STUDY PROTOCOL

Official Title:
Intraoperative Ketamine Versus Saline in Depressed Patients Undergoing Anesthesia for Non-cardiac Surgery

NCT Number: 03861988

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Double-blind trial of intraoperative ketamine versus saline in patients with major depressive disorder undergoing non-cardiac surgery
NCT 03861988

1. NAME OF STUDY
Double-blind trial of intraoperative ketamine versus saline in patients with major depressive disorder undergoing anesthesia for non-cardiac surgery

2. INVESTIGATORS:
Principle Investigator: Boris Heifets, MD, PhD
Sub-Investigators: Theresa Lii, MD, Alan Schatzberg, MD,

3. SOURCE OF INSTITUTIONAL FUNDING:
Departmental funds from the Stanford Department of Anesthesiology, Perioperative and Pain Medicine. This study is not industry sponsored.

4. SOURCES FROM WHOM WE ARE SEEKING FUNDS:
Pending the results of this trial we will seek NIH or foundation grants.

5. AIMS AND HYPOTHESIS

A. Aims:
To determine whether intravenous ketamine, when used for its FDA-approved indication to supplement anesthesia, is associated with a measurable antidepressant effect in severely depressed patients undergoing non-cardiac surgeries when compared to placebo (normal saline infusion).

B. Primary Outcome:
We plan to evaluate the antidepressant superiority of ketamine to placebo by assessing postoperative MADRS scores at multiple timepoints. MADRS (Montgomery-Asberg Depression Rating Scale) is a validated measure of depression severity used routinely in antidepressant trials.

C. Secondary Outcomes:
- Proportion of participants with clinical response (defined as a $\geq$50% reduction in MADRS score from baseline)
- Proportion of participants with remission (defined as a MADRS score of $\leq$12 on day 14)
- Hospital Anxiety and Depression Scale
- Cumulative inpatient opioid use
- Hospital length of stay
- Average inpatient opioid use per day
- Opioid use at postop day 7
- Opioid use at postop day 14
- Postoperative numeric pain scores
- Postoperative pain interference scores
- Immunological blood markers

6. GENERAL BACKGROUND

Major Depressive Disorder (MDD) is widely prevalent among patients preparing to have surgery, and it is a known risk factor for complications after surgery, including wound infection, myocardial infarction and opioid use disorder. Ketamine has emerged as an effective, rapid-acting antidepressant therapy for patients with MDD, and may be a useful tool to prevent MDD-related morbidity in the perioperative period. Ketamine has been well studied for MDD in outpatient clinics where it is given as an infusion (0.5 mg/kg over 40 minutes) in awake patients. Ketamine is often used as part of an anesthetic cocktail in sedated or anesthetized patients, but it is unknown whether ketamine has an antidepressant effect in this context.

We hope to discover whether ketamine has antidepressant efficacy in patients with severe MDD when given as an anesthetic adjunct. If ketamine is an effective antidepressant in this population under anesthesia, its use could be incorporated into a set of interventions to minimize the perioperative complications associated with MDD. While it is more efficient to deliver ketamine therapy intraoperatively, if this study finds that ketamine is ineffective in this setting, that result establishes a rationale to test treatment prior to the surgical encounter. We will also have gained important information on ketamine's antidepressant mechanism (e.g. it is blocked by other anesthetics, or it requires that the patient be conscious).

Only one published study addresses whether ketamine given with surgical anesthesia has any antidepressant effect in depressed patients (Kudoh et al., 2002). This study found a small antidepressant effect of questionable clinical significance, possibly due to studying patients with mild symptoms. This work, while promising, does not address whether ketamine has the profound antidepressant effect that has been repeatedly documented in nonsurgical psychiatric patients with severe MDD. Our proposed study specifically tests ketamine's antidepressant efficacy in this high risk group of patients with severe MDD that may particularly stand to benefit from remission of their depressive symptoms in the perioperative period. Other previous trials involving ketamine as an adjunct to anesthesia have uniformly been conducted in non-depressed patients and have limited relevance to our research question.

