised of all serious events.

Reporting of Serious Adverse Events (SAE): The study clinician will classify each AE as serious or non-serious and will follow all appropriate reporting procedures. Serious adverse events (SAEs) are defined as any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, any event that requires or prolongs inpatient hospitalization, any congenital anomaly, or any event that requires intervention in order to prevent permanent impairment/damage. An unexpected SAE is one that is not described with respect to nature, severity, or frequency in the current PDR (2007) description for ketamine. The study clinician will assess all SAEs prior to submitting reports to the appropriate IRB. Any SAE (including death) due to any cause, which occurs during the course of this investigation, whether or not related to the investigational medication, will be reported within 24-hours by written notification to the IRB, accompanied by a faxed copy of the initial SAE CRF to the Institutional Review Board (IRB).

Role of the Institutional Review Boards (IRB): The principal investigator will ensure that a duly constituted IRB complying with all Federal regulations will review all protocols and informed consent forms. The investigator will promptly report to the IRB all amendments in research activity and all SAEs and/or unanticipated problems involving risks to human subjects or others. No changes will be made to protocols without IRB approval, except where necessary to eliminate immediate hazards to human subjects. If an emergency change is necessary, the IRB will be notified within 24 working hours. The NYU School of Medicine IRB operates under Federal Wide Assurance (FWA) number: 00004952.

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