Low-dose ketamine infusions for perioperative pain management in patients undergoing laparoscopic gastric bypass

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Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

Background

Obesity has become a public health crisis in the developed world, especially in the United States. According to the CDC, more than one-third (36.5%) of adults in the United States are obese as defined by a BMI greater than or equal to 30. A 2013 study estimated that 6.6% of the US population is morbidly obese (BMI > 40) (Sturm) Negative health consequences of obesity include cardiovascular disease, obstructive sleep apnea (OSA), systemic hypertension, pulmonary hypertension, diabetes, musculoskeletal problems and various malignancies (Adams BJA 2000). Given the severe health consequences of obesity and the difficulty that many patients have maintaining a healthy weight, surgical management of obesity has become an effective therapeutic option for many patients with morbid obesity (Elder Gastroenterology 2007).

The Roux-en-Y gastric bypass is considered the “gold standard” for weight loss surgery and it is frequently performed laparoscopically. It involves anastomosing the proximal portion of the stomach to the jejunum, bypassing most of the stomach and duodenum and restricting food intake (Ogunnaike A&A2002). Despite the efficacy and overall safety of weight reduction surgery, obese patients pose significant challenges for perioperative physicians and are at higher risk for adverse events postoperatively, especially pulmonary complications (Adams BJA 2000).

Obese patients have increased oxygen consumption, increased CO2 production, reduced lung FRC and reduced chest wall compliance all of which puts them at risk for hypoxemia and hypercarbia particularly in the postoperative period (Adams BJA 2000). Opioids and other central nervous system depressants commonly administered perioperatively may potentiate these gas exchange problems and increase risk for adverse event.

Most concerning, however, is the association between obesity and obstructive sleep apnea (OSA) which is a risk factor for perioperative respiratory depression as well as respiratory arrest and death (Chung A&A2008, also multiple case reports). Up to 70% of patients undergoing bariatric surgery have OSA (Frey Obes Surg 2003). OSA is a disorder characterized by reduced tone in the upper airway muscles during sleep which causes periodic airway obstruction with subsequent apnea and oxygen desaturation. Obese patients are at particular risk of developing OSA at least in part due to fat deposits in the pharyngeal walls leading to reduced airway diameter (Romero Chest 2010). In addition, as discussed above, obese patients are more vulnerable to disordered gas exchange and have less reserve for tolerating brief periods of obstruction.

OSA patients are especially vulnerable to apneic events postoperatively due to surgical stress, the residual effects of anesthesia, disruption of the normal sleep cycle and

exposure to central nervous system depressants (Benumof Curr Op Anesth 2004). Opioids in particular are problematic as they cause respiratory depression and have been shown to depress the muscle tone of the upper airway (Craven 2007, White J Physiol 2009). However, poorly managed abdominal pain may itself compromise respiratory effort resulting in hypoventilation. Clinicians are often confronted with the challenge of balancing the risks of opioid therapy versus the respiratory consequences suboptimal pain control. Non-opioid analgesics such as acetaminophen and NSAIDs can be helpful and have little effect on the respiratory system or OSA (Chung). Other drugs such as dexmedetomidine and gabapentin have also shown promise for reducing perioperative opioids, though both drugs are also central nervous system depressants and it is unknown what effect they may have on airway muscle tone during sleep (Chung).

Ketamine is an NMDA antagonist that, at high doses (>1mg/kg), induces dissociative anesthesia with minimal effects on ventilation and airway reflexes (Gorlin). Low dose ketamine infusions (<0.3mg/kg/hour) have proven efficacy for reducing pain scores as well as reducing post-operative opioid consumption in a wide variety of surgical procedures (Gorlin JAnesthClinPharm 2016). Furthermore, even at anesthetic doses, ketamine has no negative effect on pharyngeal muscle tone (Drummond BJA 1996). For these reasons, low dose ketamine may be an ideal analgesic adjunct for patients undergoing gastric bypass. Sollazzi et al demonstrated lower PACU pain scores and opioid consumption in patients undergoing gastric bypass who received a combined ketamine/clonidine infusion in the operating room (Sollazzi SurgObesRelDis2009). However, to our knowledge, there have been no studies looking at combined intraoperative and postoperative ketamine infusions for gastric bypass.

Our hypothesis states that in laparoscopic gastric bypass patients intraoperative ketamine infusion combined with continuation for twenty-four hours post-surgery provides superior pain control and decreases post-operative opioid use versus standard non-ketamine therapy.

Study Objectives

Primary Objective

- To assess the efficacy of a standardized bolus and infusion dose of intravenous ketamine on perioperative opioid requirements in gastric bypass surgical patients.

Secondary Objective

- To assess the efficacy of a standardized bolus and infusion dose of intravenous ketamine on perioperative pain scores, patient satisfaction with pain management, and length of stay in hospital in gastric bypass surgical patients. To assess the safety and tolerability of intravenous ketamine by examining presence of post-operative nausea and vomiting, pruritus, sedation, agitation, hallucinations, delirium, and adverse respiratory events.

