Intraoperative Low-dose Ketamine Infusion for Patients with Obstructive Sleep Apnea

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Intraoperative Low-dose Ketamine Infusion for Patients with Obstructive Sleep Apnea: A Prospective, Randomized, Controlled, Double-Blind Study

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Clinical Research Coordinators: Jeff Worrell

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1.0 SUMMARY OF STUDY (Abstract with a maximum of 300 words)

Obstructive sleep apnea (OSA) has been estimated to affect between 2 and 4% of the U.S. population <Young T, NEJM 1993>. It is a serious, life-threatening condition associated with obesity, hypertension, congestive heart failure, pulmonary hypertension, coronary artery disease, and cardiac arrhythmias and has an 8 year mortality rate of nearly 40% <Parrish JM, Mayo Clin Proc 2004, He J, Chest 1988>. Following general anesthesia, patients with OSA have been noted to have a significantly increased risk of respiratory complications, morbidity and mortality <Gupta RM Mayo Clin Proc 2001, Liao P, Sleep 2007, Young T, Sleep 2007, Marshall NS, Sleep 2008 >. This may be due to residual effects of inhaled anesthetics which can decrease upper pharyngeal muscle tone leading to airway compromise in OSA patients <Bell RL, Anes Clin of NA 2005>. Also, OSA patients are exquisitely sensitive to the ventilatory depressant effects of postoperative opioids, causing decreased responsiveness to hypercarbia and episodic arterial hypoxemia <Ostermeier AM, Anes Anal 1997, Stoelting, Anesthesia and Coexisting Disease 4th ed>. Currently, there is not a well-established, general anesthetic technique that will decrease the risk of complications in OSA patients. The objective of this study is to compare the postoperative recovery profile of OSA patients receiving standard Sevoflurane inhaled anesthesia versus Sevoflurane combined with a low-dose ketamine infusion.

2.0 BACKGROUND & RATIONALE

Obese patients are known to have a delayed emergence from anesthesia due to volatile gases' high affinity for adipose tissue. Also, adipose tissue serves as a depot for anesthetic gases during prolonged exposure <Miller's Anesthesia, 6th ed>. In addition, many obese patients presenting for surgery meet clinical screening criteria for obstructive sleep apnea <Chung F, Anesthesiology 2008>. Surgical patients with obstructive sleep apnea patients are known to be very sensitive to the respiratory depressant effects of intravenous opioids in the postoperative period <Ostermeier AM, Anes Anal 1997, Stoelting, Anesthesia and Coexisting Disease 4th ed>. When possible, opioids should be avoided in favor of nonsedating agents such as acetaminophen, ketorolac or even regional anesthesia when possible. Unfortunately, after major surgery, most patients will still require IV opioids titrated to effect in order to adequately control their pain.

Ketamine is a dissociative anesthetic agent that provides profound analgesia without depressing the respiratory system <Miller's Anesthesia, 6th ed>. Ketamine is extensively metabolized by hepatic p-450 enzymes to a weak, water-soluble compound that is excreted by the kidneys and has a short context-sensitive half-time (time for plasma level to drop by 50%) even during prolonged infusions <Barash, Clinical Anesthesiology, 4th ed>. Multiple studies have demonstrated that intraoperative, subanesthetic

dosing of ketamine can significantly reduce postoperative opioid requirements following major surgery <Bell RF, Cochrane Review, 2005>. This low-dose of ketamine was also shown to decrease the incidence of posterative nausea and vomiting and was not associated with an increase adverse pyschotrophic effects. None of these studies targeted obstructive sleep apnea patients to determine whether these opioid-sparing effects persist and could mitigate the postop respiratory compromise or improve their overall recovery profile.

3.0 SIGNIFICANCE OF STUDY

Obstructive sleep apnea (OSA) affects millions of people in the U.S., and currently, there is not a well-established, general anesthetic technique that clearly decreases the risk of postoperative respiratory complications in these patients. If OSA patients in our study group have significantly decreased postoperative opioid requirements and improved recovery profiles in the PACU, our protocol could have significant implications in defining future standardized general anesthesia recommendations for patients with this disease. Ultimately, the aim of this study is to substantially reduce overall postoperative morbidity and mortality associated with obstructive sleep apnea.

4.0 OBJECTIVE(S) & HYPOTHESIS

Obstructive sleep apnea (OSA) has been estimated to affect between 2 and 4% of the U.S. population <Young T, NEJM 1993>. It is a serious, life-threatening condition associated with obesity, hypertension, congestive heart failure, pulmonary hypertension, coronary artery disease, and cardiac arrhythmias and has an 8 year mortality rate of nearly 40% <Parrish JM, Mayo Clin Proc 2004, He J, Chest 1988>. Following general anesthesia, patients with OSA have been noted to have a significantly increased risk of respiratory complications, morbidity and mortality <Gupta RM Mayo Clin Proc 2001, Liao P, Sleep 2007, Young T, Sleep 2007, Marshall NS, Sleep 2008 >. This may be due to residual effects of inhaled anesthetics which can decrease upper pharyngeal muscle tone leading to airway compromise in OSA patients <Bell RL, Anes Clin of NA 2005>. Also, OSA patients are exquisitely sensitive to the ventilatory depressant effects of postoperative opioids, causing decreased responsiveness to hypercarbia and episodic arterial hypoxemia <Ostermeier AM, Anes Anal 1997, Stoelting, Anesthesia and Coexisting Disease 4th ed>. Currently, there is not a well-established, general anesthetic technique that will decrease the risk of complications in OSA patients. The objective of this study is to compare the postoperative recovery profile of OSA patients receiving

standard Sevoflurane inhaled anesthesia versus Sevoflurane combined with a low-dose ketamine infusion.

We hypothesize that the group of obstructive sleep apnea patients that receive low-dose intraoperative ketamine will report lower pain scores, require less supplemental intravenous Morphine, and have less frequent side effects and desaturation episodes post-operatively than the group receiving saline.

5.0 INTERPRETATION OF EXPECTED RESULTS

Statistical analysis with *a priori* power analysis was performed to determine the number of patients per group sufficient to detect a decrease of >30% in postoperative opioid requirements on the basis of the results of Kararmaz et al., Anesthesia and Analgesia 2003. With a power of 80% and a type 1 error of 5%, it was estimated that 32 patients will be required per group. We will plan to enroll 65 patients total to account for unanticipated subject dropout. Mann-Whitney U-test will be used to compare VRS, modified Aldrete, and patient satisfaction scores. Student's t-test will be used to compare BMI, time to first analgesic, number of analgesic demands, amount of analgesic consumption and ODI. The *X*2 test will be used to compare frequency of side effects, race and sex distribution. The resulting values will be expressed as mean +/- SD or median and range with P< 0.05 considered statistically significant.

