Statistical Analysis Plan for the Effect and Contribution of a Perioperative Ketamine Infusion in an Established Enhanced Recovery Pathway

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Introduction

This document describes the statistical analysis plan (SAP) for a cluster randomized, pragmatic clinical trial studying the effect of ketamine within a pre-established enhanced recovery program on patients presenting for elective major abdominal surgery. Each week is considered a cluster with each cluster being randomly assigned to either the control or intervention condition.

Opioid consumption during the perioperative period is associated with adverse outcomes. In efforts to decrease opioid exposure after surgery, medical providers at Vanderbilt University Medical Center (VUMC) employ a multi-modal approach to pain control, which includes strategic combinations of non-narcotic pain medications and regional nerve blocks. Evidence is clear that combinations of non-narcotic pain medications with different mechanisms of actions are synergistically effective. What is not known, however, is the individual contribution of each medication to the overall efficacy of the regimen. This trial intends to explore the contribution of ketamine and hypothesizes patients randomized to receive ketamine will have a significant reduction in length of stay (LOS), following anesthesia start, compared to those receiving placebo.

Study Population

Adult patients presenting on a weekday for an elective major inpatient abdominal surgery at VUMC will be screened for eligibility. Indications for exclusion will be noted if they meet criteria specified in the study protocol. Two post-randomization exclusions have been prespecified for this study. First, a patient directly transferred from the operating room to the Intensive Care Unit (ICU) with an endotracheal tube placed will not be included. The rationale is that these patients are exposed to both a sedative and narcotic infusion for the duration of their intubation, which would confound the ability to determine analgesic efficacy and/or side effects from the study drug. Furthermore, Enhanced Recovery After Surgery (ERAS) protocols are not followed in the ICU, and therefore there would be significant deviations from study protocol. Importantly, we aim to study ketamine's effects within ERAS principles for specifically elective surgeries. A transfer to the ICU while intubated reflects the occurrence of a major, unintended, and unanticipated intraoperative event for these elective procedures. The focus for that patient is no longer expedited recovery, but rather life-sustaining measures. Second, abortion of planned surgical procedure will qualify as a post-randomization exclusion. These patients do not undergo the intended surgical experience, will have different care pathways and goals, and are often discharged prior to 48 hours (length of time for the intervention). This exclusion will be defined as the patient being discharged home within 23 hours of anesthesia stop time, consistent with an 'observation' status rather than 'inpatient admission' to the hospital. Manual chart review will be performed to ensure appropriate exclusion. The occurrence of these exclusions will be tracked between study arms. Eligible patients will be consented for inclusion in the trial usually on the day of their surgery; patients returning for a follow up procedure that meets inclusion criteria will be reapproached for consent and rerandomized as appropriate.

Cohort Definition for Data Analysis

Intent-to-Treat Cohort

Intent-to-treat cohort includes all participants who are eligible and did not meet exclusion criteria specified in the study protocol.

Per-Protocol Cohort

To better understand the potential efficacy of ketamine, a per protocol cohort will be analyzed which will include patients in both arms who did not have the study infusion stopped for adverse effects. The per-protocol cohort includes participants who finished the 48-hour post-operative infusion (either ketamine or placebo), as well as participants for whom the study infusion was intentionally discontinued early because the patient met appropriate recovery milestones and was preparing for discharge. However, this per-protocol cohort will exclude any patients in whom the study infusion was stopped for intolerance or side effects, including those patients who were discharged prior to 48 hours but had the post-operative study infusion stopped prior to 48 hours due to intolerances or side effects.

Treatment Arms

Randomization of treatment arms will occur in clusters of one week so that all patients in the same week will receive the same therapy (i.e., ketamine or placebo).

A. **Intervention**: Patients will receive a weight-based (up to 100 kg max) intraoperative ketamine bolus (0.5 mg/kg) followed by continuous infusion (5 mcg/kg/min), and an additional postoperative ketamine infusion (2.5 mcg/kg/min, up to 100 kg max) for 48 hours.
B. **Placebo:** Patients will receive an intraoperative saline bolus followed by continuous infusion of equivalent volume to study drug dosed for 5 mcg/kg/min, and an additional postoperative saline infusion for 48 hours at an equivalent volume of infusion as the intervention arm.

Outcomes

Primary Outcome

The primary outcome is the LOS in days for the placebo arm and the intervention (ketamine) arm. LOS is defined as the time between anesthesia start and the patient being discharged (patient physically leaving the hospital).

