STATISTICAL ANALYSIS PLAN

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

NCT Number: 03861988

Protocol last edited: 10/28/2021

Statistical Analysis Plan (SAP)

Section 1: Administrative Information

1. Title and trial registration

1a. Title
Intraoperative Ketamine Versus Saline in Depressed Patients Undergoing Anesthesia for Non-Cardiac Surgery

1b. Trial registration number
ClinicalTrials.gov Identifier NCT# 03861988

2. SAP version: 2.0

3. Protocol version: Stanford eProtocol ID 49114, last revision submitted 8/9/21

4. SAP revisions

4a. SAP revision history
10/21/2019 – version 1.0 (originally included in the study protocol)
10/28/2021 – version 2.0 (created a new, separate SAP document)

4b. Justification for each SAP revision
Version 1.0 to 2.0:

1) In our original protocol, recruitment was limited to patients with symptomatic depression presenting for hip and knee arthroplasty at Stanford. Patients undergoing this type of surgery have a predictable postoperative course, which guided our primary endpoint selection. We encountered significant difficulties recruiting patients during the COVID-19 pandemic. Therefore, we expanded eligibility criteria by including patients presenting for a wider variety of surgical procedures, which are described in our updated protocol. To account for the likely increased variability of postoperative recovery in this broader population, we updated our primary endpoint to include data from the first 3 days after surgery, instead of only a single day after surgery.
2) In our original protocol, the primary outcome measure was defined as the sum of scores from a clinician-administered scale and a self-report scale. During the recruitment phase of our trial, and prior to unblinding, we presented our analysis plan to a panel of statisticians in the Department of Biomedical Data Sciences at Stanford University. The panel recommended that we could improve the interpretability and reduce the variance in our primary outcome by only using one validated measure (rather than a composite score) as our primary outcome measure. Based on this recommendation, we updated our primary outcome measure to only include the clinician-administered scale (the Montgomery-Asberg Depression Rating Scale).

4c. Timing of SAP revisions
This revision (1.0 to 2.0) was made prior to data unblinding and prior to completion of data collection (75% of target enrollment).

5. Roles of SAP contributors
Theresa R. Lii, MD, Stanford University, Primary SAP author
Boris D. Heifets, MD, PhD, Stanford University, Chief investigator/clinical lead

6. Signatures

6a. Primary SAP author: 

6b. Chief investigator/clinical lead: 

Section 2: Introduction

7. Background and rationale

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.

8. Objectives

We hope to discover whether ketamine has antidepressant efficacy in major depressive disorder (MDD) patients 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).

Section 3: Study Methods

9. Trial design

This is a single-site phase IV randomized clinical trial utilizing a quadruple-masked, placebo-controlled, parallel arm design. Participants will be randomly allocated in a 1:1 ratio to one of two groups: Group A (n=20) will receive a ketamine infusion of 0.5 mg/kg over 40 min during surgery. Group B (n=20) will receive a saline infusion over 40 min during surgery. In both groups, the study drug will be given after anesthetic induction. The participants, care providers, investigators, and outcomes assessors will be masked.

10. Randomization

Participants will be sequentially randomized as they enter the study. We will employ block randomization with 5 blocks of 8 patients each.

11. Sample size

We will enroll a total of 40 participants. Our sample size calculation was derived from an *a priori* power analysis for the primary outcome measure with a 1:1 allocation ratio. In a randomized controlled trial of ketamine vs active placebo (midazolam) performed by

Phillips et al. (2019), participants had a mean decrease of 10.9 points (SD=8.9) in MADRS total score relative to pre-infusion scores compared with a mean decrease of 2.8 points (SD=3.6) with midazolam. Using these results, we computed an estimated total sample size of 38 participants at a two-sided alpha level of 0.05 and 80% power. An additional 2 participants were added to account for potential attrition, for a total of 40 participants. Given the increased statistical efficiency of mixed models for repeated measures (MMRM) compared to parametric pre-post tests, we assumed that 40 participants should be sufficient to power our study for MMRM analysis.

12. Framework

We plan to evaluate the antidepressant superiority of ketamine to placebo by assessing the postoperative MADRS scores from postoperative Day 1 through Day 3. Additional outcomes collected at postoperative Day 5, 7, and 14 will be used for statistical model building and exploratory analyses.

13. Interim data monitoring

13a. Statistical interim analyses planned and time points

No statistical interim analyses planned.

13b. Any planned adjustment of significance level due to interim analysis

N/A.

13c. Details of guidance for stopping the trial early

N/A.

14. Timing of final analysis

Once all data have been collected at all planned time points from the final (40th) participant, all investigators will be unmasked and all outcomes will be analyzed together in the final analysis.

15. Timing of outcome assessments

All patients will have at least one baseline psychiatric assessment prior to Day 0. Repeat baseline assessment by questionnaire will occur on the morning of surgery prior to any preoperative medication being given. The study assessments will be performed at postoperative Day 1, Day 2, Day 3, Day 5, Day 7 and Day 14. Assessments will be performed either in hospital or by phone or video.