Study Design and General Description

- **Randomization after consent is obtained to either ketamine or standard therapy**

- **Standard therapy group study protocol**
  - Calculation of ideal body weight (IBW) – see calculator
  - Pre-operative dexamethasone 4mg IV
  - Pre-operative midazolam 1-2mg IV for anxiolysis at discretion of anesthesiologist
  - Induction of anesthesia
    - Propofol 2-3mg/kg IV (IBW) at discretion of anesthesiologist
    - Fentanyl 1mcg/kg IV (IBW)
    - Neuromuscular blockade with succinylcholine and/or rocuronium at the discretion of the anesthesiologist
    - Orotracheal intubation
  - Maintenance of anesthesia
    - Sevoflurane/rocuronium
    - Additional doses of fentanyl 0.5-1mcg/kg (IBW) at discretion of anesthesiologist
  - Emergence from anesthesia
    - Acetaminophen 1g IV unless contraindicated
    - Ketorolac 30mg IV unless contraindicated
    - Ondansetron 4mg IV unless contraindicated
    - Suggamedex 2mg/kg or 4mg/kg dose (Actual BW) depending on twitch response per drug manufacturer's recommended protocol
  - Post-operative analgesia
    - Hydromorphone PCA 0.2mg/8 min
    - Acetaminophen 1g IV Q8 ATC x 3 additional doses
    - Ketorolac 15mg IV Q6 ATC x 3 additional doses
  - Other post-operative care as per usual surgical routine

- **Ketamine therapy group**
  - Ketamine 0.3mg/kg (IBW) bolus with induction
  - Ketamine infusion 0.2mg/kg/hr. (IBW) initiated after induction and terminated after 24 hours
  - Ketamine infusion will not be titrated

- Ketamine infusion may be terminated if the patient is having side-effects relating to the drug; Pain Service will follow the patient and assist with troubleshooting and determining the need for infusion termination
- The remainder of care will be identical to the standard therapy group

Number of Subjects

We will enroll up to 45 subjects to attain our goal of 17 subjects per group for a total of 34 accrued subjects. This is to ensure our goal is met based on the randomization list, as well as to account for any withdrawals that occur throughout the study.

Primary Study Outcome

Total cumulative perioperative opioid dose measured in morphine equivalents from induction of anesthesia until 48 hours after induction of anesthesia.

Secondary Study Outcomes

Visual analog pain scores measured from PACU arrival until 48 hours after induction of anesthesia. PONV and pruritus recorded from PACU arrival until discharge from hospital. Length of stay in hospital will be recorded. Patient satisfaction with pain management will be measured by questionnaires that patients complete at the time of discharge and at the postoperative visit with the surgeon or via telephone about 30 days after surgery.

Primary Safety Outcomes

There will be careful and continuous monitoring, intervention and recording of hemodynamics, sedation, agitation, hallucinations, delirium, and adverse respiratory events.
Standardized nursing procedures will be used including vital signs, RASS sedation scores, according to standard intensive post-surgical requirements. Standardized single dose regimen for ketamine.

Data

- **Pre-operative data**
  - Age
  - Gender
  - Height, weight, BMI
  - ASA classification
  - Medical problems
  - Surgical history
  - Home medications
  - Home CPAP?
  - Allergies

- Presence of *active* chronic pain? If so, what is it?
- Currently taking opioids on a daily basis for the past 1 month or greater? If so, quantitate daily dose in morphine equivalents (ME)

- **Post-operative data**
  - Total opioid dose in ME from OR to discharge
    - May look separately at OR, PACU, 1st 24 hours, 2nd 24 hours
  - Pain scores over course of hospitalization
    - May look separately at PACU, 1st 24 hours, 2nd 24 hours
  - PONV
    - Need for additional anti-emetics during hospitalization
  - Pruritus
    - Need for anti-histamines during hospitalization
  - Sedation
    - Average RASS scores 1st 24 hours
    - Any episodes of (-)3 or worse RASS
    - Any evidence of sedation in nursing notes
  - Agitation
    - Average RASS scores 1st 24 hours
    - Any episodes of (+) RASS scores
    - Any evidence of agitation from nursing notes
  - Hallucinations
    - Ketamine drip d/c
    - Review nursing and Pain Service notes
  - Delirium
    - Ketamine drip d/c
    - Review nursing and clinical notes
  - Adverse respiratory events
    - Rapid response events
    - Naloxone administration
    - Change in level of care (intermediate or ICU)
    - Review of nursing notes and clinician progress notes
  - Length of Stay
    - Hours
  - Use of CPAP while inpatient. Y/N
  - Patient satisfaction with pain management questionnaires
    - First questionnaire will be completed by the patient at the time of discharge from the hospital.
    - Second questionnaire will be completed by the patient at the postoperative visit with the surgeon or via phone contact with the patient on or around 30 days after surgery if there has been no postoperative visit.