7. PRELIMINARY UNPUBLISHED DATA

None at present. We have included an open-label, feasibility study as part of this protocol. However, there are already many published studies evaluating the antidepressant effect of ketamine at the dose used in our study, including one by the principal investigator and co-investigators (Williams et al., 2018).

8. EXPERIMENTAL DESIGN, SCREENING, STUDY PROCEDURES AND DATA ANALYSIS

A. Design

We will first conduct an open-label, feasibility study involving 5 participants to identify which postoperative day to measure our primary endpoint in order to ensure that patients can cooperate with assessment interviews. **Once we have determined when to measure our primary endpoint, we will modify our registered trial (NCT03861988) on ClinicalTrials.gov and submit to the IRB our updated study protocol for a placebo-controlled, double-blind, randomized controlled trial.**

After registering the trial and updating our protocol, we will conduct a single-center, double-blind, randomized, placebo-controlled trial involving a total of 40 participants (20 per group).

B. Study Population: Inclusion and Exclusion Criteria

Inclusion Criteria:

A subject will be eligible for inclusion when all of the following criteria are met:

1. Male or female, 18 to 80 years of age, inclusive, at screen.
2. Able to read, understand, and provide written, dated informed consent prior to screening. Participants will be deemed likely to comply with study protocol and communicate with study personnel about adverse events and other clinically important information.
3. Diagnosed with Major Depressive Disorder (MDD), single or recurrent, and currently experiencing a Major Depressive Episode (MDE) of at least eight weeks in duration, prior to screening, according to the criteria defined in the Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition. The diagnosis of MDD will be made by a trained study staff member and supported by the Mini International Neuropsychiatric Interview - Module A.
4. Meet the threshold on the total combined HADS-MADRS score of >/=31 at both screening and day of surgery visits.
5. In sufficiently good health to proceed with planned orthopedic surgery, as ascertained by a standard preoperative clinic evaluation which includes medical history, physical examination (PE), clinical laboratory evaluations, any indicated cardiac testing, and final clearance by the attending anesthesiologists on the day of surgery.
6. Body mass index between 17-40kg/m2.
7. Concurrent psychotherapy will be allowed if the type (e.g., supportive, cognitive behavioral, insight-oriented, et al) and frequency (e.g., weekly or monthly) of the therapy has been stable for at least three months prior to screening and if the type and frequency of the therapy is expected to remain stable during the course of the subject's participation in the study.
8. Concurrent antidepressant therapy (e.g. SSRI or SNRI) and/or hypnotic therapy (e.g. zolpidem, zaleplon, melatonin, or trazodone) will be allowed if the therapy has been stable for at least 4 weeks prior to screening and if it is expected to remain stable during the course of the subject's participation in the study.

Exclusion Criteria:
A potential participant will NOT be eligible for participation in this study if any of the following criteria are met:

1. Female that is pregnant or breastfeeding. These women would not be candidates for elective total joint replacement under any circumstances, and therefore would be screened out from our study population at their routine preoperative evaluation. Women of childbearing potential are routinely screened for pregnancy at their preoperative visit by urine hCG testing if clinically indicated.
2. Total HADS-MADRS score of <31 at either the screening or day of surgery visits.
3. Current diagnosis of a Substance Use Disorder (SUD; Abuse or Dependence, as defined by DSM-V) rated "moderate" or "severe" per criteria of the Mini International Neuropsychiatric Interview – Module J (MINI-J), or Alcohol Use Disorder rated "moderate" or "severe" per MINI-I criteria. These patients are rarely candidates for elective surgery. The following categories of SUD will NOT be excluded: nicotine dependence; alcohol or substance use disorder rated "mild"; alcohol or substance use disorder of any severity in remission, either early (3-12 months) or sustained (>12 months) time frames.
4. History of schizophrenia or schizoaffective disorders, or any history of psychotic symptoms in the current or previous depressive episodes.
5. In the judgment of the investigator, the subject is at significant risk for suicidal behavior during the course of his/her participation in the study.