6.0 ELIGIBILITY & EXCLUSION CRITERIA

Inclusion criteria: Total of sixty-five patients, aged 19-70, scheduled to undergo laparoscopic gastric bypass surgery for morbid obesity. Patients should have a diagnosis of obstructive sleep apnea as confirmed by sleep study *and* are not currently using a CPAP devise. If no sleep study is available, patients should have the 4 clinical predictors of obstructive sleep apnea as described by STOP (Snoring, Tiredness during daytime, Observed apnea, high blood Pressure) screening questionnaire. <Chung, F Anesthesiology 2008>

Exclusion criteria: Patients <19 yrs, positive pregnancy test, ASA> III, history of alcohol or narcotic abuse in last 90 days, significant cardiovascular or respiratory disease (baseline oxygen saturation below 92%), significant psychiatric or neurologic disease, history of significant hepatic or renal disease (baseline creatinine>1.5), history of allergy or contraindication to anesthetic agents or ketamine including patients with increased ICP, increased IOP, severe arrhythmias, history of delirium, hallucinations, or psychosis, or history of uncontrolled seizures, or potential risk for malignant hyperthermia (family history), history of difficult intubation that would preclude standard induction of anesthesia, prisoners, persons who are mentally impaired, and non-english speakers.

Criteria for early withdrawal for the study: <2 hrs surgical time, any surgical or anesthetic complication that prevents the assessment of study variables, clinically relevant residual neuromuscular blockade or other reason for patient to require prolonged tracheal intubation following surgery.

7.0 RANDOMIZATION/RECRUITMENT PROCEDURES

Patients scheduled to undergo laparoscopic gastric bypass surgery for morbid obesity will be seen in the preop clinic by our research coordinator. Patients should have a diagnosis of obstructive sleep apnea as confirmed by sleep study *and* are not currently using a CPAP devise. If no sleep study is available, patients should have the 4 clinical predictors of obstructive sleep apnea as described by STOP (Snoring, Tiredness during daytime, Observed apnea, high blood Pressure) screening questionnaire. <Chung, F Anesthesiology 2008>

Patients scheduled for surgery are required to be seen in the Anesthesiology Preop Clinic. Patients scheduled for laparoscopic gastric bypass surgery will be given the opportunity to participate in this clinical trial.

8.0 STUDY INTERVENTIONS/PROCEDURES

This is a prospective, randomized, double-blind, placebo-controlled single institution study. All patients will be provided written informed consent in the preop clinic prior to participation. Patients will be randomly allocated to the ketamine (K) study group or the control (C) group. Random allocation of patients will be performed by study coordinator using closed envelopes containing allocation group. All patients will be provided standard hospital care.

On the day of surgery, baseline oxygen saturation measurements will be recorded for each patient. The study coordinator will provide the attending anesthesiologist with a 30ml syringe containing either ketamine (K) 10mg/ml or saline (C). Both syringes will be labeled "Ketamine 10mg/ml" along with time and date of preparation by the pharmacy. In the operating room, standard ASA monitors will be used along with arterial and /or CVP monitoring according to the preference of the attending anesthesiologist. After adequate preoxygenation with 100% oxygen, general anesthesia will be induced with intravenous midazolam 2mg, fentanyl 100mcg and propofol, 2-3 mg/kg ideal body weight (IBW) followed by rocuronium 50mg before endotracheal intubation. IBW is calculated by the Hamwi Formula: men start with 106 lbs for first 5 feet + 6 lbs for each inch over 5 feet,

women use 100 lbs for first 5 feet + 5 lbs for each inch over 5 feet (Medium frame); for small frame (- 10%), large frame (+ 10%).

Anesthesia will be maintained in the both groups with inhaled Sevoflurane starting at 4% end-tidal concentration and titrated to keep the bispectral index (BIS) value at 40-50 (Bispectral Index, Aspect Biomedical, Natick, MA). After induction and before surgical incision is made, patients will receive an intravenous bolus saline or the study drug, S(+) ketamine 0.5mg/kg IBW bolus followed by a continuous infusion of 0.5 mg/kg/hr (IBW) using a Baxter syringe pump. The infusion will be stopped at the closure of the abdominal fascia layer, approximately 30 minutes before the end of surgery. In both groups, neuromuscular blockade will be maintained with rocuronium and titrated to train-of-four (TOF) ratio until the abdominal fascia is closed. Oxygen, air (no nitrous oxide), IV fluids, vasoactive drugs, and fentanyl (up to 5mcg/kg IBW) will be titrated at the anesthesiologist's discretion to maintain hemodynamics at 25% of baseline. Glycopyrolate and neostigmine will be given to facilitate reversal of neuromuscular blockade. Sevoflurane will be discontinued immediately prior to completion of surgery. All patients will receive IV ketorolac 30mg at conclusion of closure of abdominal fascia. Endotracheal tube will be removed when patient meets extubation criteria (spontaneous breathing with min 6ml/kg IBW tidal volume, following commands with ability to sustain hand grip and 5-sec head lift). All patients will then be discharged from the operating room to the post-anesthesia care unit (PACU).

Upon arrival in the PACU, all patients will be monitored according to standard post-anesthesia protocols for a period of at least 2 hours. The PACU nurse that is blinded to treatment group will assess and record baseline vital signs including HR, BP, RR, SpO2, and VRS score. Modified Aldrete score including presence of nausea/vomiting, sedation level or evidence of dysphoria will be recorded at 15 minute intervals. SpO2 will be monitored continuously with documentation of oxygen flow required to maintain oxygen saturation of at least 94%. As per PACU protocol, initially patients will receive oxygen 40% by open face mask, with weaning to NC or RA, maintaining SpO2 > 94%. Desaturation episodes will be scored automatically by pulse oximetry analysis software (Nellcor, NPB-290). Data evaluated will include: comparison of patient demographics, time to first analgesic, number of analgesic demands, amount of analgesic consumed in the OR and PACU, frequency of side effects, and ODI (oxygen desaturation index). ODI is defined as the number of desaturations (lower than 4% from baseline) per hour of recording, which correlates with PSG-determined apnea/hypopnea index and can be used as an indicator of postoperative apneic episodes <Ahmad S, Anesthesia and Analgesia 2008>}. Time to first analgesia request will be recorded and pain (VRS >/= 4) will be treated with intravenous morphine 2mg. This will be repeated at 5 minutes intervals until pain score improves or patient has untoward side

effects, at which time the PACU physician should be immediately called to the patient's bedside. Further monitoring for of patients in PACU or on the floor may be indicated in some patients according to the discretion of the attending anesthesiologist and surgeon; however it is not mandatory for this study. According to Terris et al., "Significant complications [of OSA] generally emerge within 2 hours after surgery. Therefore a decision regarding the level of postoperative monitoring needed may be made with confidence during the period of time that the patient is in the recovery room" <Terris DJ, Laryngoscope 1998>.

When patients are deemed suitable for discharge from the PACU, patients will be transferred to the floor where they will receive standard hospital care and monitoring including routine vital signs continuous pulse oximetry. At 24 hrs post-op, patient vital signs, VRS, and morphine usage will be assessed along with patient satisfaction related to overall anesthesia care according to a 5-point scale (1= very unsatisfied, 2=unsatisfied, 3=equivocal, 4=satisfied, 5=very satisfied).

Projected Overall Study Timeline

	Study Start-Up	Enrollment	Data Entry and Analysis	Study Write-Up
MM YYYY	06 2010			
MM YYYY		07 2010		
MM YYYY			07 2012	
MM YYYY				07 2012

9.0 CONCOMITANT THERAPIES

Not applicable

10.0 DRUG INFORMATION

The risks associated with IV ketamine when used alone at doses of 1-4 mg/kg include emergence reaction. Medication package insert includes a black box warning listing: "incidence of 12%; psychological manifestations vary in severity between pleasant dream-like states, vivid imagery, hallucinations, and emergence delirium; may be assoc. w/ confusion, excitement, and irrational behavior; duration usually a few hours, recurrences up to 24h post-op in few cases; no residual psychological effects; decr. incidence in <15 y/o and >65 y/o, if IM dose, or previous exposure; decr. incidence w/ lower doses in combo w/ diazepam during

anesthesia induction and maintenance; use small hypnotic dose of short- or ultrashort-acting barbiturate to end severe emergence rxn

Other possible severe adverse reactions include: respiratory depression, laryngospasm, ICP incr., IOP incr., hypotension, severe, bradycardia, arrhythmias, delirium, hallucinations, tonic clonic movements, anaphylaxis, withdrawal syndrome (long-term use).

