PENNSTATE

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Effect of intraoperative ketamine and magnesium on postoperative pain in patients undergoing gastric sleeve resection.

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1.0 Objectives

1.1 Study Objectives

The goal of our research proposal would be to determine if intra-operative ketamine and magnesium decrease the amount of opiate use in the first 24 hours after laparoscopic bariatric surgery.

1.2 Primary Study Endpoints

1. Total hydromorphone use in 1st 24 hours post-operatively.

1.3 Secondary Study Endpoints

1. Pain Scores using Visual Analogue Scale (VAS) [Time Frame: 1st 24 hours post-op]
2. Sedation scores using Ramsey Sedation Scale [Time Frame: 1st 24 hours post-op]
3. Nausea Scores using PONV Impact Scale Score [Time Frame: 1st 24 hours post-op] – see data collection sheet
4. Intraoperative fentanyl use [Time Frame: Intraoperative period]
5. Intraoperative minimum alveolar concentration (MAC) of desflurane
6. Sentec CO2 meaurements, average PCO2 will be taken every hour [Time Frame: 1st 24 hours post-op].

2.0 Background

2.1 Scientific Background and Gaps

Post-operative pain control is a crucial aspect of care for any patient undergoing any operation. Management of post-operative pain improves patient satisfaction and leads to earlier mobilization, decreased length of hospital stay and even decreased hospital costs[1,2,3] Opiates are the predominant drug of choice intra-operatively to help control post-operative pain and, while effective, have a long list of serious side effects that may ultimately delay the patient's recovery. Decreasing the respiratory drive is one of most serious side effects of opiate use when attempting to control post-operative pain. This is especially true in the obese population in which other respiratory disorders are more commonplace. These include obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS). The prevalence of OHS in the general adult population is estimated to be 0.15% to 0.3%[4]. In patients undergoing bariatric surgery the incidence is approximately 8%[5]. Achieving adequate safe analgesia in this patient population can be difficult and requires a multimodal approach.

2.2 Previous Data

Ketamine[6,7] and magnesium[8] have each been shown independently to safely improve pain scores and decrease opiate consumption when given intra-operatively. N-methyl-D-aspartate (NMDA) receptor antagonism is the primary mechanism of action by which they are thought to act as analgesics. Both drugs, however, potentially have more than one mechanism by which they achieve analgesia.

2.3 Study Rationale

Opioid sparing anesthesia is extremely important in the post-operative obese population. With more and more obese patients entering the operating room a multi-modal approach to analgesia is crucial. Finding effective alternatives to opioid therapy in this population is the rationale of this proposal. Ketamine and magnesium have been well studied and have been proven to be safe adjuncts to a general anesthetic and are used daily by many anesthesia providers for a variety of cases. The purpose of this study is to look at their effects in the obese population specifically, as they may benefit more from opioid sparing therapy relative to normal weight individuals. Currently many anesthesiologists use these drugs in this fashion; however, literature involving ketamine and magnesium in bariatric surgical patients is very sparse.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Subjects undergoing laparoscopic sleeve gastrectomy
2. Consenting adults age 18-80
3. American Society of Anesthesiologists (ASA) Physical Status classification II to ASA III
4. Required to be hospitalized for at least 24 hours post-op

3.2 Exclusion Criteria

1. Patient refusal
2. Chronic opiate use (daily opiate use for >3 months)
3. Chronic Kidney disease (Creatinine>2)
4. History of heart failure
5. Known allergy or adverse effect of ketamine, magnesium or hydromorphone
6. Patients with schizophrenia or bipolar disorder
7. Patient unable to give informed consent
8. Patient with limited or no English fluency

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3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

1. Procedure converted from laparoscopic to open
2. Patient who will have more than 20 % change in hemodynamics from their pre-operative values after induction of anesthesia

3.3.2 Follow-up for withdrawn subjects

1. Patients who are withdrawn from the study prior to administration of anesthesia will not be followed.
2. Patients who are included in the study but removed under Section 3.3.1 will continue to be followed for 24 hours and opiate use, pain scores and vital signs recorded.

