1. Title of project: The Effect and Contribution of a Perioperative Ketamine Infusion in an Established Enhanced Recovery Pathway.

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3. Background and significance:

Over the last 20 years, opioid use disorder and related deaths have risen to epidemic proportions in the United States. Unfortunately, data suggests that long-term opioid use often begins from a discharge prescription intended to treat acute surgical pain. Additionally, opioid consumption during hospitalization is associated with adverse outcomes, including respiratory arrest, delirium, bowel ileus, nausea, and prolonged length of stay.

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. This intentional practice, termed 'enhanced recovery pathway', has been extremely successful over the last few years, with internal data showing significant reductions in opioid consumption, improved surgical outcomes, and earlier discharges from the hospital. Our results are consistent with experiences from other enhanced recovery programs.

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. Thus, we aim to perform a series of randomized, controlled trials in which we systematically isolate each component of our bundled pathway.

We propose to conduct a randomized controlled trial to investigate the weight of ketamine, within a the construct of a pre-established enhanced recovery program, on a) length of stay, b) total inpatient opioid consumption, and c) surgical outcomes after major abdominal surgery. Eligible patients in our enhanced recovery program will be randomized to receive either ketamine or saline during the perioperative period, with

the remainder of the multimodal analgesic regimen consistent between the groups. Breakthrough pain will be addressed pragmatically, in accordance with suggested pathway guidelines and routine practice of our physicians.

4. Rationale, specific aim(s), and hypotheses:

AIMS: Examine the effects of ketamine, within the constructs of a multimodal pain regimen, on a) length of stay, b) opioid consumption, and c) surgical outcomes after major abdominal surgery.

4.1 Primary Outcome: total length of hospital stay (days). LOS is defined as the time between anesthesia beginning and the patient being discharged.

4.2 Secondary Outcomes:

a) total consumption of inpatient opioids in morphine milligram equivalents

b) surgical outcomes including rapid response, transfer to icu, and ileus

c) the incidence of side effects, including hallucinations, sedation, adverse reactions requiring early cessation

4.3 Exploratory Outcomes

a) Instances of reoperation within the index encounter

b) Hospital readmissions to VUMC within 30 days post-discharge

4.4 Primary Hypothesis: Utilization of ketamine as part of a perioperative multimodal pain regimen will result in a significant reduction in length of stay as defined as the time between anesthesia beginning and the patient being discharged.

5. Preliminary results including animal studies and previous human studies (if applicable):

Ketamine has been used as a core intraoperative component of several VUMC enhanced recovery pathways since we adopted the practice. As evidence of its safety and utility became more available, we expanded its use to include the postoperative period as well (2016 consensus guidelines).

To date, no study has looked at the contribution of ketamine within an established enhanced recovery pathway. However, studies looking at perioperative ketamine infusions individually are summarized below:

PMID: 30113350: 129 patients either “opioid tolerant” or “naiive.” Were randomized to Ketamine 0.12 mg/kg/h x 24 hours or a saline placebo. The primary outcome was opioid consumption during the first 24 h postoperatively. The secondary outcome was numerical pain scores during the first 24 h and central

nervous system side effects. Postoperative hydromorphone consumption was significantly reduced in the opioid-tolerant ketamine group, compared with the opioid-tolerant placebo group [0.007 (95% CI 0.006 to 0.008) versus 0.011 (95% CI 0.010 to 0.011) mg kg^{-1} h^{-1}, Bonferroni corrected $P < 0.001$]. Postoperative low-dose ketamine infusion reduces opioid requirements for the first 24 h following spinal fusion surgery in opioid-tolerant, but not in opioid-naïve patients.

PMID: 26283834: Zakine et al. [49] performed a double-blinded study comparing the effectiveness of ketamine administration in two different settings with one control group which received placebo. The first ketamine group received a 0.5 mg/kg bolus perioperatively and a 2 μg/kg/min infusion thereafter for 48 hours; the second ketamine group received a 0.5 mg/kg bolus perioperatively and a 2 μg/kg/min infusion only for the duration of the surgical procedure. All of the patients were given morphine PCA. The authors found that cumulative morphine consumption was significantly lower in the group receiving the 48-hour infusion when compared to the shorter infusion and control groups. VAS scores were measured postoperatively and were significantly lower in the ketamine groups when compared to the control group. As an added effect, while all patients in the study received hydroxyzine preoperatively, the 48-hour infusion group experienced significantly less nausea than the control group (4% versus 27%,). It is worth nothing that there were no side effects of the ketamine, psychotomimetic, or otherwise.