Other common adverse reactions include: hypersalivation, anorexia, nausea/vomiting, elevated BP, elevated HR, diplopia, nystagmus, fasciculations, depressed reflexes, hallucinations, bradycardia hypotension.

Ketamine is contraindicated or should be used with caution if patients with: hypersens. to drug/class/compon., HTN, stroke, head trauma, intracranial mass/hemorrhage, caution if ICP incr., caution if IOP incr., caution if CAD, caution if CHF, caution if thyrotoxicosis, caution if psychosis, caution if hepatic impairment, caution if acute alcoholism, caution if chronic alcohol use, caution if substance abuse, caution in elderly pts. < www.epocrates.com >

Other severe side effects are rare and are typically reversible with cessation of drug infusion. Common side effects are also typically reversible with cessation of infusion. Multiple studies have demonstrated that low-dose ketamine, when given with anesthetic induction agents and inhalational anesthetic gas, is safe and effective with few if any, adverse side effects. <Bell RF, Cochrane Review, 2005>

Investigational New Drug (IND) Application Required?: No

11.0 STATISTICAL CONSIDERATIONS

Statistical analysis with *a priori* power analysis was performed to determine the number of patients per group sufficient to detect a decrease of >30% in postoperative opioid requirements on the basis of the results of Kararmaz et al., Anesthesia and Analgesia 2003. With a power of 80% and a type 1 error of 5%, it was estimated that 32 patients will be required per group. We will plan to enroll 65 patients total to account for unanticipated subject dropout. Mann-Whitney U-test will be used to compare VRS, modified Aldrete, and patient satisfaction scores. Student's t-test will be used to compare BMI, time to first analgesic, number of analgesic demands, amount of analgesic consumption and ODI. The $X2$ test will be used to compare frequency of side effects, race and sex distribution. The resulting values will be expressed as mean +/- SD or median and range with $P< 0.05$ considered statistically significant.

12.0 PATIENT SAFETY AND DATA SECURITY MONITORING

Assessment of Level of Risk:

This study poses a very low level of risk to the study participants. While participating in this study, the possible risks include: experiencing side effects from low dose ketamine and possible loss of confidentiality. The most common side effect, emergence delirium is unlikely using low-dose ketamine, when given with anesthetic induction agents and inhalational anesthetic gas. Multiple studies have demonstrated safety and efficacy with few if any, adverse side effects <Bell RF, Cochrane Review, 2005>.

Oversight of this investigation will be provided by primary investigator, Peter Nagi, M.D. Additional oversight will be provided by the Department of Anesthesiology Human Subjects Research Committee and its related support staff.

The mechanisms for HIPAA compliance [including a detailed electronic personal health information (PHI) data path]:

Patient privacy will be protected through participation as per HIPPA guidelines. Patient confidentiality will be protected through password protected computers within the UAB anesthesiology department. Only study investigators listed on this IRB will have access to protected patient information.

Patients will be identified as potential study participants in the during their preoperative clinic visit. Study coordinator will be contacted to provide the patient written and verbal informed consent several days prior to surgery.

Study coordinator will provide the patient written and verbal informed consent several days prior to surgery. Patient will be required to return home to read informed consent along with study background and protocol information. They will contact study coordinator if interested in participating in the study.

13.0 REPORTING ADVERSE EVENTS

Patients at risk for severe adverse reactions will be excluded from the study. This includes patients with a history of adverse reaction to ketamine, patients with increased ICP, increased IOP, arrhythmias, history of delirium, hallucinations, or psychosis, or history of uncontrolled seizures.

Patient will be removed from the study if any surgical or anesthetic complication necessitates deviation from routine anesthetic management or prevents the assessment of study variables. Also, patient will be withdrawn if clinically relevant residual neuromuscular blockade or other reason for patient to require prolonged tracheal intubation following surgery.

Any adverse events occurring in the enrolled study subjects will be immediately reported to the UAB Department of Anesthesiology Human Subjects Research Committee and the UAB IRB. As an integral element of data and patient safety monitoring, a completed departmental-level Data Protection and Patient Safety Monitoring Form will be presented to the UAB Department of Anesthesiology Human Subjects Research Committee every three months.

14.0 REFERENCES CITED (minimum of 10 citations)

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Human Subjects Protocol (HSP)

Form Version: June 25, 2015

- **You are applying** for IRB review of the research described in this form.
- **To avoid delay**, respond to all items in order and include all required approvals and documents.
- **To complete the form**, click the underlined areas and type or paste in your text; double-click checkboxes to check/uncheck. For more tips, see www.uab.edu/irb/forms .
- **Mail or deliver all materials to AB 470**, 701 20th Street South, Birmingham, AL 35294-0104.

Indicate the type of review you are applying for:

☒ Convened (Full) IRB *or*

☐ Expedited—See the Expedited Category Review Sheet, and indicate the category(ies) here: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

1. IRB Protocol Title: Intraoperative Low-dose Ketamine Infusion for Patients with Obstructive Sleep Apnea: A Prospective, Randomized, Controlled, Double-Blind Study

2. Investigator, Contacts, Supervisors

a. Name of Principal Investigator: Peter Nagi
Degree(s)/Title: MD/ Associate Professor BlazerID: panagi
Dept/Div: Anesthesiology/Pain Mailing Address: JT 862 UAB ZIP: 6810
Phone: 934-7384 Fax: 996-7272 E-mail: panagi@uabmc.edu

b. Name of Contact Person: Alicia Kindred Title: Research Associate Phone: 934-4711
E-mail: aliciakindred@uabmc.edu Fax: 975-0761
Mailing Address (if different from that of PI, above): JT 867

c. Name of Contact Person: Judy L. Shanks Title: Administrative Associate Phone: 934-6501
E-mail: jlshanks@uabmc.edu Fax: 996-7272
Mailing Address (if different from that of PI, above):____

d. Name of Contact Person: Betty Hérard Title: Program Coordinator Phone: 934-0045
E-mail: bherard@uabmc.edu Fax: 996-0691
Mailing Address (if different from that of PI, above):____

INVESTIGATOR ASSURANCE STATEMENT & SIGNATURE

By my signature as Principal Investigator, I acknowledge my responsibilities for this Human Subjects Protocol, including:

- Certifying that I and any Co-Investigators or Other Investigators comply with reporting requirements of the UAB Conflict of Interest Review Board;
- Certifying that the information, data, and/or specimens collected for the research will be used, disclosed and maintained in accordance with this protocol and UAB policies;
- Following this protocol without modification unless (a) the IRB has approved changes prior to implementation or (b) it is necessary to eliminate an apparent, immediate hazard to a participant(s);
- Verifying that all key personnel listed in the protocol and persons obtaining informed consent have completed initial IRB training and will complete continuing IRB training as required;
- Verifying that all personnel are licensed/credentialed for the procedures they will be performing, if applicable;
- Certifying that I and all key personnel have read the *UAB Policy/Procedure to Ensure Prompt Reporting of Unanticipated Problems Involving Risks to Subjects or Others to the IRB, Institutional Officials, and Regulatory Agencies* and understand the procedures for reporting;

- Applying for continuing review of the protocol at least annually unless directed by the IRB to apply more frequently;
- Conducting the protocol as represented here and in compliance with IRB determinations and all applicable local, state, and federal law and regulations; providing the IRB with all information necessary to review the protocol; refraining from protocol activities until receipt of initial and continuing formal IRB approval.