6. Has dementia, delirium, amnestic, or any other cognitive disorder.
7. Has a clinically significant abnormality on the screening physical examination that would otherwise preclude the patient from having surgery.
8. Participation in any clinical trial with an investigational drug or device within the past month or concurrent to study participation.
9. Lifetime history of surgical procedures involving the brain or meninges, encephalitis, meningitis, degenerative central nervous system disorder (e.g., Alzheimer's or Parkinson's Disease), epilepsy, mental retardation, or any other disease/procedure/accident/intervention associated with significant injury to or malfunction of the central nervous system (CNS), or a history of significant head trauma within the past two years.
10. Presents with any of the following lab abnormalities w/in the past 6 months:

a. Thyroid stimulating hormone (TSH) outside of the normal limits and clinically significant as determined by the investigator. Free thyroxine (T4) levels may be measured if TSH level is high. Subject will be excluded if T4 level is clinically significant.
b. Any other clinically significant abnormal laboratory result at the time of the screening exam.

11. History of hypothyroidism and has been on a stable dosage of thyroid replacement medication for less than six months prior to screening.(Subjects on a stable dosage of thyroid replacement medication for at least six months or more prior to screening are eligible for enrollment.)
12. History of hyperthyroidism which was treated (medically or surgically) less than six months prior to screening.
13. Any current or past history of any physical condition which in the investigator's opinion might put the subject at risk or interfere with study results interpretation.
14. Patients currently maintained on high dose opioids (>90 morphine equivalents per day) prior to surgery.

C. Statisical Analysis

Sample Size

Based on published data from other investigators (Zarate et al., 2006) and our own published work (Williams et al., 2018), we estimate a sample size of 15 patients per group, alpha=0.05, power = 80% to detect a 30% change in depression rating from baseline. We will include an additional 5 patients per group to account for participant dropout, for a total of 20 patients per group.

Analysis Plan

1. Statistical analyses will be performed by the investigators using R and GraphPad Prism 9.
2. Baseline characteristics and demographics between groups will be compared using t-tests for continuous and ordinal variables and chi-square tests for categorical variables.
3. Primary outcome: Significance will be determined with a mixed model for repeated measures. MADRS scores obtained on postoperative Day 1, 2, and 3 will be combined and treated as a single timepoint in a mixed model, rather than separately testing each day for significance which can inflate type I error rate. We will use an uncorrected two-sided alpha of 0.05 as a cutoff for statistical significance.
4. Secondary outcomes will be compared using t-tests for continuous and ordinal variables and chi-squared tests for categorical variables. No correction for multiple comparisons needed due to the exploratory nature of these outcomes.

D. Study Procedures from Screening to Closeout

Screening

Patients may be informed about the study if they are contacted as part of a perioperative mental health screening service (IRB-54043, approved as not clinical research and not requiring IRB oversight), at which time they may be offered psychiatric care referrals, counseling and information about multiple ongoing clinical trials. Potential subjects may also be introduced to the study through handouts and brochures placed in surgical and pre-anesthesia clinics. Patient identified through Epic as likely to be depressed may also be approached at pre-op appointments and study staff will describe the study and consent if appropriate. Surgery schedulers will ask surgery patients if they are interested in the study and give them a letter or by reading/sending a phone script. Specific procedures for introducing patients to the study and which patient data will be assessed to identify depression are described in detail in section 8g.

Informed consent will be obtained prior to full evaluation of inclusion and exclusion criteria.

Informed consent may be obtained in one of two ways: in-person or over the phone.

In-person consent:

> If the patient has an already scheduled preoperative appointment at Stanford, research staff may meet the patient before or after this appointment to obtain informed consent. Alternatively, the patient may choose to make a separate visit to Stanford Medical Center for the consenting process.