PMID: 23814653: Hadi et al. [40] used low-dose IV ketamine as an adjunct to therapy during and after lumbar microdiscectomy surgery. Patients were divided into a control group, a group receiving 1 μg/kg/min perioperatively and a group receiving both 1 μg/kg/min perioperatively and 1 μg/kg/min postoperatively. The patients in the control group required first analgesic demand dose earlier than the ketamine groups. Total morphine consumption, visual analog scale (VAS) pain scores, and rates of nausea and vomiting were significantly lower in the group receiving both peri- and postoperative ketamine versus the control group.

PMID: 22374377: Suppa et al. [48] performed a similar study in women undergoing elective Cesarean sections, using a 0.5 mg/kg ketamine bolus 10 minutes after birth in addition to a 2 μg/kg/min IV ketamine infusion for 12 hours thereafter. Usage of ketamine reduced morphine requirements at the 4–8, 8–12, and 12–24-hour time points. The patients in the ketamine group showed reduced pain sensitivity at the T-10 dermatome, suggesting an antihyperalgesic effect. At three years after surgery, patients reported no differences in residual pain or dysesthetic symptoms.

PMID: 19923527: Remérand studied the effects of a 24-hour ketamine infusion in patients undergoing primary elective total hip arthroplasty in France. In a prospective, randomized, placebo-controlled, double-blind study of 154 patients, the group received an IV bolus of 0.5 mg/kg of study drug (either ketamine or placebo/saline) followed by an IV infusion for 24 hours at a dose of 2 mcg/kg/minute. ll patients received general anesthesia, acetaminophen, ketoprofen (NSAID), and a morphine/droperidol mixture via IV PCA. The primary outcome of interest was 24-hour morphine consumption. The ketamine treatment group had a mean 24-hour morphine consumption of 14 mg versus 19 mg in the placebo group ($P = 0.004$). Although statistically significant, the clinical relevance of a 5 mg decrease in IV morphine is unclear. However, on secondary analysis, the ketamine treatment group had statistically significant decreases in (1) the need for two crutches or a walking frame at Postoperative Day 30 (31% vs 56%; $P = 0.0035$); (2) pain at rest from Postoperative Days 30 to 180 ($P = 0.008$); and (3) persistent pain in the operative hip at rest at Postoperative Day 180 (8% vs 21%; $P = 0.036$; relative risk reduction, 67%).

6. Inclusion/exclusion criteria:

6.1 Inclusion criteria:

- 18 years old or greater
- presenting for major, elective, abdominal surgery on the colorectal, ventral hernia, or surgical oncology services on a weekday

6.2 Exclusion criteria:

- allergy or contraindication to ketamine
- unable or refused to receive a neuraxial or regional nerve block
- patient refusal
- direct transfer from operating room to ICU with endotracheal tube placed
- treating team elects to exclude the patient prior to study drug administration
- abortion of surgical procedure

7. Enrollment/randomization:

Patients presenting for elective major abdominal surgery at VUMC are automatically screened to receive care within our enhanced recovery program. Patients are approached on the day of their surgery by a physician member of our Perioperative Medicine team, who describes our goals, multimodal pathways, and obtains consent to perform a regional nerve block. Eligible patients will be consented for inclusion in the trial during this initial encounter; patients returning for a follow up procedure that meets inclusion criteria will be reapproached for consent and rerandomized as appropriate. Consent for the trial will be included as an adaptation to our current consent form for neuraxial or regional nerve block procedures, with the addition of the following language:

"Vanderbilt University Medical Center (VUMC) is a learning healthcare system where we evaluate how well our routine treatments and interventions for pain control work after surgery and possible side effects they may produce. As part of your perioperative care, you will receive a bundled approach of different pain regimens that have been shown to work both alone and together to relieve pain. At VUMC, we are studying different aspects of our routine bundled pain regimen to determine the most effective parts and combinations.

