Pilot Study: The Effect of Intraoperative Ketamine on Analgesia Post-Cardiac Surgery and Prevention of Postoperative Pain

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Background

Pain control post-sternotomy is an essential part of fast-track surgery, a program to promote early recovery. Up to 75% of patients complain of moderate-to-severe pain after cardiac surgery, with poorly controlled pain leading to an increased risk of myocardial ischemia and chronic post-sternotomy pain, which is seen in 11% of patients.[1-2] Given the relative contraindications to epidural analgesia and non-steroidal anti-inflammatories after coronary artery bypass grafting (CABG) surgery, options for multimodal analgesia are limited.[3]

Ketamine is an NMDA antagonist which potentiates the release of inhibitory neurotransmitters, modulating the sensory processing of pain.[4] Ketamine is a well-established treatment for a variety of pain syndromes, and is approved by Health Canada to be used as a supplemental agent during anesthesia.[5-7] There is a growing literature showing that Ketamine contributes to pain control after surgery as well. It has been shown that Ketamine decreases opioid needs after spine surgery, as well as after thoractomy.[8-10] While these studies used the racemic form of Ketamine, the only version approved for use in Canada, a Finnish study on the cardiac surgery population evaluated the S(+) enantiomer of Ketamine, which has not been available in Canada. This was shown to reduce postoperative opioid requirements by 20%.[11]

There are limited downsides to the administration of Ketamine. The most common adverse effects of ketamine in awake patients include nightmares, hallucinations, a dissociative state, headaches, and hepatotoxicity.[5,12] In clinical studies of low dose Ketamine used for perioperative pain control, there has not been shown to be a significant increase in side effects between treatment and placebo groups.[9]

Ketamine, while used at times, is not routinely used during cardiac anesthetics. It has not been studied for its effect on postoperative pain control and its effect on post-sternotomy chronic pain.

Given that the S(+) enantiomer of Ketamine previously studied in cardiac surgery patients is not available in Canada, this study will investigate the racemic form of Ketamine that is available in Canada, which, to our knowledge, has not been studied in the cardiac surgery population. This is the form of ketamine will has well established use during anesthesia care and the form of ketamine with which the vast majority of the literature on postoperative pain has been based.

Specific Aim & Hypothesis

The main goal of this pilot study is to assess the effect of an intraoperative intervention, the administration of ketamine, on analgesia post-cardiac surgery. This pilot study will also help assess the feasibility of recruiting and retaining patients, safely administering a blinded medication in the operating room, accurately measuring a primary outcome of postoperative narcotic consumption, and blinding those involved in the care of cardiac surgery patients.

The long-term goal of this study and subsequent follow-up studies is to improve pain control after cardiac surgery, with the hope of allowing patients to perform earlier physiotherapy, regain functional status, and allow for an earlier discharge from hospital.

The specific aim of this study is to ascertain whether an intraoperative infusion of racemic Ketamine can improve postoperative pain control after CABG surgery. The hypothesis is that the intraoperative administration of this medication will improve postoperative pain

control demonstrated through a decrease in postoperative opioid consumption of more than 25%.

Study Design

This is a randomized, blinded, placebo-controlled pilot study. A stratified block randomization procedure will be used to ensure that each group has an equal number of men, and an equal number of women. Blocks will be made in groups of 4 for each sex. Given that the majority of cardiac surgery patients are male, each group is not expected to be made of an equal number of men and women. The randomization procedure will be done with pre-prepared numbered envelopes. Separate piles of envelopes will be kept to randomize each sex separately. Each envelope will contain the group assignment of either “Ketamine” or “Placebo”. Group assignment papers will be inserted in the envelopes in a random order. A list of the group assignment in each numbered envelope will be kept separate from study materials while the study is being carried out. This measure will help ensure that the research coordinator will be blinded during data collection. A separate list will be made by a co-investigator not involved in the data analysis denoting which envelopes corresponded to “Group A” and “Group B” to allow for the primary investigator to be blinded during data analysis, and for the study coordinator to ensure stratified randomization has distributed an equal number of patients of each sex in each group by the end of the study.

Either the cardiac surgeon, the cardiac anesthetist or a nurse involved in the patients’ care will ask the patient if the research coordinator can approach the patient to discuss

inclusion in the study. The research coordinator will then discuss risks and benefits of being included in the study and obtain consent.

On the day of the procedure the research coordinator will randomly select a numbered envelope for the appropriate sex, and hand this to one of the two other co-investigators prior to surgery. One of the two co-investigators will prepare the study drug.