Phone consent:

> If the patient gave permission for research research staff to contact them about the study (see Section 8g), research staff will call the patient to introduce the study. If the patient agrees to consent, research staff will mail, fax, or email a PDF of the consent form to the patient. Research staff will confirm receipt of the consent form, and then obtain informed consent over the phone. The participant will bring the signed consent form with them during an in-person screening visit, or on the day of surgery or will sign the consent through Redcap. Research staff will verify signatures and sign the researcher signature line at that time.

After providing informed consent, the participant will be offered the option to complete SCREENING in the following ways:

1. During a preoperative visit to Stanford Medicine Outpatient Center.
2. By phone or video interview (using Facetime or Zoom, which is PHI compliant)prior to surgery.
3. In-person visit to Stanford Medical Center.
4. On the day of surgery, prior to surgery at Stanford Hospital; patients will be asked to check in 30-45 minutes early to allow time for screening.

Participants will have the standard preoperative workup and management for surgery, including diagnostic labs/studies and perioperative medication adjustment as needed.

During screening, investigators must document a patient history of Major Depressive Disorder (MDD), single or recurrent. The patient must be currently experiencing a Major Depressive Episode (MDE) of at least eight weeks in duration prior to screening, according to the criteria defined in the Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition. The diagnosis

of MDD will be made by a trained study staff member and supported by the Mini International Neuropsychiatric Interview (MINI) - Module A. Patients with a current diagnosis of Alcohol or Substance Use Disorder (Abuse or Dependence, as defined by DSM-V), with the exception of nicotine dependence, at screening or within six months prior to screening will be excluded. The diagnosis of Alcohol or Substance Abuse Disorder will be made by a trained study staff member and supported by the Mini International Neuropsychiatric Interview – Modules I and J.

Concurrent psychotherapy will be allowed if the type (e.g., supportive, cognitive behavioral, insight-oriented, etc.) and frequency (e.g., weekly or monthly) of the therapy has been stable for at least 3 months prior to screening and if the type and frequency of the therapy is expected to remain stable during the course of the subject's participation in the study.

Concurrent antidepressant therapy (e.g. SSRI or SNRI) and/or hypnotic therapy (e.g. zolpidem, zaleplon, melatonin, or trazodone) will be allowed if the therapy has been stable for at least 4 weeks prior to screening and if it is expected to remain stable during the course of the subject's participation in the study.

Once patients agree to participate in the study and have signed the informed consent document, the following screening procedures will be performed:

By Physician or Study Staff:
- Concomitant Medication Review
- Medical and Psychiatric History
- Review of preoperative evaluation data including physical exam, vital signs, any lab work (including a pregnancy test, if applicable) or cardiac testing performed in the course of standard preoperative medical clearance
- Urine toxicology screen test for drugs of abuse
- Mini International Neuropsychiatric Interview (MINI) - Modules A, I & J
- Columbia Suicidality Severity Rating Scale - short screen
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Maudsley Staging Method (MSM)

By the Participant, reviewed by Investigators:
- Hospital Anxiety and Depression Scale (HADS)
- Brief Pain Inventory (BPI)

Participant Compensation:
- $50 after completion of Screening and $50 upon completion of study at day 14. If patients come to Stanford Hospital for the purpose of screening, they will be reimbursed an additional $50 for their time and transportation costs.

<u>Safety Plan for Patients Who Endorse Active Suicidality</u>
A patient may be identified to be at risk for suicidal behavior after consent and during our extended screening process. The Columbia Suicide Severity Rating Scale (CSSRS) – Short Screen is administered face to face, by phone, or by video call (Stanford Zoom) by a study staff member. A patient may be identified as “low”, “moderate” or “high” risk. For any patient scoring “moderate” or “high” risk, the study staff will immediately contact Dr. Boris Heifets or Ms. Robin Okada (RN and study coordinator).