If you are eligible for enrollment in a study about treatment of your pain, you may be assigned to one of multiple routinely used regimens to help control your pain. Upon enrollment, you will be randomized to receive either a ketamine or saline infusion. We are doing this study to understand which regimens have better pain control and fewer side effects in different patients. You will have pain medicine available as you need it regardless of the regimen used. Potential side effects of those pain medicines include confusion, sleepiness, agitation, slowing of your breathing, and changes in blood pressure. Data will be collected from your medical record to evaluate how well your pain

is controlled and whether or not you have any side effects. The risk of the study is that your data could be seen by people not part of the study. To help prevent this, data will be stored in a secure database to minimize the risk of anybody seeing your information. You can choose not to have your data be part of the study. Ultimately, the health care providers involved in your care will determine the best treatment plan for your pain, regardless of your taking part in the study or not. You do not have to take part in the study. If you decide not to take part in the study, none of your care will be changed because you opted not to take part. You can also choose to stop taking part in the study at any time. Patients can choose to opt out of taking part in the study by initialing the following statement:

> I would like to opt-out of any studies evaluating how well my surgical pain regimen works. I understand that the physicians caring for me will determine the best treatment plan for my pain, and that this plan may still include the bundled pain regimen being studied. However, data from my medical record will not be used to evaluate how well the pain treatment regimen works or its side effects.

Randomization will be in cluster format, scheduled and tracked by the OR pharmacy. Patients and their medical providers will be blinded to their randomization arm. Provisions for breaking the blind include medical emergencies, adverse medication reactions, and participant or medical provider request.

A subset of patients may be readmitted for an additional surgery during the study period. In these instances, if the planned surgery meets inclusion criteria, the patient will be re-randomized and the readmission will be considered a new instance/encounter. For patients undergoing re-operation within the same encounter/admission, we will not re-randomize these patients. Instead, providers will order ketamine or not as appropriate per their clinical judgement.

8. Study procedures:

Procedure/Activity	**Frequency**
Patient 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 choice being determined by a pre-generated random sequence.
intraoperative ketamine bolus (0.5mg/kg) vs placebo followed by continuous infusion 5 mcg/kg/min	once
postoperative ketamine infusion (2.5 mcg/kg/min, up to 100kg max) vs placebo for 48 hours	once
electronic medical record chart review	for data capture and statistical review

Data will be abstracted from the EMR. Some data will be obtained through the Research Derivative. The Research Derivative is a database of clinical and related data derived from the Medical Center's clinical systems and restructured for research. Data is repurposed from VU's enterprise data warehouse, which includes data from StarPanel, VPIMS, and ORMIS (Operating Room Management Information System), EPIC, Medipac, and HEO among others. The medical record number and other person identifiers are preserved within the database. Data types include reimbursement codes, clinical notes and documentation, nursing records, medication data, laboratory data, encounter and visit data, among others. Output may include structured data points, such as ICD 9 codes or encounter dates, semi-structured data such as laboratory tests and results, or unstructured data such as physician progress reports. The database is maintained by the Office of Research Informatics under the direction of Paul Harris, Ph.D.

Due to a national shortage of ketamine, study enrollment was paused on April 3rd, 2023 and then resumed on September 18th, 2023.

9. Risks:

Ketamine is an analgesic that has been proven to reduce opioid consumption after surgery. It also has a role in reducing the development of chronic pain. Compared to opioids, ketamine has a favorable side-effect profile, including the maintenance of respiratory and cardiovascular stability. Ketamine does not act at the mu opioid receptor, and therefore is not associated with nausea, itching, constipation, and tolerance.

We have been safely utilizing perioperative ketamine VUMC for several years as part of our enhanced recovery pathways.

Ketamine is a controlled substance and is highly regulated, recorded, and tracked. Patients are evaluated daily at the bedside by our Preoperative Medicine Service, and patients are screened for side effects of ketamine on daily rounds. Nurses are trained to immediately report any suspicion of an adverse ketamine reaction to a member of our team, who is in-house 24/7.

Adverse reactions to ketamine: Adverse reactions and allergies to ketamine are routinely reviewed by both medical providers and pharmacy personnel prior to ordering and administering the drug. Ketamine is a controlled substance and is highly regulated, recorded, and tracked. Patients are evaluated daily at the bedside by our Preoperative Medicine Service, and patients are screened for side effects of ketamine on daily rounds. Nurses are trained to immediately report any suspicion of an adverse ketamine reaction to a member of our team, who is in-house 24/7.

Selection of patients: Only patients receiving care through our enhanced recovery pathway (which includes the standard administration of ketamine) will be eligible for participation.

Ineffective pain control: Patients with breakthrough pain will receive routine treatment guided by our preoperative protocols and discretion of medical providers.

