Ketamine and Propofol Combination versus Propofol for Upper Gastrointestinal Endoscopy
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Mount Sinai	Protocol Name:	Ketamine and Propofol Combination versus Propofol for Upper Gastrointestinal Endoscopy
	Principal Investigator:	Daniel J Katz, MD
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	Date Revised:	08/28/2015
	Study Number:	IF#: 1790780

HRP-503 PROTOCOL TEMPLATE

- *Note that, depending on the nature of your research, certain questions, directions, or entire sections below may not be applicable. Provide information if and when applicable, and in cases where an entire section is not applicable, indicate this by marking the section "N/A". Do not delete any sections.*
- ***For any items below that are already described in the sponsor's protocol, the investigator's protocol, the grant application, or other source documents, you may simply reference the title and page numbers of these documents in the sections below, rather than cutting and pasting into this document. Do not refer to the Sample Consent document, or information on the application form in this document..***
- *Keep an electronic copy of this version of the document. You will need to modify this copy when making changes.*

Brief Summary of Research (250-400 words):

Upper gastrointestinal endoscopies are commonly performed in patients planned to undergo bariatric surgery in order to detect and possibly treat lesions that could otherwise affect the surgery to be performed. Also, it can identify lesions that may complicate surgery or produce additional symptoms in the post-operative period. Obese patients present a challenge to the anesthesiologist due to their propensity for airway obstruction when exposed to agents commonly used for upper endoscopies including propofol, midazolam, and fentanyl. The increased incidence of obstructive sleep apnea (OSA) in this population further puts these patients at risk for obstruction in the peri-operative and post-operative period. Ketamine is an agent that has a possibility to provide some benefit to this population through its ability to maintain spontaneous airway reflexes and have less of an effect on spontaneous ventilation as the aforementioned agents. Through the combination of ketamine with propofol we hope to decrease the incidence of airway obstruction in this population while still maintain an adequate depth of anesthesia to allow the gastroenterologist to carry out the upper endoscopy efficiently.

1) Objectives

Research Question: Can ketamine combined with propofol create an adequate depth of anesthesia for an upper gastrointestinal endoscopy while decreasing the incidence of airway obstruction?

The frequency of bariatric surgery is increasing, and the incidence of comorbidities, such as obstructive sleep apnea are being recognized more and more often in this patient population. This produces challenges for managing these patients safely in the perioperative and post-operative period. We hope to establish that a ketamine and propofol combination can produce adequate procedural conditions while decreasing the incidence of airway obstruction without a significant increase in time to discharge compared to the use of propofol as a sole agent.

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2) Background

Provide the scientific or scholarly background for, rationale for, and significance of the Human Research based on the existing literature.

Literature was reviewed regarding the use of ketamine for procedural sedation in the bronchoscopy and endoscopy suite as well as sedation for emergency department procedures. The combination of ketamine with other anesthetic agents has been shown to result in decreased dosage requirements of other agents, decreased incidence of airway obstruction requiring assistance, and mixed results regarding recovery time with some studies demonstrating quicker recovery including in obese patients and others demonstrating unchanged or prolonged recovery times with higher doses (2mg/kg) of ketamine. A large portion of the literature focuses on the use of ketamine in procedural sedation for emergency department (ED) procedures, especially in the pediatric population. Studies involving adults and endoscopy/bronchoscopy demonstrate overall positive results, however there is a dearth of literature involving the use of ketamine in the obese population.

The benefits of ketamine compared to most other anesthetic agents lie in its ability to produce hypnosis and analgesia with minimal respiratory depression and in some cases stimulatory effects on respiratory drive. The population that would stand to benefit most from these attributes of the medication are those prone to airway obstruction such as overweight individuals. This is especially salient given the fact that individuals with a higher BMI may require higher doses of propofol, which causes significant respiratory depression and increased incidences of airway obstruction.