If Dr. Heifets or Ms. Okada are notified of a patient at risk for suicidal behavior, Dr. Heifets will contact that patient, verify their response and decide if a wellness check from police is needed or other interventions. That patient will be offered immediate assistance, including calling an

ambulance for transport to the Emergency Department, and their primary physician will be informed.

Randomization
Only Investigational Drug Services (IDS) Pharmacy will be aware of drug allocation prior to completion of data collection for the randomized, placebo-controlled study. A computer-generated randomization scheme will be used to randomize participants to receive either ketamine or saline (allocation ratio 1:1, blocks of 4). The study participants, intraoperative anesthesiologists, and study staff conducting postoperative assessments will be blinded to drug allocation until data collection is completed.

Infusions
The study intervention will occur during surgery (Study Day 0). Participants will be randomized to one of two groups: Group A (n=20) will receive a ketamine infusion of 0.5 mg/kg over 40 min during surgery, beginning after anesthetic induction with propofol. Group B (n=20) will receive a saline infusion over 40 min during surgery, beginning after anesthetic induction with propofol. Infusion (instead of bolus) dosing of ketamine was chosen since infusions have demonstrated antidepressant efficacy in outpatient psychiatric populations, as well as theoretically lower risk of adverse events due to lower peak serum concentrations compared to bolus dosing. A patient who is **not** enrolled in the study has a reasonable chance of receiving the same treatments (ketamine or saline) at comparable doses as those tested in the study.

Monitoring
Routine vital signs will be collected before and after surgery by the participant's nurse and reviewed by investigators. Each participant will have continuous physiological monitoring during their anesthetic. A SedLine® Brain Function Monitor will be used to evaluate depth of anesthesia/sedation. If the participant experiences an adverse event temporally related to the infusion where corrective action by the intraoperative anesthesiologist requires unblinding, then the study infusion drug will be revealed to the anesthesiologist.

Data Collection Procedures
The first 5 patients that meet inclusion/exclusion criteria will be entered into the open-label feasibility study; all will receive a ketamine infusion. All other patients enrolled thereafter will be entered into the double-blind, randomized, placebo-controlled study. The day of surgery will be considered Day 0 of the study. Baseline assessments must be performed before the patient receives any psychoactive premedication (e.g. midazolam, fentanyl, gabapentin, oxycodone). Assessments will be performed either in the hospital or, if the patient has been discharged (typically on postoperative Day 2), by phone.

Participants who remain in the hospital for at least 24 hours post-surgery will be asked to give blood samples for immunological analyses. Two blood samples (10mL for each draw) will be collected from each participant.

Day 0 (Baseline Assessments):
By Physician or Study Staff:
- Vital Signs
- Concomitant Medication Review
- Adverse Events Review
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Collect breath sample #1

By the Participant, reviewed by Investigators:

- Hospital Anxiety and Depression Scale (HADS)
- Brief Pain Inventory (BPI)

Day 0 (During Surgery):
By the Intraoperative Anesthesiologist:
- Ketamine infusion or placebo (saline) infusion
- Continuous physiological monitoring
- SedLine® Brain Function Monitor to evaluate depth of anesthesia/sedation
- Collect breath sample #2, after infusion is complete

Day 1:
By Physician or Study Staff:
- Vital Signs
- Concomitant Medication Review
- Adverse Events Review
- Montgomery-Asberg Depression Rating Scale (MADRS)

By the Participant, reviewed by Investigators:
- Hospital Anxiety and Depression Scale (HADS)
- Brief Pain Inventory (BPI)

Day 2:
By Physician or Study Staff:
- Vital Signs (inpatient only)
- Concomitant Medication Review
- Adverse Events Review
- Montgomery-Asberg Depression Rating Scale (MADRS)

By the Participant, reviewed by Investigators:
- Hospital Anxiety and Depression Scale (HADS)
- Brief Pain Inventory (BPI)