Signature of Investigator: _____ **Date:** 4/6/18

3. Protocol Personnel

Including the PI, list all key personnel (each individual involved in the design and conduct of this protocol including recruitment, informed consent, analysis of the data, and reporting of the results). Complete either the UAB (3.a.) or non-UAB (3.b) table, as applicable. Use the checkboxes to show each person's role, whether the investigator has financial interests as defined by the UAB CIRB, and briefly describe the individual's responsibilities for the research and qualifications to perform those responsibilities. Insert additional rows as needed.

FDA: For studies involving investigational drugs, list all investigators who will be listed on FDA Form 1572 and include a copy of the 1572. Send the IRB a copy of Form 1572 any time you update the form with the FDA.

a. UAB Personnel

Name	Blazer ID	Role	Financial Interest?*	Protocol Responsibilities and Qualifications
Peter A. Nagi, MD	panagi	Principal Investigator	☒ No ☐ Yes	Associate Professor in Department of Anesthesiology and Perioperative Medicine. Serve as PI and develop the study design, data collection methods, data analysis methods and informed consent.
Jeffrey Dobyns, DO	jdobyns	☒Sub-Investigator ☐Other	☒ No ☐ Yes	Assistant Professor in Department of Anesthesiology & Perioperative Medicine. Will assist in study design, data collection, data analysis and obtain informed consent
Richard D. Stahl, MD	rstahl	☒ Sub-Investigator ☐ Other	☒ No ☐ Yes	Assistant Professor in Department of Surgery (Gen Surg Gastrointestinal Division). Will assist in data collection, data analysis and obtain informed consent
Kirk Withrow, MD	kwithrow	☒ Sub-Investigator ☐ Other	☒ No ☐ Yes	Assistant Professor in Department of Surgery (Otolaryngology Division). Will assist in data collection, data analysis and obtain informed consent
Timothy Ness, MD	loch	☒ Sub-Investigator ☐ Other	☒ No ☐ Yes	Professor in Department of Anesthesiology & Perioperative Medicine. Will assist in data collection, data analysis and obtain informed consent
Ayesha Bryant, MD	shiekh	☒ Sub-Investigator ☐ Other	☒ No ☐ Yes	Assistant Professor in Department of Anesthesiology & Perioperative Medicine. Will assist in data collection, data analysis and obtain informed consent Research Assistant in Department of Anesthesiology & Perioperative Medicine. Will assist in data collection, data analysis and obtain informed consent
Perry Smith, MD	pws	☒ Sub-Investigator ☐ Other	☒ No ☐ Yes	Associate Professor in Department of Anesthesiology & Perioperative Medicine. Will assist in data collection, data analysis and obtain informed consent
Herrick J. Siegel, MD	hsiegel	☒ Sub-Investigator ☐ Other	☒ No ☐ Yes	Associate Professor in Department of Surgery (Orthopaedic Division). Will assist in data collection, data analysis and obtain informed consent
Alicia Kindred, MS	akindred	☐ Sub-Investigator ☒ Other	☒ No ☐ Yes	Research Associate in Department of Anesthesiology & Perioperative Medicine. Will assist in data collection, data analysis and obtain informed consent
Adam Sturdivant	absturdi	☐ Sub-Investigator ☒ Other	☒ No ☐ Yes	Research Assistant in Department of Anesthesiology & Perioperative Medicine. Will assist in data collection, data analysis and obtain informed consent
Shanna Graves	shoush	☐ Sub-Investigator ☒ Other	☒ No ☐ Yes	Research Assistant in Department of Anesthesiology & Perioperative Medicine. Will assist in data collection, data analysis and obtain informed consent

Judy Lynn Shanks		☐ Sub-Investigator ☒ Other	☒ No ☐ Yes	Administrative Associate in Department of Anesthesiology and Perioperative Medicine. Ms. Shanks will provide administrative assistance for this study.
Betty Hérard	bherard	☐ Sub-Investigator ☒ Other	☒ No ☐ Yes	Program Coordinator in Department of Anesthesiology and Perioperative Medicine. Ms. Hérard is a person of contact for this study.

*** Financial Interest** – for each investigator listed above, answer **Yes** or **No** as to whether the investigator or an immediate family member has any of the following:

- An ownership interest, stock options, or other equity interest related to the investigator's institutional responsibilities of any value.
- Compensation greater than $5,000 in the previous two years when aggregated for the immediate family
- Proprietary interest including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- Board of executive relationship, regardless of compensation.
- Any other Financial Interest as defined by the UAB CIRB.

If the investigator has a Financial Interest, a disclosure has to be made to the UAB CIRB. A completed CIRB evaluation has to be available before the IRB will complete its review.

b. Non-UAB Personnel - Include individuals who will interact or intervene with participants, obtain consent, or have access to private, identifiable information for research purposes.

Name	Title	Do the Non-UAB personnel have their own IRB approval?	Financial Interest?*	Protocol Responsibilities and Qualifications
Name: Institution:	☐ Sub-Investigator ☐ Other	☐ No - UAB IRB will determine if they are engaged in research. ☐ Yes - attach IRB approval	☐ No ☐ Yes	

c. Do the investigators listed above include any students using this research for their thesis or dissertation?

☒ No, continue with Item 3.d.
☐ Yes, complete the following

Student Name	Thesis/Dissertation Title

d. Is the principal investigator a student, fellow, or resident? ☐Yes ☒No

If Yes, complete items below and obtain signature of faculty advisor or supervisor:

Supervisor's Name: ____
Degree(s) / Job Title: ____
Additional Qualifications pertinent to the study: ____
Telephone: ____
E-Mail: ____
Signature: ____

e. Describe the principal investigator's activities related to this protocol and provisions made by the PI to devote sufficient time to conduct the protocol:

As an attending anesthesiologist, the PI is able to devote sufficient time to conduct and provide oversight for this protocol.

f. Is medical supervision required for this research? ☒Yes ☐No

If Yes, who will provide the supervision?