As more patients turn to bariatric surgery as a method of weight loss when conservative measures fail, there is an increased need for upper endoscopies on this population prior to the surgery. High BMI patients present a unique challenge to the anesthesiologist due to an unfortunate coupling of increased medication dosage and a higher risk of airway obstruction and desaturation due to changes in body habitus. As mentioned previously, the benefits of ketamine could significantly benefit this population due not only to the attributes of this medication but its ability to decrease the overall propofol dosage required to tolerate upper endoscopy.

Prior experiences in upper endoscopy in the bariatric population often involves the avoidance of adjuncts such as midazolam or fentanyl that can perpetuate the incidence of airway obstruction in the peri-operative and post-operative period in addition to causing delay in discharge from the PACU. These procedures result in higher dosing of propofol with increased incidence of hypotension along with increased incidence of apnea. Ketamine has been used on occasion to assist with anesthetic depth without increasing incidence of airway obstruction and respiratory depression, but the use is not regular

enough to truly evaluate any benefit or harm that is modulated by the addition of ketamine to the anesthetic.

There is no preliminary data.

As the prevalence of obesity continues to increase in the United States, so does the incidence of comorbidities such as gastroesophageal reflux, hiatal hernia, and the occurrence of bariatric surgery. All of these situations often result in patients undergoing an upper endoscopy for diagnostic or therapeutic purposes. Selecting patients who are planned to undergo bariatric surgery will result in a snapshot of the high BMI population. Evaluating an induction technique that has the potential to provide protection of airway reflexes while providing adequate depth for endoscopy has the potential to provide additional information regarding an anesthetic technique that may be especially safe and beneficial to this patient population.

Few anesthetic drugs are able to provide hypnotic and analgesic effects without significant depression of airway reflexes or spontaneous breathing. Ketamine is one of these rare agents and its use in the obese patient population, who are already more prone to airway obstruction and respiratory depression, could result in evidence for a safer anesthetic technique.

References:

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Newton A., and Fitton, L. *Intravenous ketamine for adult procedural sedation in the emergency department: a prospective cohort.* Emergency Medicine Journal. 2008(25);498-501.

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Pambianco, D. *Future Directions in Endoscopic Sedation*. Gastrointestinal Endoscopy Clinicians of North America. 2008(18);789-799.

3) Setting of the Human Research

This will be conducted at the Icahn School of Medicine in Manhattan with recruitment done in the endoscopy waiting area to our target patient population of Dr. Brijen Shah's bariatric surgery patients.

4) Resources Available to Conduct the Human Research

Staff is composed of four clinicians, Daniel Katz, MD., Brijen Shah, MD., Jonathan Ko, MD., and David Maerz, MD. Dr. Katz is currently involved in a number of projects at Mount Sinai, and is extremely familiar with the population and protocols of Mount Sinai having gone to medical school, residency, and is now currently an attending here in the Department of Anesthesiology. Dr. Jonathan Ko is heavily involved in anesthetic delivery in endoscopy on a daily basis and is well versed in the endoscopy environment and the various populations that receive services here. Dr. Brijen Shah is heavily involved in upper endoscopies on patients planning to undergo bariatric surgery and will be involved in the selection and exclusion process of patients as well as the main proceduralist. Dr. David Maerz is a currently resident at Mount Sinai and is familiar with the endoscopy department and the care of bariatric patients and will be heavily involved in data collection.

The four clinicians involved in patient selection, protocol creation, and carrying out the study are all in constant communication throughout the process. The endoscopy center performs these procedures on a daily basis, many of whom would be candidates for our study. We aim to recruit 100 patients, and predict we can reach this goal within 6 months based on prior schedules.

5) Study Design

a) Recruitment Methods

Primarily recruitment of subjects will be through Dr. Brijen Shah's practice involving patients receive an upper endoscopy prior to bariatric surgery.

Recruitment materials will primarily consist of a verbal explanation of the procedure to be performed, how it is normally carried out from the anesthetic perspective, and our primarily goal of adding ketamine to the induction agent.

b) Inclusion and Exclusion Criteria

Eligible patient population will consist of Dr. Brijen Shah's patient population who are undergoing an upper GI endoscopy prior to consideration for bariatric surgery.