The intervention group will receive Ketamine, while the placebo group will have an identical syringe of normal saline prepared. The placebo will be prepared to blind the cardiac anesthetist caring for the patient. This blinding is important as the quantity of narcotic administered during the surgery is at the anesthetist's discretion, and knowing whether or not a co-analgesic is being administered may affect the quantity of narcotic administered. The quantity of narcotic administered could be considered a co-intervention of the primary outcome, so we are taking all precautions to ensure that the amount of narcotic administered is not influenced by the anesthesiologist's knowledge of the study drug.

The cardiac anesthesiologist will receive the medication in the operating room, delivering a bolus prior to skin incision and administering the medication at a rate determined by the patient's weight. The dose of medication administered should not have any hemodynamic effects, and so unblinding of the cardiac anesthetist should not be necessary. If, for whatever reason unblinding should become necessary, the co-investigator who prepared the medication will make the primary anesthetist aware of the contents of the study drug.

Upon transfer to the intensive care unit, nurses and intensive care physicians will be made aware that the patient is involved in the study. The research coordinator will have documented the volume of study drug administered in the anesthetic record at the end of the

case. If the treatment allocation needs to be known by the intensive care team, they will be able to contact the primary investigator to be immediately unblinded.

Patients will be asked if they would allow the research coordinator to call them at 3 and 6 months after surgery to ask if any pain is present at the site of incision, followed by ten yes or no questions about the pain, and what medications they may be taking for pain, if the pain is still present. These questions can be found in the attached questionnaire.[14]

Study Population

The study population will be patients coming for CABG surgery via midline sternotomy at the Jewish General Hospital. This population was selected to ensure all patients have a similar incision and number of chest tubes, two of the main contributing factors to postoperative pain. Patients with a left ventricular ejection fraction less than 50% will be excluded, as these patients are more likely to require a longer duration of circulatory support and mechanical ventilation. Extended mechanical ventilation and sedation will make it difficult to assess the primary outcome of the study. Patients with a history of regular opioid use will be excluded, as these patients have an increased tolerance to opioids and require larger doses to achieve adequate pain control. Including these patients in a small randomized study would risk having a significant effect on the primary outcome. Patients with known hepatic or renal dysfunction will be excluded as well, given the theoretical accumulation of ketamine. Patients with a contraindication to ketamine will also be excluded, such as those with a previous cerebrovascular accident, or with known hypersensitivity to the drug. Patients unable to

provide consent will also be excluded, as the reporting of pain in these patients will likely be unreliable.

Exposure

Exposure will be randomized to an intervention or placebo. The intervention arm will consist of ketamine as a 0.5mg/kg as a bolus, and a 0.5mg/kg/hr infusion throughout the surgery. For an 80kg patient, with a Ketamine concentration of 10mg/mL, this would amount to a 2mL bolus and 2mL of fluid administration per hour of surgery, or approximately 10mL of fluid for the duration of a surgery. The placebo arm will consist of a saline infusion at the same volumes. This dose of ketamine is based on previous studies that have shown effectiveness in surgical populations.[1-4] The doses at which Ketamine will be administered is not expected to have any hemodynamic effects, and therefore compliance by the anesthesiologist with the treatment is be expected to be near 100%.

Both treatment arms will receive a full cardiac anesthetic in addition to the study intervention. Since the total quantity of intraoperative opioids administered will depend on infusion rate and duration of anesthesia, the total dose administered will be noted for each patient.

Postoperative opioids will be prescribed at a dose and frequency according to the standard postoperative orders for cardiac surgery patients. An intensive care nurse will administer opioids at the doses prescribed on the post-operative orders. This strict protocol for pain management improves the internal validity of the trial, understanding that this may

somewhat decrease external validity in comparison to other centers who do not manage postoperative pain with the same regimen.

Outcomes

The primary outcome is the quantity of opioid administered over the first 48 hours postoperatively. Forty-eight hours was selected as the duration to monitor opioid consumption, as this is the period during which pain post-cardiac surgery has been shown to be most intense.[1] This primary outcome was selected as it will be reliably documented and straightforward to assess, given the strict guidelines for documentation of opioids.