4.0 Recruitment Methods

4.1 Identification of subjects

Patients will be initially identified by the bariatric surgical team in their clinic and the scheduler will notify anesthesia of potential study patients.

4.2 Recruitment process

The primary surgical team will advise the patients that they are eligible for the study and they will receive more information from the anesthesia team about this at either their anesthesia pre-op visit or on the day of surgery. The surgeon will give the patient a handout describing the

study. Patients will be officially recruited to the study when they are seen in the anesthesia clinic or in the Same Day Unit (SDU) prior to their operation. At this time the patient will be screened using a screening questionnaire. Prior to the study team asking these questions, the patient will be advised that by answering these screening questions they are allowing the study team to use this information for screening purposes. If the patient meets the criteria to be included into the study, a member of the research team will obtain consent from the patient.

4.3 Recruitment materials

Screening questions: see the attached document
Study handout

4.4 Eligibility/screening of subjects

All potential subjects will be asked screening questions (see screening document). If eligible, subjects will be offered enrollment in the research (see section 4.2).

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Following screening (Section 4.1) written consent will be obtained. This will take place in either the surgeons office, the anesthesia clinic or SDU.

5.1.1.2 Coercion or Undue Influence during Consent

It will be explained to the patient that research is voluntary. The patient will be encouraged to ask questions and it will be explained to the patient that their decision to participate or not participate will have no effect on their level of care.

5.1.2 Waiver or alteration of the informed consent requirement

Not applicable

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Written consent will be obtained. A signed and dated copy will be retained by the patient. A signed and dated copy will also be stored in the locked office of the research team and stored in the patient's medical record.

5.2.2 Waiver of Documentation of Consent

Implied consent will be obtained for the screening questions used to determine eligibility prior to review of the consent document and enrollment in the research study.

5.3 Consent – Other Considerations

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☒ Authorization will be obtained and documented as part of the consent process.
☒ Partial waiver is requested for recruitment purposes only *(Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained)*
☐ Full waiver is requested for entire research study *(e.g., medical record review studies)*
☐ Alteration is requested to waive requirement for written documentation of authorization

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Waiver of Authorization is requested for the screening questions used to determine eligibility prior to review of the consent document and enrollment in the research study.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accordance with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team.

All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

The will be a prospective, randomized, controlled, and blinded study.

7.2 Study Procedures

7.2.1 Day 1 –Screening and Consent

Patient will initially be identified by the surgeon. These will be patients scheduled for laparoscopic sleeve gastrectomy. Information regarding the study will be provided to the subject at this time. Consent will take place in either the surgeons office, the anesthesia clinic, or in SDU on the day of surgery. Prior to consent the patient will be screened using a screening questionnaire. Prior to the study team asking these questions, the patient will be advised that by answering these screening questions they are allowing the study team to use this information for screening purposes. If they meet the criteria to be included into the study, a member of the research team will obtain written consent from the patient. Patients will be advised that although they are being consented for the study, the ultimate decision on whether they will be included will be made based on their time of surgery (OR schedule). If a patient is scheduled for surgery less than 24 hours following the previous patient, they will be withdrawn from the study.

7.2.2 Day before surgery

A member of the research team may call the patient to ensure that they are planning on coming in for their scheduled surgery (ie: not sick, running a fever, has transportation)., he study team will advise the investigational pharmacy that the drug for the study patient can be prepared.
The subject will then be randomized by a computer-generated randomization list using SAS software (SAS Institute, Cary, NC) and stratified in blocks of nine to allow an equal number of participants in each of three groups:

- Group 1. Ketamine group (Ketamine 0.5mg/kg + placebo for Magnesium, Normal Saline)
- Group 2. Ketamine (0.5mg/kg) plus magnesium (2g) group
- Group 3. Control group (Placebo for Ketamine, Normal Saline + Placebo for Magnesium, Normal Saline)

The patient and anesthesia team will be blinded to the group that the subject was randomized to. In the event that the patient has a concerning reaction or becomes unstable in any fashion the patient will be immediately unblinded from the study.

7.2.3 Day of Surgery - Pre-op

The patient will receive a study bracelet with his study ID number and initials to allow for study verification when the study drug is received in the operating room.