Exclusion criteria consist of: History of schizophrenia/schizoaffective disorder/bipolar disorder/dementia, glaucoma, craniofacial abnormalities, epilepsy, allergy to study drugs (propofol or ketamine), or history of current intracranial mass lesion.

c) Number of Subjects

A preliminary power analysis predicted we need 30 patients per group (total 90) to have significance using a Wilcox Rank Sum Test assuming skewed data. We therefore intend to enroll 100 patients to account or potential subjects who may not be appropriate for inclusion in statistical analysis after data collection.

d) Study Timelines

Each individual subject will be followed until discharge from the PACU when the patient has made both the clinical endpoints as well as standard discharge criteria. We anticipate to enroll all patients within one year. We estimate that the study will be completed six months after the enrollment of all subjects.

e) Endpoints

Primary endpoint is the incidence of gagging on endoscope insertion.

Secondary endpoints consist of: mean arterial pressure and heart rate during procedure, dosage required to achieve conditions necessary to proceed with upper endoscopy, total dosage of medication used, incidence of peri-procedure or post-operative nausea and vomiting, incidence of airway obstruction necessitating airway maneuvering (chin lift, jaw thrust, etc.), incidence of emergence delirium, and time required until eligible for discharge from endoscopy post-anesthesia care unit (PACU).

Since repeat ketamine doses will not be administered there are no specific primary or secondary endpoint parameters that would result in an end of study. In the event that unsafe vital signs changes or reaction to endoscopy occurred, the procedure would be aborted as would be standard protocol at our institution.

f) Procedures Involved in the Human Research

The study design is a prospective clinical study regarding the use of a 1:2 Ketamine:Propofol mixture (50mg Ketamine to 100mg Propofol) for induction in the study arm compared to a sole 100mg Propofol induction technique. Following this all follow up boluses will consist of only propofol in both arms. Subjects will be evaluated for response to initial insertion of endoscope, need for follow up doses, changes in vital signs, incidence of airway obstruction, incidence of emergence delirium, and time to discharge from the PACU. No further follow up or evaluation is planned.

The primary study protocol procedure is the administration of a ketamine vs. propofol and ketamine mixture with induction of anesthesia. The remainder of monitoring for safety and risk management are part of the normal anesthetic care all patients receiving upper endoscopy and evaluation prior to PACU discharge receive. Standard anesthetic monitors and vital sign monitoring will only differ in study patients in the use of a pre-determined 3-minute non-invasive blood pressure monitoring interval instead of the minimum 5-minute interval advised by the ASA.

Exclusion criteria is almost entirely based on comorbidities and conditions that have an association with an untoward reaction or intolerance to ketamine. In addition, the blood pressure monitoring intervals of 3 minutes are more frequent than the standard recommendation of 5 minutes, which allows providers to be more aware of any blood pressure changes as a result of the ketamine administration. In addition, upper endoscopy will not proceed until patient demonstrates an adequate Ramsay sedation scale score of >5 to reduce incidence of patient discomfort or recall.

Source records will include the patients chart for the specific endoscopy encounter in epic which will be used for demographic information and to monitor the patient's length of stay and any events that occurred in the endoscopy PACU. Compurecord will be used to collect data regarding medication administration, vital signs, and any intraoperative events including toleration of upper endoscopy and incidence of airway obstruction.

No data will be collected in the form of long-term follow up.

g) Specimen Banking

N/A

h) Data Management and Confidentiality

Data will be collected on paper that will indicate the patient's medical record and her study number assignment, and her initials. There will be no indication on these sheets of the patient's name. The data collection sheet is attached. The data on the sheets will be transferred to an Excel computerized spreadsheet without the patient's initials. The excel data base is in a computer with a password. Also, the excel program is protected by a password. Data will also be encrypted for confidentiality. We will have a separate binder that will have the patients name along with their medical record # should we need to recheck records for any reason. The binder with the data sheet will be kept in the co-investigator's office near the endoscopy suite that is kept locked at all times and can only be accessed through T-9 door code. The binder with the identifying information will be kept in the principal investigator's office, also a locked office via T9 code that is in a different building. Only the PI will have access to these records.