Breach of confidentiality: The investigators have access to the medical data as part of their job standing. All database work will be performed on VUMC approved and password protected servers that are physically located in the VUMC computing environment and maintained by VUMC security standards. Only the PI and KSP will have access to study specific data.

10. Reporting of adverse events or unanticipated problems involving risk to participants or others:

Quality controls will include regular data verification and protocol compliance checks. Protocol adherence will be monitored by the PI throughout the study. Events determined by the PI to be unanticipated problems involving risks to subjects will be reported by the PI to the IRB as per VHRPP Policies and Procedures

If any breach of confidential patient material were to occur, the Institutional Review Board at Vanderbilt University Medical Center would be immediately contacted.

11. Study withdrawal/discontinuation:

Patients and their medical providers will be blinded to their randomization arm. Provisions for breaking the blind include medical emergencies, adverse medication reactions, and participant or medical provider request. Patients can request to be withdrawn from the study at any time. Should a patient choose to withdraw from continued study drug administration, outcomes will continue to be collected from the EMR unless the patient indicates they do not want their data collected.

12. Statistical considerations including sample size justification (power analysis) and statistical analysis plan (optional at this stage for investigators not versed in statistical methodology):

This study is a cluster randomized, pragmatic clinical trial. Initial analysis will use descriptive statistics and data visualizations to both identify and address spurious values, and to characterize the study cohort. Characteristics will be grouped by study arm, but we do not plan to compare the study arms with statistical tests.

The primary outcome is length of stay, measured in days. It is expected that length of stay is a skewed distribution, and so non-parametric methods are preferred. However, it

is not possible to consider the clustering or baseline covariates using a Wilcoxon test. Therefore, a proportional odds regression model will be used. Clustering will be taken into account using a mixed-effects model. If there are patients included twice because they underwent two elective major abdominal surgeries, patient will also be included as a random effect. The model will include baseline characteristics such as age, BMI, history of substance use (smoking status and opioid status if available), and type of surgical procedure. The common odds ratio from the model will be estimated; this quantity can be interpreted similar to the concordance probability and is robust to the proportional odds assumption. We will also report the model-assisted estimands of mean and median length of stay. Bootstrapping will be used to generate appropriate confidence intervals.

We will use an intention to treat analysis and all participants who are randomized will be included in the statistical analysis and analyzed according to group assignment. Participants will be removed from the analysis if their provider deems the patient ineligible prior to study drug administration. If a participant or provider withdraws the participant from the study following study drug administration, the participant will receive care at the provider's discretion, but will remain in the statistical analysis.

The secondary outcomes will be explored in a similar way. The proportional odds model will be used to evaluate differences in opioid use in the hospital. Occurrence of events will be reported as rates with confidence intervals. Logistic regression will be used to compare the odds of events between groups.

In all statistical modeling, emphasis will be placed on effect sizes over p-values. In addition, continuous variables will be modelled flexibly using cubic splines. Differential treatment effects will be explored by examining the interaction between the treatment indicator and the putative subgrouping variable. We will explicitly test for effects of treatment by sex. As before, continuous variables will not be categorized, and the interaction will be with the continuous variable. Subgroup analyses will not occur in reporting the main results of this trial unless there is evidence of a differential treatment effect.

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. If the effect size were bigger, say 20%, then 370 patients would be required. An increase in sample size is necessary to accommodate for the two post-randomization exclusions that are pre-specified. We expect ~30 participants to be impacted by these post-randomization exclusions and will therefore increase the sample size by 30 to account for this (n=1544). Given surgical volumes, we expect 20 patients to be enrolled each week, and for the trial to last approximately 18 months. The current accrual rate has been more aligned with ~15 patients enrolled each week. Accordingly, the trial is anticipated to last approximately 26 months.

13. Privacy/confidentiality issues:

Study team members will access the EMR in order to collect data for our primary and secondary outcomes. All team members have been trained in proper care of PHI. After enrollment with PHI, participants will be assigned a corresponding number to de-identification purposes, and they key will be secured in a database separate from the study data collected. All database work will be performed on VUMC approved and password protected servers that are physically located in the VUMC computing environment and maintained by VUMC security standards. Only the PI and KSP will have access to study specific data.

14. Follow-up and record retention details:

Identifiers will be maintained only through the duration of the study and subsequent publication, after which the information will be destroyed.

15. References:

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