There will be several secondary outcomes. The quantity of opioids used at 24 hours will be noted. Postoperative pain will be measured daily via the "brief pain inventory" by the research coordinator on postoperative days 0, 1, and 2.[13] Patients will be asked their current pain, the worst and best pain levels throughout the day, as well as their average pain levels. The need for additional analgesic medications will be assessed as a binary outcome for each type of additional medication (NSAIDs, additional opioids, gabapentinoids, etc), measuring whether or not additional agents are added to treat poorly controlled pain. Additional analgesics would likely affect the dose of post-operative opioids administered, making it a co-intervention which may need to be accounted for in the analysis. The presence or absence of postoperative nausea and vomiting requiring treatment, as well as the diagnosis of delirium will be measured as binary outcomes. Intensive care unit and hospital length of stay will be measured in number of days, while the time to extubation, time to first mobilization to a chair, and time to first ambulation will be measured in number of hours after arrival to the intensive care unit through

chart review. While the dose of ketamine used in this study is not likely to cause psychological side effects, the number of patients reporting hallucinations or severe nightmares will be tracked.

On follow-up phone call at 3 and 6 months patients will be asked whether or not they have persistent pain at the site of the sternotomy. Whether or not persistent pain is present will be noted, along with any medications that they may be taking for the pain. If persistent pain is present, they will be asked ten yes or no descriptive questions about the pain concerning to determine if it is neuropathic in origin.[14] The answer to each question, as well as the overall score will be noted.

Confounders

Possible baseline confounders will be tracked to look for differential distribution between intervention groups. These will include age, sex, body mass index, left internal mammary harvesting. We will stratify our randomization by sex to ensure sexes are balanced in the 2 groups, as sex has been shown to be one of the main confounders for postoperative pain. With a relatively small sample size of 80 patients, a differential distribution of confounders between groups is possible, and an adjustment will be done in our analysis for any factor that is differentially distributed. Injuries during cardiac surgery such as rib fracture and dislocation, or fractured sternum may contribute to postoperative pain as well. Unfortunately, these variables often go undetected and cannot be adequately tracked. We will therefore rely on randomization to ensure equal distribution in both groups.

Analysis Plan

While nearly complete compliance is expected with the therapy, an intention-to-treat analysis will be performed in case any unforeseen issues with compliance arise during the study. Continuous data such as postoperative opioid dose, intensive care unit and hospital length of stay, and time to mobilization and ambulation will be evaluated using the t test if it is determined that the means are normally distributed, or the Wilcoxon Rank Sum test if the means are not normally distributed. Ordinal data such as visual analog scale scores and binary data such as need for additional analgesics and the presence or absence of PONV will be evaluated by a Chi-Square test. If confounding is suspected due to baseline differences in the variables noted above, we will perform a propensity score depending on the variable(s) and the size of the difference. As a secondary analysis, data will be analyzed in subgroups by sex to look for any potential difference in response.

Sample Size & Power Analysis

Using the data in the trial evaluating S(+)-Ketamine, an estimate of 125mg of oxycodone over the 48 hours post cardiac surgery was used as a baseline.[1] In this same study, both the intervention and controls groups had standard deviation of oxycodone of 45mg. To detect a decrease in opioid requirements of 25% with a power of 80% and a two-sided alpha of 0.05, a total of 68 patients would be required in the trial, with 34 in each group. For a power of 90%, a total of 90 patients would be required in the trial with 45 patients in each arm. The Jewish General Hospital, a McGill University teaching hospital, performs approximately 600 cardiac surgeries per year, with approximately 350 CABG surgeries via sternotomy. The goal will be to

enroll 80 patients. With the nature of this study and the need for hospitalization post-cardiac surgery, there should be minimal, if any, drop-outs or loss to follow-up, and therefore the sample size of 80 patients should allow for a power of over 80%.

Strengths & Limitations

Strengths of the study include the ability to randomize, and the ability to blind the patients, nurses, anesthesiologists and pain evaluators. This study will be performed at a single center, which allows for easier standardization of therapy, at the same time limiting generalizability of the findings. The primary outcome, opioid use, is easily measurable. Limitations will include the inter-individual variability in both patient thresholds for analgesia request, and nurse thresholds to administer analgesia. Injury during cardiac surgery may contribute to pain (rib fracture or dislocation), and will not be able to be accurately measured.

Timetable

The Jewish General Hospital currently performs approximately 350 CABG surgeries per year, which is approximately 30 per month. Once ethics approval is obtained, and organizational logistics are arranged, the goal would be to recruit 80 patients over the span of four months. Another 2 to 3 months will likely be required for full data analysis and manuscript preparation.

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