i) Provisions to Monitor the Data to Ensure the Safety of Subjects

There is no anticipation of more than minimal risk involved to subjects.

j) Withdrawal of Subjects

The primary circumstance for which a subject would be withdrawn without their consent would result in vital signs on initial exam that are otherwise incompatible with proceeding with upper endoscopy, such as unexpected poor saturation on room air (SO2 <92%), vital signs and symptoms compatible with hypertensive urgency or emergency, or previously undiagnosed arrhythmia on EKG with associated clinical findings. Decisions based on these findings will vary with the anesthesia provider involved but could include withdrawal from study protocol and proceeding with upper endoscopy, or cancellation of upper endoscopy entirely with planned rescheduling once patient undergoes further workup.

6) Risks to Subjects

Reasonable risks include mild side effects from ketamine administration including hallucinations, dissociative sensation, or untoward sensory phenomenon, all of which can occur with propofol as well. This can result in prolonged PACU stay due to treatment. Studies in other areas using ketamine have shown a decreased incidence of these side effects when giving low doses such as ours for single administration.

7) Provisions for Research Related Harm/Injury

Every patient is followed intra and post operatively and assessed for complications and treated appropriately. The study patients will be treated the same in this regard.

8) Potential Benefits to Subjects

There is no expected long-term benefit from participation in the study.

9) Provisions to Protect the Privacy Interests of Subjects

No long-term follow up or post-operative phone contact beyond a normal post-operative check is planned for study participants. No personal information beyond what is required by a standard anesthesia pre-operative assessment will be collected and this information will be kept private by the same means it always is. Patient interviews will be conducted in individual private bays in the holding area as they always are unless otherwise indicated by the patient (wish to have partner present etc). Only patient initials will be used on the data collection sheet. This data will be stored in a locked cabinet and later on a password protected Mount Sinai computer. Only the PI will have access to the patient's identifiable information. Patients will be reassured that all their information will remain confidential and private.

10) Economic Impact on Subjects

No planned economic impact.

11) Payments to Subjects

N/A

12) Consent Process

Consent will be obtained in the endoscopy waiting area prior to the patient being brought to the operating room. This will take place during the anesthesiologist's pre-operative examination. If the subject desires they will have a waiting period of whatever length suits them in order to consult friends, family, their primary care physician, their gastroenterologist, or any other personnel or individuals they wish to speak with.

The application personnel involved in the consent process will be Dr. Brijen Shah and a member of the anesthesiology team of either Drs. Katz, Ko, or Maerz. An average of 5-10 minutes will be required to discuss the study and its ramifications on the patient with additional time as required for follow up questions or requests.

Undue influence or coercion will be minimized by assuring patients that they will undergo their upper GI endoscopy regardless of their decision to participate in the study or not. In addition, this will occur after the typical pre-operative exam and anesthetic consenting process to avoid individuals believing their pre-operative exam or anesthetic consent could be unduly influenced by their response to the study consent.

In order to assure the understanding of potential subjects, they will be asked to explain in their own words their interpretation of the purpose of the study, how it will be carried out, and any potential risks explained to them regarding the study. No additional tools or aids are planned as part of the consent process.

Consent for the study prior to arrival in the suite is NOT feasible as the patients are referred to Dr. Shah from a multitude of surgeons. Dr. Shah does not see these patients in the office prior, nor do they come for pre-anesthesia testing. As such, consent prior to day of procedure is not possible.

Children

N/A

Cognitively Impaired Adults

N/A

Non-English Speaking Subjects

Non-English speaking subjects will be excluded from the study selection process. The primary reason for doing so involves the secondary endpoint of the incidence of post-operative delirium. The inability to speak and understand influence fluently has the potential to introduce a significant confounder regarding a patient's orientation to person, place, and time if a licensed interpreter is not readily available for a study participant.

Waiver or Alteration of the Consent Process

N/A

13) Process to Document Consent in Writing

Standard PPHS consent template to be used.