☒ PI will provide -*OR*- Name:____ Telephone:____

If other than PI, obtain signature of person providing medical supervision:

Signature ____

g. Describe the process that ensures that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions: **At study initiation, meetings will be held with all study personnel to discuss the specifics of the project and to address any questions raised. All personnel involved in obtaining informed consent will be current in their training in the protection of human subjects involved in research. All personnel and Anesthesia Providers will be given a copy of a study summary and/or outline for guidance.**

4. Funding

Is this study funded? ☐Yes ☒No

If No, specify that costs of the study will be covered by funds from the UAB department or other source named: **Department of Anesthesiology & Perioperative Medicine**

If Yes, attach one copy of completed application or request for funding sent to sponsor, and complete a-d.

a. Title of Grant or Contract:____

b. PI of Grant or Contract:____

c. Office of Sponsored Programs Proposal Number:____
(*or enter "Pending" and provide upon receipt from OSP*)

d. Sponsor, Funding Route (*check and describe all that apply*):

- ☐ Gov't Agency or Agencies—Agency name(s):____
  - ☐ Department of Defense (DoD): Identify DoD component:____
  - ☐ Department of Energy (DOE)
  - ☐ Department of Justice (DOJ)
  - ☐ Department of Education
- ☐ NIH Coop. Group Trial—Group name:____
- ☐ Private Nonprofit (e.g., Foundation)—Name:____
- ☐ Industry, investigator-initiated—Name:____ Describe the funding arrangement:____
  Note. Western IRB reviews industry-sponsored protocols unless the investigator initiated the research, or the study qualifies for expedited review or involves gene therapy.
- ☐ UAB Departmental/Division Funds—Specify:____

5. Locations Involved

a. Describe the facilities available for the conduct of the research. For research on UAB campus, include building names and room numbers:____

b. Indicate all "performance sites" that will provide space, services, facilities, potential or actual participants, or other support for this protocol.

- ☒ The Kirklin Clinic (TKC)
- ☒ University of Alabama Hospital (UAHosp)
- ☐ The Children's Hospital of Alabama (TCHA)
- ☒ Callahan Eye Foundation Hospital (CEFH)
- ☒ UAB Highlands
- ☐ Jefferson County Dept. of Health (JCDH)
- ☐ Birmingham Veterans Affairs Medical Center (BVAMC)
- ☐ General Clinical Research Center (GCRC)—inpatient

☐ General Clinical Research Center (GCRC)—outpatient
☐ General Clinical Research Center (GCRC) at The Kirklin Clinic (TKC)
☐ Other (i.e., Any performance site not listed above, including those covered by subcontracts related to this protocol)—Describe:____

c. Is this study a clinical trial requiring clinical services at one of the performance sites listed in Item b above? ☐Yes ☒No
If Yes, Fiscal Approval Process (FAP)-designated units complete a FAP submission and send to fap@uab.edu. For more on the UAB FAP, see www.uab.edu/osp/clinical-billing-review.

d. Is this a field study? ☐Yes ☒No
If Yes, describe the community and include information about how the community will be involved in the design, implementation and analysis of the research. This would include focus groups, training local facilitators/community health advisors:____

e. Is the study to be undertaken within a school, business, or other institution that does not have an institutional review board? ☐Yes ☒No
If Yes, attach a statement of any contacts with and approvals from the appropriate institution officials.
Note. Documentation of all such approvals must be received by the UAB OIRB before IRB approval will be issued.

f. Has this protocol or project been reviewed by another IRB, similar review board, or departmental review committee(s) that authorizes the use of its patient populations? ☐Yes ☒No
If Yes, provide name of the review board(s):____ and for each board listed, enter either the date of latest approval(s) or "PENDING":____ or reasons not approved:____. *If this protocol is subsequently rejected or disapproved by another review board, the UAB IRB must be notified promptly.*
Attach copies of approvals/disapprovals.

g. Will any of the participants be from the Birmingham Veterans Affairs Medical Center? ☐Yes ☒No
If Yes, attach VA IRB approval or notification from the VA Research and Development Department that the study has been submitted to the VA IRB for review.

h. Will the study be conducted at or recruit participants from the Jefferson County Department of Public Health (JCDH)? ☐Yes ☒No
If Yes, attach notification that the protocol has been approved by JCDH or the Alabama Department of Public Health IRB.

6. Multi-Site Studies

a. Is the investigator the lead investigator of a multi-site study? ☐Yes ☒No
b. Is UAB a coordinating site in a multi-site study? ☐Yes ☒No
c. If you answered **Yes** to *a* or *b*, describe the management of information obtained in multi-site research that might be relevant to the protection of participants. Include, at a minimum, the following items:
- IRB approvals from other sites

- Unanticipated problems involving risks to participants or others. (For example, if there is an unanticipated problem involving risks to participants or others, which site is responsible for reporting it?)
- Interim results.
- Protocol modifications.

7. **Drugs:** Will any drugs or supplements be used/studied in this protocol? ☒Yes ☐No
If Yes, attach the Drug Review Sheet.

8. **Devices:** Will any devices be studied in this protocol or used for a purpose other than for which they were approved by the FDA? ☐Yes ☐No
If Yes, attach the Device Review Sheet.

9. **Special Approvals**

a. Does this project involve the use of radioisotopes? ☐Yes ☒No
If Yes, attach documentation of approval from the Radiation Safety Division.

b. Does this project include patients with contagious infections (e.g., mumps, measles, chickenpox, TB, meningitis)? ☐Yes ☒No
If Yes, attach documentation of approval from Chairman of the Infection Control Committee of the appropriate facilities.

c. Does this project involve obtaining remnant biopsy or surgical material from the Department of Pathology or any other source? ☐Yes ☒No
If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Anatomic Pathology Release of Pathologic Materials).

d. Does this project require obtaining any remnant clinical laboratory specimens, body fluids, or microbiological isolates from the Department of Pathology or any other source? ☐Yes ☒No
If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Laboratory Medicine Release of Pathologic Materials).

e. Does this project use stored (existing) specimens from a repository? ☐Yes ☒No
If Yes, attach documentation of approval for use of specimens, and describe how existing specimens are labeled:____

10. **Use of Specimens**

Does this project involve collecting specimens from participants and storing them for future research? ☐Yes ☒No
If Yes, complete a-h. If no, skip to Item 11

a. How will specimens be obtained, processed, distributed, and stored?

b. How will specimens be labeled (e.g., unique identifier, medical record number, Social Security number, name, date of birth)?

c. How will clinical data associated with the specimens be collected and stored?

d. What participant-identifying information will be collected and linked to the specimens?

e. What steps will be taken to maximize the confidentiality of linked identifiers? For example, procedures could include using a password-protected computer database to link identifiers, with limited personnel knowledgeable of the password, or coded identifiers released without the ability to link to clinical data (also called "stripped" or "anonymized" specimens).

f. Will specimens be shared with other investigators in the future? ☐Yes ☒No
If Yes, what identifiers, clinical information and demographic information will be shared; or will the specimens be stripped of identifiers (i.e., anonymized)? Also **if yes**, outline your procedure for assuring IRB approval for release and use prior to release of specimens.

Note. Investigators who receive and/or use these specimens must document approval from the appropriate IRB(s) before the specimens may be released.

g. Will biological samples be stored for future use? ☐Yes ☒No
If Yes, indicate whether they will be used for the disease under study in this protocol or research on other diseases.

h. Is genetic testing planned? ☐Yes ☒No
If Yes, describe the planned testing here and see "DNA/Genetic Testing" in the Guidebook for consent requirements.

11. Gene Therapy

Does this project involve gene therapy or administering recombinant materials to humans? ☐Yes ☒No
If Yes, submit the Gene Therapy Project Review Panel Report -OR- If this is a vaccine trial that is exempt from the NIH Guidelines For Research Involving Recombinant DNA Molecules, submit the Protocol Oversight Review Form For Clinical Vaccine Trials.