Day 3 (inpatient or via phone):
By Physician or Study Staff:
- Vital Signs (inpatient only)
- Concomitant Medication Review
- Adverse Events Review
- Montgomery-Asberg Depression Rating Scale (MADRS)

By the Participant, reviewed by Investigators:
- Hospital Anxiety and Depression Scale (HADS)
- Brief Pain Inventory (BPI)

Day 5 (inpatient or via phone):
By Physician or Study Staff:
- Vital Signs (inpatient only)
- Concomitant Medication Review
- Adverse Events Review
- Montgomery-Asberg Depression Rating Scale (MADRS)

By the Participant, reviewed by Investigators:
- Hospital Anxiety and Depression Scale (HADS)
- Brief Pain Inventory (BPI)

Day 7 (inpatient or via phone):

By Physician or Study Staff:
- Vital Signs (inpatient only)
- Concomitant Medication Review
- Adverse Events Review
- Montgomery-Asberg Depression Rating Scale (MADRS)

By the Participant, reviewed by Investigators:
- Hospital Anxiety and Depression Scale (HADS)
- Brief Pain Inventory (BPI)

Day 14 (inpatient or via phone):

By Physician or Study Staff:
- Ask participants what treatment they believe they received
- Reveal treatment to participant
- Vital Signs (inpatient only)
- Concomitant Medication Review
- Adverse Events Review
- Montgomery-Asberg Depression Rating Scale (MADRS)

By the Participant, reviewed by Investigators:
- Hospital Anxiety and Depression Scale (HADS)
- Brief Pain Inventory (BPI)

Participant Compensation:
- $50 after completion of all study assessments

Study Procedures Matrix

	Screen-ing	Day 0 (Baseline)	Day 0 (Intraop)	Day 1	Day 2	Day 3	Day 5	Day 7	Day 14
PHQ-8	X								
Inclusion/Exclusion Criteria	X								
Demographic data	X								
Consent	X								
Concomitant Medication Review	X	X		X	X	X	X	X	X
Medical and Psychiatric History	X								
Physical Exam	X								
Vital Signs	X	X		X	X	O	O	O	O
Continuous physiological monitoring			X						
Urine toxicology screen test	X								
Labs and studies as warranted by standard preoperative medical clearance (includes pregnancy test)	X								
Mini International Neuropsychiatric Interview (MINI) - A , I & J	X								

Hospital Anxiety and Depression Scale (HADS)	X	X		X	X	X	X	X	X
Montgomery Asberg Depression Rating Scale (MADRS)	X	X		X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (CSSRS) – Short Screen	X								
Maudsley Staging Method (MSM)	X								
Brief Pain Inventory	X	X		X	X	X	X	X	X
Randomization	X								
Ketamine infusion or Placebo (saline) infusion			X						
SedLine® Brain Function Monitor			X						
Ask participants what treatment they believe they received									X
Treatment revealed to participant									X
Participant compensation	X								X

X – required
O - inpatient only

9. SIGNIFICANCE

Major Depressive Disorder (MDD) is widely prevalent among patients preparing to have surgery, and is a known risk factor for complications after surgery, including wound infection, myocardial infarction and opioid use disorder. Ketamine has emerged as an effective, rapid-acting antidepressant therapy for patients with MDD, and may be a useful tool to prevent MDD-related morbidity in the perioperative period. Ketamine has been well studied for MDD in outpatient clinics where it is given as an infusion (0.5 mg/kg over 40 minutes) in awake patients.

Ketamine is often used as part of an anesthetic cocktail in sedated or anesthetized patients, but it is unknown whether ketamine has an antidepressant effect in this context. We will determine whether a ketamine infusion, compared to placebo (normal saline infusion), has an antidepressant effect when given during surgical anesthesia. If ketamine is an effective antidepressant in this population under anesthesia, its use could be incorporated into a set of interventions to minimize the perioperative complications associated with MDD.

10. REFERENCES

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