14) Vulnerable Populations

Include	Exclude	Vulnerable Population Type
	X	Adults unable to consent
	X	Individuals who are not yet adults (e.g. infants, children, teenagers)
	X	Wards of the State (e.g. foster children)
	X	Pregnant women
	X	Prisoners

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

No results will be shared.

18) External IRB Review History

This has not been previously submitted to an IRB,

19) Control of Drugs, Biologics, or Devices

Ketamine and Propofol vials will be procured following standard department protocol as part of a drug kit taken out from the operating room pharmacy by one of the study personnel (Drs. Katz, Ko, or Maerz). The Ketamine and Propofol or simply Propofol syringe will be prepared and provided from one of the aforementioned personnel's drug kit and given to the practitioner caring for the study patient. As per department protocol this will be documented with the patient's name and MRN on the study personnel's drug sheet for that kit. In order to preserve blinding of the practitioner providing care, the induction agent will be added to compurecord at the conclusion of the case by the study personnel involved in the drug syringe preparation.

Regarding the remainder of controlled substance handling, it will be done according to department policy which is listed below:

I. Dispensing Controlled Substances

A. OR

1. To procure controlled substances, the anesthesia personnel obtains a Controlled Substance Administration Record from the pharmacy and the pharmacist will fill in the appropriate information:
    - Date
    - Operating room or cluster scheduled
    - Printed name of requesting anesthesia personnel
2. A kit of controlled substances will be dispensed to the anesthesia personnel. The kit will be labeled with the anesthesia personnel's name, the drug content of the kit, and the issue number of the Controlled Substance Administration Record.

3. The drug kit must remain with the anesthesia providercand cannot be left unattended at any time.

4. The anesthesia personnel signs for drugs on the Controlled Substance Administration Record.

5. The Controlled Substance Administration Record will be retained by the anesthesia personnel for documentation of the day's cases.

6. No preexisting drug kit will be supplemented with additional drugs without the pharmacy slip issued with the original drug kit. If an attending wishes to supplement a resident's drug pack, they may do so only if they present the pharmacy drug slip to the pharmacist.

II. Documentation

A. Controlled Substance Administration Record

1) For each case, the anesthesia personnel will fill in the required information on the Controlled Substance Admin istration Record, including:
    - Patient name

Number of ampules/tubexes of each drug administered
Signature of the administering anesthesia personnel

2) Full doses not administered must be returned to the Pharmacy. Partial doses remaining after parenteral administrationmay not be discarded, but must be returned.

3) In the event an ampule/tubex is broken, the record of breakage should be noted on the Controlled Substance Administration Record and co-signed by a witnessing physician, R.N. or pharmacist.

4) Each ampule or vial of a controlled substance can only be used for an individual patient, and the waste returned (see "return of Drugs" below)

III. Return of Drugs

A. OR

1. The anesthesia personnel must return all unused drugs to the pharmacy before 7:00 PM along with the Controlled Substance Administration Record.

2. The anesthesia personnel reconciles any discrepancies and signs daily dispersing log. Amt. Returned = Amt. Issued –c(Amt. Administered + Amt. Wasted + Amt. Broken)

3. All drugs including unused propofol, etomidate, remifentanil and ketamine, must be accounted for, documented and returned to the pharmacy with the proper patient information.

4. Narcotic bags obtained from discontinued PCA's or epidural infusions must be accounted for, documented and returned to the pharmacy with the proper patient information.

5. No drawn up drug is to be wasted, i.e., squirted out, and must be accounted for, documented and returned to the pharmacy, including unused propofol, etomidate, ketamine, thiopental, fentanyl, midazolam etc.

6. No one is to exchange an intact vial of medication for a drug previously drawn up I nto a syringe.

7. When the anesthesia care team is relieved by another team, any unused, controlled medications in syringes, must be returned to the pharmacy by the original anesthesia care giver and must not be turned over to the new anesthesia care team to be given later in the case.

8. Anesthesia personnel on-call and those whose cases extend beyond 7:00 PM return unused drugs and the Controlled Substance Administration Record to a locked repository box outside the pharmacy.

9. Any discrepancy is reconciled by the anesthesia personnel the following morning