Subject Selection Enrollment and Withdrawal

Inclusion Criteria

- Patients > or equal to18 years old and < 70 years old undergoing laparoscopic gastric bypass at Mayo Clinic Arizona
- BMI > or equal to 35
- Consent obtained as per Mayo Clinic policy

Exclusion Criteria

- Intolerance to ketamine
- History of schizophrenia, schizoaffective disorder or other psychiatric diagnosis with psychotic features
- Presence of unstable cardiovascular disease. (The presence of acute coronary syndrome, unstable angina, hypertension emergency, acute TIA or stroke.)
- Presence of acute elevation of intracranial or intraocular pressure
- Presence of seizure disorder
- History of substance abuse or addiction
- Creatinine > 1.5
- End-stage liver disease
- Pregnancy

- **Patients with chronic pain and/or chronic opioid therapy:**
    - In order to more closely replicate the study patient population of interest we will not exclude this patient population
    - However, we will exclude patients taking >50 morphine equivalents (ME) per day for greater than 1 month prior to surgery

Subject Recruitment, Enrollment and Screening

Appointment calendars will be screened. Those eligible will be consented by physician or study coordinator either in POE or Surgery Clinic.

Study Procedures

- Patient Consent
    - Patients who appear to meet the inclusion criteria and none of the exclusion criteria will be invited to participate in this study. The study will be explained to the patient, including risks and benefits by the Study Coordinator, and one of the physicians, if available.

- Each patient who agrees to participate will be required to sign and date an informed consent document prior to any study-specific testing and procedure. A copy of the signed and dated consent will be provided to the patient.

- Method for Assigning Patients to Treatment Groups
  - If the patient meets inclusion/exclusion criteria and consents to participate in the study, the morphine equivalents will be calculated by one of the investigators.
  - The REDCap database will be completed with the inclusion/exclusion criteria and morphine equivalents. REDCap will provide the randomization group for the patient.
  - The randomization group will be conveyed to the study team by the Study Coordinator.

- Data Collection and Monitoring
  - All required data is collected during the hospitalization from the electronic medical record.
  - The floor nurses will follow the already existing ketamine guidelines for Pain Service and stopping criteria.
  - The investigators will carefully monitor the subject during hospitalization for any adverse events.

- Discharge from the Hospital
  - At the time of discharge from the hospital, the patient will complete the Patient Satisfaction with Pain Management at Discharge questionnaire.

- Postoperative Visit
  - At the postoperative visit with the surgeon, the Patient Satisfaction with Pain Management questionnaire at Post-op Visit will be completed by the patient. If no postoperative visit is scheduled, this will be done via telephone contact on or around 30 days after surgery. We will allow a window of 30-60 days in case there is difficulty reaching the patient..

- Adverse events
  - Adverse events will be captured and monitored for the first 30 days following surgery to ensure patient safety.

- Data Entry into REDCap
  - The residents will complete data entry into the REDCap database.

Time Frame
Enrollment will be completed within 48 months.

Statistical Plan

Sample Size and Power Calculation

Our primary hypothesis is to check if the new management will keep patient to get less “48 hours morphine equivalent (mg)“. A sample size of 17 in each group will have 80% power to detect a probability of 0.746 that an observation in new management group is less than an observation in control group using a Wilcoxon (Mann-Whitney) rank-sum test with a 0.050 one-sided significance level. In other words, we will arrange the total doses at 48 hours of patients from smallest to biggest. If 13 or more out of first 17 comes from the new management group, we will claim a success.

Statistical Methods

Basic patient characteristics, using mean$\pm$SD or median (range) for continuous variable and frequency (% percentage) for categorical data, will be summarized in a table. 2- group t-test, Wilcoxon rank sum test, Pearson Chi-square test or Fisher exact test will be used to compare the two kinds of management when appropriate. The “48 hours morphine equivalent (mg)” will be compared between the two groups using Wilcoxon Rank sum test. A p-value less than 0.05 will be treated as statistical significant. All statistical analyses will be performed by SAS version 9.4 software (SAS institute Inc, Cary NC).

Adverse Event Reporting Period
For this study, the follow-up period is defined as 30 days following surgery.

Medical Monitoring
It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring will include a regular assessment of the number and type of serious adverse events

Data Security and Confidentiality
All electronic data will be stored in a password-protected database (RedCap). The data storage will be restricted to facility computers that are password protected. Relevant clinical information will be reported only with collective data with no identities revealed.

Study Monitoring Plan

Subjects will be closely monitored for adverse events during treatment. All study-related AEs must be followed until resolution or stabilization. The investigator will allow adequate time for such monitoring activities.

Funding Source

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