The placement of scopolamine patches are dictated on a case to case basis and are not used as a standard of care. The patch has been omitted from the protocol so that the effects of the experimental medications on PONV will not be confounded by other agents acting on PONV.

7.2.4 Day of Surgery Pre-Operation and Operating Room

During routine check of preoperative vital signs in the SDU the patient will be fitted with the Sentec CO2 monitor. Standard preoperative checklists/questions will be asked by the nursing staff as per hospital protocol.
The investigational pharmacy will deliver the appropriate study medication to the OR window, or the drug will be picked up by the coordinator at the investigational pharmacy. Prior to induction of anesthesia the patient will receive 1-2 mg of IV midazolam for anxiolysis if needed. Anesthesia will be induced with propofol (1.5-2.5 mg/kg) and fentanyl 1-2μg/kg. Muscle relaxant will be administered to facilitate tracheal intubation and to maintain muscular relaxation. Following securement of the endotracheal tube, the study medication will be administered over 10 minutes via an IV infusion pump. Dexamethasone 4 mg and 1 gm of Tylenol IV will be given after the study medication has been delivered, as per standard of care. Maintenance of anesthesia will be with desflurane and fentanyl dosing at the discretion of the primary team. End tidal CO_2 will be maintained between 30-35 mm hg (Apollo SW4.5n, Anesthetic Gas Module, Telford,PA, USA). No long-acting opiate will be used. 4 mg ondansetron will be given during skin closure at the end of surgery. Subjects will then be fully reversed and allowed to emerge from anesthesia and will be extubated per the primary anesthesia team. The above protocol is standard care for a patient undergoing a sleeve gastrectomy. The only non-standard part of this anesthetic is the addition of the study medications.

7.2.5 Post- op

As per standard of care, the patient will be taken to the post anesthesia care unit (PACU) and set up with standard ASA monitoring as well as the Sentec CO2 monitor which was applied in the SDU.. A hydromorphone patient controlled analgesia (PCA) pump will be set-up by nursing and given to the patient. Standard dosing of 0.2 mg bolus, every 6 minutes with a maximum 2 mg per hour will be the starting dose as is standard for these patients post-operatively. As per standared of care, 1 gm of Tylenol every 8hrs will also be scheduled to be administered via IV route for 1st 24hrs. If reported pain scores are beyond the patients previously determined acceptable pain score (asked pre-operatively per hospital standard) the PACU resident may give additional doses of IV hydromorphone at his/her discretion. When patient meets discharge criteria they will be sent from the PACU to their room with monitoring of continuous pulse oximetry and $ETCO_2$ until 24 hours post-operation.

During the post-operative period, data will be recorded immediately upon arrival to PACU and every 4 hours thereafter with a maximum recording of 24 hours post-op. For study purposes, a data sheet will be assigned to the patient pre-operatively with pre-operative pain anxiety, and PONV scores recorded. The sheet will then be attached to the patients chart and data recorded by the nursing staff. At the end of the 24 hour period the sheets will be collected by one of the research team members.

7.3 Duration of Participation

The patient will remain in the study for up to 24 hours postoperatively.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

7.4.2 Treatment Regimen

Arms	Assigned Interventions (Each participant will receive 2 IV infusions that are labeled in a blinded manner)
Ketamine 0.5mg/kg IV dose	1. Ketamine 0.5mg/kg IV dose 2. Placebo for Magnesium Sulfate (NaCl 0.9%) IV infusion
Ketamine 0.5mg/kg IV dose Magnesium Sulfate 2 grams IV	1. Ketamine 0.5mg/kg IV dose 2. Magnesium Sulfate 2 grams IV infusion
Placebo (NaCl 0.9%)	1. Placebo for Ketamine (NaCl 0.9%) IV dose 2. Placebo for Magnesium Sulfate (NaCl 0.9%) IV infusion

7.4.3 Method for AsAAssigning Subject to Treatment Groups

Public Health Sciences will supply the randomization list to the investigational pharmacy as the research team is blinded. On the day of surgery, subjects consented for the study will be randomized by a computer-generated randomization list using SAS software (SAS Institute, Cary, NC) and stratified in blocks of nine to allow an equal number of participants in each of the three study groups.