12. HIPAA Privacy and Security

Will the PI or others obtain, review, or make other use of participants' "personal health information" (i.e., information, whether oral or recorded in any form or medium that (a) is created or received by a health care provider and (b) relates to past, present, or future physical or mental health or condition of an individual; or provision of health care; or payment for provision of heath care)? ☒Yes ☐No

If Yes, complete a-e as described.

a. Will the data/information be stored or managed electronically (on a computer)? ☒Yes ☐No

b. Is the principal investigator requesting that the UAB IRB waive patient HIPAA authorization from another institution or entity (e.g., insurance company, collaborating institution). ☐Yes ☒No

If Yes, attach copy of privacy notices from institution/entity, and provide the name of institution/entity:____

c. Indicate which, if any, of the listed entities below would provide information or maintain health information collected for this protocol and/or where health information that been collected will be stored/maintained.

- ☒ The Kirklin Clinic
- ☒ University of Alabama Hospital
- ☐ The Children's Hospital of Alabama
- ☐ Callahan Eye Foundation Hospital
- ☒ UAB Highlands
- ☐ Jefferson County Department of Health
- ☐ School of Dentistry
- ☐ School of Health Professions
- ☐ School of Medicine
- ☐ School of Nursing
- ☐ School of Optometry
- ☐ University of Alabama Health Services Foundation
- ☐ UAB Health Centers
- ☐ Viva Health
- ☐ Ophthalmology Services Foundation
- ☐ Valley Foundation
- ☐ Medical West - UAB Health System Affiliate

Health System Information Systems:

- ☐ HealthQuest
- ☒ Cerner Millennium (Lab, Radiology, UED, Surgery)
- ☐ EMMI - Master Member Index
- ☒ Horizon - IPV (IVR/CDA/CRIS)
- ☐ CareFlow Net
- ☐ Eclipsys (PIN)
- ☒ IMPACT
- ☐ None—**If None, skip to Item 13.**

d. Indicate which of the listed identifiers would be associated/linked with the protected health information (PHI) used for this protocol.

- ☒ Names
- ☐ Geographic subdivisions smaller than a State
- ☒ Elements of dates (except year) related to an individual
- ☒ Telephone numbers
- ☐ Fax numbers
- ☐ Email addresses
- ☐ Social security numbers
- ☒ Medical record numbers
- ☐ Health plan beneficiary numbers
- ☐ Account numbers
- ☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers
☐ Device identifiers and serial numbers
☐ Biometric identifiers
☐ Web universal resource locators (URLs)
☐ Internet protocol address numbers
☐ Full-face photographic images
☐ Any other unique identifying number—Describe:____
Note. Codes are not identifying as long as the researcher cannot link the data to an individual
☐ None—**If None, skip to Item 13.**

e. Choose one plan to describe your use of the personal health information:
☐ The data collected meet the specifications for a "limited data set"
—Attach Data Use Agreement or Business Associate Agreement

☒ Research staff will obtain authorization from each patient to use the information
—Attach Patient Authorization form, complete except for patient name and IRB protocol number

☐ PI requests Waiver of Patient Authorization to use the information
—Attach Waiver of Authorization and Informed Consent form

PROPOSED RESEARCH

- The IRB will not accept grant applications and/or sponsor's protocols in lieu of the items as outlined below.
- Do not separate responses from items. Instead, insert your response to each item below the item, keeping the information in the order of this form.
- Number each page of the Human Subjects Protocol (i.e., Page *X* of *Y*).

13. Purpose—in nontechnical, lay language

Summarize the purpose and objectives of this protocol, including any related projects, in one short paragraph.

Obstructive sleep apnea (OSA) affects millions of people in the U.S., and currently, there is not a well-established, general anesthetic technique that clearly decreases the risk of postoperative respiratory complications in these patients. If OSA patients in our study group have significantly decreased postoperative opioid requirements and improved recovery profiles in the PACU, our protocol could have significant implications in defining future standardized general anesthesia recommendations for patients with this disease. Ultimately, the aim of this study is to substantially reduce overall postoperative morbidity and mortality associated with obstructive sleep apnea. The objective of this study is to compare the postoperative recovery profile of OSA patients receiving standard Sevoflurane inhaled anesthesia with normal saline infusion versus Sevoflurane combined with a low-dose ketamine infusion. We hypothesize that the group of obstructive sleep apnea patients that receive low-dose intraoperative ketamine will report lower pain scores, require less supplemental intravenous Morphine, and have less frequent side effects and desaturation episodes post-operatively than the group receiving saline.

14. Background—in nontechnical, lay language

Summarize in 2-3 paragraphs past experimental and/or clinical findings leading to the formulation of this study. Include any relevant past or current research by the Principal Investigator. For drug and device studies summarize the previous results (i.e., Phase I/II or III studies).

Obstructive sleep apnea (OSA) has been estimated to affect between 2 and 4% of the U.S. population. It is a serious, life-threatening condition associated with obesity, hypertension, congestive heart failure, pulmonary hypertension, coronary artery disease, and cardiac arrhythmias and has an 8 year mortality rate of nearly 40%. Following general anesthesia, patients with OSA have been noted to have a significantly increased risk of respiratory complications, morbidity and mortality. This may be due to residual effects of inhaled anesthetics which can decrease upper pharyngeal muscle tone leading to airway compromise in OSA patients. Also, OSA patients are exquisitely sensitive to the ventilatory depressant effects of postoperative opioids, causing decreased responsiveness to hypercarbia and episodic arterial hypoxemia. Currently, there is not a well-established, general anesthetic technique that will decrease the risk of complications in OSA patients.

Obese patients are known to have a delayed emergence from anesthesia due to volatile gases' high affinity for adipose tissue. Also, adipose tissue serves as a depot for anesthetic gases during prolonged exposure. In addition, many obese patients presenting for surgery meet clinical screening criteria for obstructive sleep apnea. Surgical patients with obstructive sleep apnea patients are known to be very sensitive to the respiratory depressant effects of intravenous opioids in the postoperative period. When possible, opioids should be avoided in favor of nonsedating agents such as acetaminophen, ketorolac or even regional anesthesia when possible. Unfortunately, after major surgery, most patients will still require IV opioids titrated to effect in order to adequately control their pain.

Ketamine is a dissociative anesthetic agent that provides profound analgesia without depressing the respiratory system. Ketamine is extensively metabolized by hepatic p-450 enzymes to a weak, water-soluble compound that is excreted by the kidneys and has a short context-sensitive half-time (time for plasma level to drop by 50%) even during prolonged infusions. Multiple studies have demonstrated that intraoperative, subanesthetic dosing of ketamine can significantly reduce postoperative opioid requirements following major surgery. This low-dose of ketamine was also shown to decrease the incidence of postoperative nausea and vomiting and was not associated with an increase adverse psychotropic effects. None of these studies targeted obstructive sleep apnea patients to determine whether these opioid-sparing effects persist and could mitigate the postop respiratory compromise or improve their overall recovery profile.

15. Participants (Screening and Selection)

a. How many participants are to be enrolled at UAB? 150
If multi-center study, total number at all centers: N/A

b. Describe the characteristics of anticipated or planned participants.
Sex: Male or Female
Race/Ethnicity: All representative of patients undergoing general ENT or Orthopedic surgery; Expand the patient population to include all patients undergoing surgery requiring to general anesthesia due to the limited amount of patients that are able to be recruited.
Age: 18-100
Health status: Patients with an American Society of Anesthesiologists (ASA) Physical Classification of 1-3 and who are morbidly obese patients with obstructive sleep apnea scheduled general ENT or Orthopedic surgery. ASA Classification of 1 = A normal healthy patient, ASA Classification of 2 = A patient with mild systemic disease (examples: current smoker, social alcohol drinker), ASA Classification of 3 = A patient with significant systemic disease (examples: Poorly controlled diabetes or hypertension), and ASA Classification of 4 = A patient with severe systemic disease that is a constant threat to life (examples: MI, CVA, TIA, or CAD/stents, ongoing

cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis).