Secondary Outcomes

1. Total consumption of post-enrollment inpatient opioids in morphine milligram equivalents during the perioperative period to hospital discharge
2. The incidence of following surgical outcomes:
    a. rapid response team calls
    b. transfer to ICU (not including direct transfer from OR to ICU as these patients are excluded from the study) after patient has been sent to the PACU or floor
3. The incidence of the following indications or side effects requiring early cessation of the study medication, as documented by the provider at the time of discontinuing the order (from Best Practice Advisory, BPA)
    a. Meeting milestones/preop for discharge
    b. Mild side effects, but prefers discontinuation
    c. Debilitating hallucinations
    d. Debilitating dizziness
    e. Hemodynamic instability
    f. Other severe side effect

4. The incidence of ileus requiring gastric decompression as defined by orogastric or nasogastric tube placement in the postoperative period

Exploratory Outcomes

1. Instances of reoperation within the index encounter
2. VUMC hospital readmissions within 30 days post-discharge (not including ED visits)

Design Considerations

Randomization

Randomization will occur in clusters of one week. All patients in the same week will receive the same therapy (ketamine or placebo), with the selection being determined by a pre-generated random sequence.

Power and Sample Size

We anticipate the use of ketamine will reduce LOS following surgery start. To determine how long this trial will need to run to have sufficient power to detect a meaningful difference, we assumed 85% power, a type I error rate of 5%, and a 10% reduction in LOS. We estimated the within period correlation from preliminary data concerning the length of stay for major abdominal surgeries to be about 0.014. Given these assumptions, about 1514 patients would need to be included overall. An increase in sample size is necessary to accommodate for the two post-randomization exclusions that are pre-specified. We expect approximately 30 participants to be impacted by these post-randomization exclusions and will therefore increase the sample size by 30 to account for this exclusion (n=1544). Given surgical volumes, we expect 20 patients to be enrolled each week, and for the trial to last approximately 18 months.

Statistical Approach

Descriptive Analysis

We will describe the study cohort both overall and by treatment arm. To characterize the study sample, demographic and clinical data will be described. Categorical variables will be described using frequencies and proportions; continuous variables will be described using means and standard deviations as well as medians and interquartile ranges (IQR). Missingness will be recorded for each variable. To further assess the distribution of variables, graphical summaries will be displayed using graphs such as boxplots, dotplots, and/or histograms. No statistical testing will be performed to compare characteristics between groups. At a minimum, the following baseline variables will be described:

- Age (years)
- Sex assigned at birth (male, female, unknown)
- Race
    - Caucasian
    - African American
    - American Indian
    - Asian
    - Decline to answer
    - White

    - Hispanic/Latino/a
    - None of these
    - Other
    - Unknown
- Ethnicity (Hispanic/Latino, Non-Hispanic/Not Latino, Unknown)
- Weight (kg) and height (m^2), and BMI (kg/m^2) will be calculated with weight and height
- Van Walraven modified Elixhauser score
- History of Smoking
- Type of Surgical Procedure (colorectal, ventral hernia, or surgical oncology – mutually exclusive categories)
- Epidural vs. truncal nerve block
- Intraoperative time, as defined by anesthesia start time to anesthesia stop time
- The last American Society of Anesthesiologists (ASA) Physical Status classification associated with the surgery (anesthesia encounter)
- Opioid exposed or naïve, as defined by the perioperative medicine initial consult note
- Known history of anxiety, as defined as any code present in the patient's chart prior to, and including the date of enrollment
- Known history of depression, as defined as any code present in the patient's chart prior to, and including the date of enrollment
- Known history of PTSD, as defined as any code present in the patient's chart prior to, and including the date of enrollment

Main Analysis

The main statistical analyses will be performed with the intent-to-treat cohort. As a part of sensitivity analyses, the per-protocol analysis will be performed with the primary outcome and the first secondary outcome defined in Secondary Outcomes section (i.e., total consumption of post-enrollment inpatient opioids in morphine milligram equivalents).

Primary analysis: A mixed-effect proportional odds model will be used to compare the primary outcome (i.e., LOS) between the intervention and placebo arms with cluster as a random effect. The model will include baseline characteristics such as age, body mass index (BMI), Van Walraven modified Elixhauser score, history of smoking, epidural vs. truncal nerve block, intraoperative time, the last ASA Physical Status classification associated with the surgery, opioid naïve status, known history of anxiety, known history of depression, and known history of PTSD. Continuous variables will be modeled using cubic splines to examine non-linear relationship. For missing covariates, if the proportion of missingness is very small, single imputation will be used as appropriate; otherwise, multiple imputation will be used.

Secondary analyses: The secondary outcomes will be analyzed with the same covariates. A mixed-effect proportional odds model will be used to evaluate difference in opioid use in the hospital between the intervention and placebo arms. For each of the binary outcomes, a mixed-effect logistic regression will be used to compare the odds of events between the two arms.

Exploratory analyses: The exploratory outcomes will be presented in tables comparing the incidences of reoperation and hospital readmission within 30 days post-discharge between two arms.

Differential Treatment Effects

Differential treatment effects will be explored by examining the interaction between the treatment indicator and each variable that potentially interacts with treatment, one variable at a time, but subgroup analysis will not be performed. The variables we consider include sex, opioid naïve status, type of surgical procedure (colorectal, ventral hernia, or surgical oncology), epidural vs. truncal nerve block, known history of depression, and known history of PTSD.

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