7.4.4 Subject Compliance Monitoring

The Anesthesiologist will verify that the label on the study drug that they receive in the operating room matches the study ID and initials on the subject's study ID bracelet.

7.4.5 Blinding of the Test Article

The pharmacy will prepare solutions of ketamine alone, ketamine plus magnesium and plain normal saline in similar looking containers. In order to maintain the blind, each study patient will receive 2 IV infusions (see Section 7.4.2).

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article
The study drugs are already in hospital formulary.

7.4.6.2 Storage
The investigational pharmacy will handle storage and distribution of study drugs according to their approved handling protocols.

7.4.6.3 Preparation and Dispensing
The pharmacy will prepare solutions of ketamine alone, ketamine plus magnesium and plain normal saline in similar looking containers. The containers will be labeled with the participant's study number and initials. In order to maintain the blind, each patient will receive 2 IV infusions. All patients will receive an IV bag with either 2 grams of Magnesium diluted in Normal Saline or Normal Saline alone and an IV containing Ketamine at a concentration of 1 mg/mL or 2mg/mL once diluted in Normal Saline or Normal Saline alone. Once prepared, the investigational pharmacy will deliver the bags to the OR window, or the drug will be picked up by the coordinator at the investigational pharmacy.
Following securement of the endotracheal tube, the study medication will be administered by the anesthesiologist over 10 minutes via an IV infusion pump.

7.4.6.4 Return or Destruction of the Test Article
Study drug will be discarded as per usual procedures.

7.4.6.5 Prior and Concomitant Therapy
Not applicable as we are using standard of care protocols.

8.0 Data and Specimen Banking For Future Undetermined Research
Not applicable.

9.0 Statistical Plan

9.1 Sample size determination
Up to 250 subjects will be enrolled in order to obtain enough data to determine if a significant difference exists between the treatment groups. This number will allow exclusions and withdrawals, in order to obtain the goal of 36 completed subjects per group.

Based on the Martinez study[6], the mean (and standard deviation) for the 48-hour morphine use in the ketamine group was 52 mg + 22 mg. Assuming that magnesium would yield a similar result as ketamine, a conservative expectation for the combination of ketamine and magnesium is a 25% reduction for the 24-hour morphine use to 19.5 mg. In order to achieve 80% statistical power with one-sided, 0.05 statistical tests, a sample size of 36 for each of the three groups is needed (total sample size of 108 completed patients for statistical analysis).

9.2 Statistical methods
Our current plan is to use ANOVA, along with pairwise comparisons, to compare the three groups with respect to pain scores (nonparametric ANOVA) and total hydromorphone use (parametric ANOVA) in the first 24 hours post-operatively, to determine whether there are any significant differences. We will use SAS, Version 9.4, for all statistical analyses.

10.0 Confidentiality, Privacy and Data Management

See Research Data Plan form.

11.0 Data and Safety Monitoring Plan

11.1 Periodic evaluation of data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review.

11.2 Data that are reviewed

The data to be reviewed will be:

- Safety data
- Untoward events
- Efficacy data

11.3 Method of collection of safety information

Safety information will be collected by the research staff preoperatively and post operatively as described in Section 7.2.

11.4 Frequency of data collection

Data will be collected immediately post-op, and every 4 hours thereafter, until 24 hours post-op, on the day of surgery.

11.5 Individual's reviewing the data

Oversight for the conduct of the study will be provided by the PI, and the research coordinator will monitor the data. They will ensure that all eligible criteria and consent requirements are met prior to a subject's participation in the study and that the procedures and adverse event reporting occur according to the IRB approved protocol.

11.6 Frequency of review of cumulative data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review.

11.7 Statistical tests

Not applicable.

11.8 Suspension of research

Not applicable.