Note. If data from prior studies indicate differences between the genders or among racial/ethnic groups in the proposed research or if there are no data to support or to negate such differences, Phase 3 clinical trials will be required to include sufficient and appropriate entry of gender and racial/ethnic subgroups so that trends detected in the affected subgroups can be analyzed. If ethnic, racial, and gender estimates are not included in the protocol, a clear rationale must be provided for exclusion of this information. If prior evidence indicates that the results will not show gender or racial differences, researchers are not required to use gender or race/ethnicity as selection criteria for study participants. They are, however, encouraged to include these groups. See Section II. Policy of the NIH POLICY AND GUIDELINES ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH – Amended, October, 2001) for further details.

c. From what population(s) will the participants be derived?
The study population will be derived from those patients who are morbidly obese scheduled to undergo general ENT and orthopedic surgery.
Describe your ability to obtain access to the proposed population that will allow recruitment of the necessary number of participants:
All patients scheduled for the above surgical procedure will be seen preoperatively in the PAC at TKC and Highlands. The opportunity to participate will be offered at such time.

Describe the inclusion/exclusion criteria:
Inclusion criteria: aged 19-100, scheduled to undergo general ENT or Orthopedic Surgery. Patients should have a diagnosis of obstructive sleep apnea as confirmed by sleep study or deemed high risked for obstructive sleep apnea by clinical predictors (greaterthan 4 clinical predictors of obstructive sleep apnea as described by STOP BANG).

Exclusion criteria: positive pregnancy test, ASA> III, history of alcohol or narcotic abuse in last 90 days, significant cardiovascular or respiratory disease (baseline oxygen saturation below 92%), significant psychiatric or neurologic disease, history of significant hepatic or renal disease (baseline creatinine>1.5), history of allergy or contraindication to anesthetic agents or ketamine including patients with increased ICP, increased IOP, severe arrhythmias, history of delirium, hallucinations, or psychosis, or history of uncontrolled seizures, or potential risk for malignant hyperthermia (family history), history of difficult intubation that would preclude standard induction of anesthesia, prisoners, persons who are mentally impaired, and non-English speakers.

d. If participants will comprise more than one group or stratification, describe each group (e.g., treatment/intervention, placebo, controls, sham treatment) **and** provide the number of participants anticipated in each group.
Participants will be randomly assigned to either the low-dose Ketamine infusion group or the normal saline infusion group. The two groups will comprise the study population, n=150.

e. Indicate which, if any, of the special populations listed below will be involved in the protocol. Include the Special Populations Review Form (SPRF) if indicated.
☐ Pregnant Women: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates

☐ Fetuses: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Neonates/Nonviable Neonates: SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Prisoners: Attach SPRF—Prisoners
☐ Minors (<18 years old): Attach SPRF—Minors
☒ Employees or students at institution where research conducted
☐ Persons who are temporarily decisionally impaired
☐ Persons who are permanently decisionally impaired (e.g., mentally retarded)
☐ Non-English Speakers

For each box checked, describe why the group is included **and** the additional protections provided to protect the rights and welfare of these participants who are vulnerable to coercion: **Employees and students may be eligible to participate and should be allowed to do so. It is an undue burden to exclude them. The suggested language has been included in the informed consent document to fully disclose that this project is separate from the expectations and their relationship with UAB as an employee or a student.**

f. List any persons other than those directly involved in the study who will be at risk. If none, enter "None": **None**

g. Describe the process (e.g., recruitment, chart review) that will be used to seek potential participants (e.g., individuals, records, specimens). Research recruitment by non-treating physicians/staff may require completion of Partial Waiver of Authorization for Recruitment/Screening. (See http://main.uab.edu/show.asp?durki=61981.)

Patients being seen in the pre-operative anesthesia clinic (PAC) that are scheduled for general, ENT, or orthopedic surgery will be screened by the clinician for possible eligibility for this study. Recruitment will take place in the PAC clinic (at the Kirklin Clinic or Highlands PAC clinic) during the PAC clinic visit. Specifically: 1) Study Personnel and Anesthesia providers will be provided a study summary and/or a study outline for reference and guidance. 2)The "Attention Pre-op Clinic" flier will be posted in the PAC clinician's work area - as a reminder to the clinicians to screen for potential study patients and as a guide to identify potential study subjects. The flier is for clinician referral. 3) If a patient is identified as a potential study candidate then the PAC clinician or staff will contact (via pager or cell phone) the PI or the study research assistant to inform them of a possible study candidate is in the PAC clinic.

h. If you will use recruitment materials (e.g., advertisements, flyers, letters) to reach potential participants, attach a copy of each item. If not, identify the source (e.g., databases) from which you will recruit participants.

See item 15.g.

i. Describe the procedures for screening potential participants.

Once a potential participant has been identified (see steps outlined in item g above), then the study PI and/or the research assistant will perform a chart review to complete the Eligibility Checklist. If a patient meets the eligibility criteria, as outlined on the Eligibility Checklist, then the PI or the research assistant will meet the patient and present the details of this study to the patient. If the patient agrees to participate, then informed consent will be obtained. Eligibility determination and screening will occur in the Preoperative Assessment Clinic (PAC) in The Kirklin Clinic (TKC) and Highlands.

16. Protocol Procedures, Methods, and Duration of the Study—in nontechnical language

a. Describe the procedures for all aspects of your study. Tell us what you are doing.
Participants in this study will be randomized to two groups: One group will receive an intravenous (IV) dose of ketamine during the surgery. The other group will receive a normal saline placebo IV (control group). For the patients that are randomized to the ketamine group, the PI will submit an order for the ketamine to the research pharmacist. The pharmacist will determine the dosing of ketamine based on a standard calculation and prepare the syringe that will be used to dispense the ketamine. For both groups, the IV infusion will be discontinued at the conclusion of the surgery. Participants will receive standard anesthetic drugs and appropriate pain medication to control their postoperative pain in keeping with the current practice. We will compare recovery data including vital signs and pain scores as well as potential side effects of controlled versus study group. Approximately 24 hours after surgery, a patient assessment form will be completed ("24 Hr Post-Operative Data Collection Form") by the PI or research study team.

b. What is the probable length of time required for the entire study (i.e., recruitment through data analysis to study closure)?
Approximately two years

c. What is the total amount of time each participant will be involved?
Participants will be involved during surgery, during their recovery in the PACU, and at one time point approximately 24 hours postoperatively (to complete the Post-Operative Patient Satisfaction Assessment Form).

d. If different phases are involved, what is the duration of each phase in which the participants will be involved? If no phases are involved, enter "not applicable."
Not applicable

e. List the procedures, the length of time each will take, and the frequency of repetition, and indicate whether each is done solely for research or would already be performed for treatment or diagnostic purposes (routine care) for the population. *Insert additional table rows as needed.*