Section 4: Statistical Principles

16. Level of statistical significance

We will use an uncorrected two-sided alpha of 0.05 as a cutoff for statistical significance.

17. Adjustment for multiplicity and controlling type I error

The primary outcome (MADRS score) that is measured on postoperative Day 1, 2, and 3 will be combined and treated as a single timepoint in the mixed model, rather than separately testing each day for significance which can inflate type I error rate. Postoperative Days 1, 2, and 3 were chosen due to previously published data showing that the antidepressant effect of ketamine persists up to 3 days after administration.

18. Confidence intervals to be reported
We will report 95% confidence intervals for the primary outcome.

19. Adherence and protocol deviations

19a. Adherence to protocol and how this is assessed
Adherence to protocol is defined as: 1) participant meets eligibility criteria prior to randomization; 2) all planned assessments are completed; and 3) the patient receives the complete dose of the blinded study drug intravenously over a course of 40 minutes, initiated after induction of anesthesia and completed before extubation or transfer to the post-anesthetic recovery area.

19b. How adherence to protocol will be presented
Adherence to protocol will be presented as a proportion.

19c. Protocol deviations
Emergency protocol deviations are defined as those occurring in an emergency situation where departure from the protocol (such as unblinding the study drug) is required immediately to protect the life or physical well-being of the participant.

Non-emergent deviations are defined as those that do not occur in an emergency situation. Examples potentially encountered in our study include, but are not limited to: 1) participant is randomized to a treatment intervention but does not meet eligibility criteria, 2) the anesthesiologist administered the study drug incorrectly or incompletely, 3) the participant inadvertently received the intervention meant for the other trial arm, 4) the participant was not available for assessment of the planned outcome either because of loss to follow-up or for another reason, 5) study staff were not available for assessment of the planned outcome either because of a personal emergency or another reason.

19d. Which protocol deviations will be summarized
All emergency and non-emergent protocol deviations will be summarized.

20. Analysis populations
As recommended by CONSORT guidelines for parallel group randomized controlled trials, intention-to-treat and per-protocol analyses (if needed) will be performed and reported for all planned outcomes to allow readers to interpret the effects of the intervention.

Section 5: Trial Population

21. Screening data
Screening data to be collected and reported in CONSORT flow diagram include:

Patient Health Questionnaire score
HADS-MADRS composite score
English-speaking status
Age
Body mass index
History of significant CNS disease or brain surgery
History of moderate to severe substance use disorder (except nicotine)
History of schizophrenia, schizoaffective disorder, or psychosis
Chronic high dose opioid use (>90 morphine milligram equivalents per day)
High suicide risk
Other reasons

22. Eligibility

22a. Inclusion criteria
A subject will be eligible for inclusion only if 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. PHQ-8 score >= 12.

4. Diagnosed with Major Depressive Disorder (MDD), single or recurrent, and currently experiencing a Major Depressive Episode (MDE) of at least 4 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.

5. Meet the threshold on the total combined HADS-MADRS score of >/=31 at both screening and day of surgery visits.

6. In sufficiently good health to proceed with planned 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.

7. Body mass index between 17-40kg/m2.

8. 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 4 weeks 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.

9. 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.

22b. 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 surgery 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. We will not be including pregnant women from other surgical populations as well.

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 that conflicts with this trial, 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

23. Recruitment
Information to be collected and reported in CONSORT flow diagram include:

Patients with a history of depression screened
Excluded due to PHQ score < 12
Excluded due to other exclusion criteria
Declined to participate
Lost to follow-up during screening
Excluded after consent
Withdrew after consent prior to intervention
Participants consented

24. Withdrawal and follow-up

24a. The following withdrawal/lost to follow-up data will be recorded:

- Number of participants who withdraw or are lost to follow-up
- Timing of withdrawal or lost to follow-up
- Reasons of withdrawal or lost to follow-up

24b. The above withdrawal/lost to follow-up data will be presented as:

- Percentages (%) of participants who withdraw or are lost to follow-up
- Kaplan-Meier curves of withdrawal or lost to follow-up (if any)
- Reasons of withdrawal or lost to follow-up summarized in the Results section