12.0 Risks

Risks specific to this study include:

- Risk of randomization - patient will be assigned to a treatment program by chance. The treatment received may prove to be less effective than the other research treatment(s) or other available treatments.
- Loss of confidentiality associated with being part of a research study collecting personal health information.
- Ketamine adverse effects at proposed dosing include:
    - Uncommon: hypertension, increased cardiac output, increased intracranial pressure, tachycardia, tonic-clonic movements, visual hallucinations, vivid dreams, bradycardia,

diplopia, hypotension, increased intra-ocular pressure, injection-site pain, nystagmus, anaphylaxis, cardiac arrhythmia, depressed cough reflex, fasciculations, hyper salivation, increased metabolic rate, hypertonia, laryngospasm.

- Magnesium adverse effects at proposed dosing include:
  - Uncommon: flushing, drowsiness, circulatory collapse, respiratory paralysis, hypothermia, pulmonary edema, depressed reflexes, hypotension, depressed cardiac function, diaphoresis, hypocalcemia, hypophosphatemia, hyperkalemia, visual changes.
- Adverse effects related to the study medications at proposed dosing are uncommon. Most adverse effects noted were at higher dosing; there is limited literature noting adverse effects at proposed dosing.

13.0 Potential Benefits to Subjects and Others

13.1 Potential Benefits to Subjects

Potential benefits of being a subject in the study include improved pain control, less nausea/vomiting, less sedation, fewer side effects from opiates, and decreased length of hospital stay.

13.2 Potential Benefits to Others

This study will provide data that may potentially create improved pain management protocols in obese patients undergoing general anesthesia for any operation.

14.0 Sharing Results with Subjects

N/A – results of the study will have no impact on clinical care already received by the patients and many of the subjects may be lost to follow-up.

15.0 Economic Burden to Subjects

15.1 Costs

There will be no costs to the subject associated with their participation in the study other than those associated with normal standard of care medical care utilization. The study drug, ketamine and/or magnesium will be provided by Hershey Medical Center.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Number of Subjects

See Section 9.

17.0 Resources Available

17.1 Facilities and locations

This study will be completed at Penn State Hershey Medical Center. This is a large university based tertiary care center where gastric sleeves are frequently completed.

17.2 Feasibility of recruiting the required number of subjects

The required number of patients (see Section 9) needed should be attainable in 8-10 months according to current numbers being operated on at Hershey Medical Center. The project will continue until this number is obtained. The access to these patients will not be limited by the surgical team.

17.3 PI Time devoted to conducting the research

The PI has completed multiple research projects previously and has significant experience as well as appropriate RTA time.

17.4 Availability of medical or psychological resources

All resources needed for the protocol, as well as for any possible adverse event, are available at Penn State Hershey Medical Center.

17.5 Process for informing Study Team

Meetings will be held periodically as needed to ensure all research team members are informed about the protocol and their duties. Team emails will also be used to keep team members updated.

18.0 Other Approvals

Departmental Scientific Review

19.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not applicable.

20.0 Multi-Site Research

Not applicable.

21.0 Adverse Event Reporting

21.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected	An adverse event or suspected adverse reaction is considered "unexpected" if it is

adverse event or Unexpected suspected adverse reaction.	not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

21.2 Recording of Adverse Events

All adverse events (serious or non-serious) and abnormal test findings observed or reported to the study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention, including significant additional concomitant drug treatment or other therapy. **Note:** Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study.
- The test finding is considered an adverse event by the investigator.

21.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

21.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

Not applicable

21.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

21.6 Unblinding Procedures

In the event a patient becomes unstable for any reason, or has a possible reaction to a study medication as determined by the primary anesthetic provider, the patient will immediately be unblinded from the study.

21.7 Stopping Rules

In the event of a reaction requiring unblinding, the study protocol will be stopped.

22.0 Study Monitoring, Auditing and Inspecting

22.1 Study Monitoring Plan

22.1.1 Quality Assurance and Quality Control

This is a low risk therapeutic study using agents with a known safety profile.
The PI will ensure that this study is conducted, and that the data are generated, documented (recorded), and reported, in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

22.1.2 Safety Monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **research coordinator** will complete the appropriate report forms and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or DSMB of all Unanticipated Problems/SAE's.

23.0 References

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24.0 Appendix