25. Baseline patient characteristics

25a. List of baseline characteristics to be reported

1) Sex (n, %)
2) Age (years, mean and SD)
3) Body mass index (mean, SD)
4) Hispanic/Latino ethnicity (n, %)
5) Race
    a. White (n, %)
    b. Black/African American (n, %)
    c. Asian (n, %)
    d. Native Hawaiin/Pacific Islander (n, %)
    e. Other (n, %)
    f. Unknown (n, %)
6) Married (n, %)
7) Disabled (n, %)
8) Current smoker (n, %)
9) PHQ score at screening (points, mean and SD)
10) HADS at screening (points, mean and SD)
11) MADRS at screening (points, mean and SD)
12) HADS-MADRS composite score at screening (points, mean and SD)
13) Age at first MDD onset (years, mean and SD)
14) Duration of current episode (months, mean and SD)
15) Recurrent major depression (n, %)
16) Previous clinical ketamine exposure (n, %)
17) Previous recreational ketamine exposure (n, %)
18) Charlson Comorbidity Index (points, mean and SD)
19) Maudsley resistance stage (points, mean and SD)
20) Numerical pain score (points, mean and SD)
21) Pain interference from BPI (points, mean and SD)

25b. Preoperative psychoactive medications

1) Opioids (n, %)

2) MME/day, if on opioids (mean, SD)
3) Anticonvulsants (n, %)
4) Benzodiazepines (n, %)
5) Muscle relaxants (n, %)
6) Antidepressants (n, %)
7) Antipsychotics (n, %)
8) Lithium (n, %)
9) Prescription sleep medications (n, %)
10) Opioid antagonists (n, %)
11) Stimulants (n, %)

25c. Surgical characteristics

1) Type of surgery
    a. ENT/OMF(n, %)
    b. Thoracic (n, %)
    c. Breast (n, %)
    d. Plastic non-breast (n, %)
    e. Spine (n, %)
    f. Major joint (n, %)
    g. Other orthopedic/limb (n, %)
    h. Intraabdominal general surgery (n, %)
    i. Urologic and gynecologic (n, %)
    j. Vascular (n, %)
    k. Transplant (n, %)
2) Type of anesthesia
    a. General anesthesia (n, %)
    b. Monitored anesthesia care (n, %)
3) Intraoperative nitrous oxide (n, %)
4) Intraoperative propofol infusion (n, %)
5) Intraoperative opioid infusion (n, %)
6) Length of surgery (hours, mean and SD)
7) Peripheral or neuraxial catheter placed (n, %)

Section 6: Analysis

26. Outcome definitions

26a. Primary outcome

Postoperative MADRS scores from postoperative Days 1 through 3.

26b. Main secondary outcomes

1) Proportion of participants with clinical response (defined as a ≥50% reduction in MADRS score from baseline).
2) Proportion of participants with remission (defined as a MADRS score of ≤12 on day 14).

26c. Other exploratory secondary outcomes

1) MADRS scores at postoperative Days 5, 7, and 14
2) Hospital Anxiety and Depression Scale
3) Cumulative inpatient opioid use
4) Hospital length of stay
5) Average inpatient opioid use per day
6) Opioid use at postop day 7
7) Opioid use at postop day 14
8) Postoperative numeric pain scores
9) Postoperative pain interference scores

27. Analysis methods

27a. Analysis of the primary outcome

A mixed model for repeated measures (MMRM) will be used to analyze the difference in postoperative MADRS score which is our primary outcome. The model will include treatment and time as fixed effects, with a treatment*time interaction term. The data will be modeled with random intercepts and random slopes to account for variation in baseline scores and postoperative trajectories. MADRS scores measured on postoperative Day 1, 2, and 3 will be combined and treated as a single timepoint in the mixed model, rather than separately testing each day for significance which can inflate type I error rate. Postoperative Days 1, 2, and 3 were chosen due to previously published data showing that the antidepressant effect of ketamine persists up to 3 days after administration.

27b. Sensitivity analyses

Sensitivity analyses will be conducted for the following scenarios:

1) Missing data: See section 28
2) Intention-to-treat vs per-protocol analysis (if needed)
3) MMRM analysis using HADS (self-report) as a confirmatory measure
4) MMRM analysis using the previously proposed primary outcome measure (a composite score defined as the sum of scores from MADRS and HADS)

27c. Subgroup analyses

We will conduct several pre-specified subgroup analyses. While the trial will not specifically be powered for these subgroups, we hope to gain further insight into sub-populations that may particularly benefit from the intervention. Example subgroup analyses to be considered:

1) Preoperative use of antidepressants
2) Preoperative use of opioids
3) Intraoperative exposure to nitrous oxide
4) Intraoperative exposure to opioid infusions
5) Postoperative use of neuraxial or peripheral nerve catheters

28. Missing data
For the primary outcome, it will be assumed that the missing data are missing at random. Sensitivity analysis will be performed to evaluate the robustness of the MMRM to the missing-at-random assumption.

29. Adverse events
Adverse events will be recorded in the Stanford REDCap database using the Adverse Event (AE) Form and Serious Adverse Event (SAE) Form. Refer to document GUI-P13 (https://researchcompliance.stanford.edu/panels/hs/policies/guidances) for definitions of AEs and SAEs. All AEs and SAEs will be summarized.

30. Statistical software
Statistical analyses will be conducted using R statistical software. Data figures for visualization will be generated using either R or Graphpad Prism.