Procedure	Length of Time Required of Participants	Frequency of Repetition	Research (Res) – OR- Routine Care
Pregnancy testing for women of childbearing potential	**<5 minutes**	**once**	☐Res ☒Routine
Weight measurement	**<5 minutes**	**once**	☐Res ☒Routine
Normal Saline or Ketamine infusion	**<three hours**	**once**	☒Res ☐Routine
Monitoring and measurement of electrocardiogram, heart rate, blood pressure, respiratory rate, and oxygen saturation	**From onset of surgery until discharge from the PACU**	**Continuously during the stated time**	☐Res ☒Routine
24 hr postoperative patient forms: 1) "Post-Operative Patient Assessment Form" to be completed by the PI or study staff, and 2) "24 hour Post-Operative Patient Satisfaction	**<5 minutes for each form**	**Once**	☒Res ☐Routine

Assessment Form" that will be completed by the subject			

f. Will an interview script or questionnaire be used? ☒Yes ☐No
If Yes, attach a copy.

g. Will participants incur any costs as a result of their participation? ☐Yes ☒No
If Yes, describe the reason for and amount of each foreseeable cost.
____

h. Will participants be compensated? ☐Yes ☒No
If Yes, complete i-v:
i. Type: (e.g., cash, check, gift card, merchandise):____
ii. Amount or Value:____
iii. Method (e.g., mail, at visit): ____
iv. Timing of Payments: (e.g., every visit, each month):____
v. Maximum Amount of Payments per Participant:____

17. Describe the potential benefits of the research.

The benefit of participating in this study is the possibility that participants could have less pain and fewer complications after their general ENT or Orthopedic Surgery. Participants will have the opportunity to help in finding a better surgical management approach in adults with obstructive sleep apnea undergoing General ENT or Orthopedic Surgery. There is also the possibility of a recovery with fewer complications for other people general ENT or Orthopedic Surgery in the future.

18. Risks

a. List the known risks—physical, psychological, social, economic, and/or legal—that participants may encounter as a result of procedures required in this protocol. Do not list risks resulting from standard-of-care procedures. *Note. Risks included in this protocol document should be included in the written consent document.*
Multiple studies have demonstrated that low-dose ketamine, when given with anesthetic induction agents and inhalational anesthetic gas, is safe and effective with few if any, adverse side effects.

Rare adverse reactions include:
Psychological manifestations which vary in severity between pleasant dream-like states, vivid imagery, hallucinations, and emergence delirium, and may be assoc. with confusion, excitement, and irrational behavior. The duration is usually just a few hours with recurrences up to 24 hours postoperatively in only a few cases. There are no known residual psychological effects. The incidence of these effects is noted with lower doses and in combination with diazepam during anesthesia induction and maintenance. The use of a small hypnotic dose of short- or ultrashort-acting barbiturate can be used to end severe emergence reaction. These adverse effects are typically reversible with cessation of the drug infusion.

Other possible severe adverse reactions include: respiratory depression, laryngospasm, increase in intracranial pressure, increase in intraocular pressure, hypotension, bradycardia, arrhythmias, delirium, hallucinations, tonic clonic movements, anaphylaxis, and withdrawal syndrome (with long-term use).

Common adverse reactions include:

Hypersalivation, anorexia, nausea/vomiting, hypertension, hypotension, tachycardia, bradycardia, diplopia, nystagmus, fasciculations, depressed reflexes, and hallucinations. Common side effects are typically reversible with cessation of the infusion.

b. Estimate the frequency, severity, and reversibility of each risk listed.
Please see item 18.a.

c. Is this a therapeutic study or intervention? ☒Yes ☐No
If Yes, complete the following items:
i. Describe the standard of care in the setting where the research will be conducted: **Balanced general anesthetic with postoperative intravenous opioids.**
ii. Describe any other alternative treatments or interventions: **N/A**
iii. Describe any withholding of, delay in, or washout period for standard of care or alternative treatment that participants may be currently using: **None**

d. Do you foresee that participants might need additional medical or psychological resources as a result of the research procedures/interventions? ☐Yes ☒No
If Yes, describe the provisions that have been made to make these resources available.

____

e. Do the benefits or knowledge to be gained outweigh the risks to participants? ☒Yes ☐No
If No, provide justification for performing the research:____

19. Precautions/Minimization of Risks

a. Describe precautions that will be taken to avoid risks and the means for monitoring to detect risks.
Supportive medications and care will be provided to avoid or treat adverse effects experienced by participants.

If study involves drugs or devices skip Items 19.b. and 19.c., go to Item 20, and complete the Drug or Device Review Sheet, as applicable.

b. If hazards to an individual participant occur, describe (i) the criteria that will be used to decide whether that participant should be removed from the study; (ii) the procedure for removing such participants when necessary to protect their rights and welfare; and (iii) any special procedures, precautions, or follow-up that will be used to ensure the safety of other currently enrolled participants.
Criteria for early withdrawal for the study: <2 hrs surgical time, any surgical or anesthetic complication that prevents the assessment of study variables, clinically relevant residual neuromuscular blockade or other reason for patient to require prolonged tracheal intubation following surgery.

c. If hazards occur that might make the risks of participation outweigh the benefits for all participants, describe (i) the criteria that will be used to stop or end the entire study and (ii) any special procedures, precautions, or follow-up that will be used to ensure the safety of currently enrolled participants.
The overall study will be suspended if is determined that, at any point, study procedures are not adequate to protect the participant's safety. All efforts will be made during procedures to ensure that the participant's risk is minimized.

20. Informed Consent

a. Do you plan to obtain informed consent for this protocol? ☒Yes ☐No
If Yes, complete the items below.
If No, complete and include the Waiver of Informed Consent or Waiver of Authorization and Informed Consent, as applicable.

b. Do you plan to document informed consent for this protocol? ☒Yes ☐No
If Yes, complete the items below.
If No, complete the items below **and** include the Waiver of Informed Consent Documentation.

c. How will consent be obtained? **Consent will be obtained from the potential participant preoperatively during their evaluation in the PAC by a member of the research team named in this submission or named in later revisions/amendments.**

d. Who will conduct the consent interview? **See above**

e. Who are the persons who will provide consent or permission? **See above**

f. What steps will be taken to minimize the possibility of coercion or undue influence?
Participation is voluntary and the potential participant will have every opportunity to ask any questions or raise any concerns and have those addressed to their satisfaction prior to obtaining and documenting consent.

g. What language will the prospective participant or the legally authorized representative understand? **English**

h. What language will be used to obtain consent? **English**

i. If any potential participants will be, or will have been, in a stressful, painful, or drugged condition before or during the consent process, describe the precautions proposed to overcome the effect of the condition on the consent process. If not, enter "no such effect."
No such effect

j. If any project-specific instruments will be used in the consenting process, such as flip charts or videos, describe the instrument(s) here, and provide a copy of each. If not, enter "not used."
Not used

k. How long will participants have between the time they are told about the study and the time they must decide whether to enroll? If not 24 hours or more, describe the proposed time interval and why the 24-hour minimum is neither feasible nor practical. **The consent process will begin during the potential participant's preoperative visit to the PAC. Participants may not have more than 24 hours after learning of the study before documenting their consent to participate, but they will have additional days following screening and documentation of consent before the day or surgery and the implementation of any study specific procedures.**

21. Procedures to Protect Privacy

Describe the provisions included in the research to protect the privacy interests of participants (e.g., others will not overhear your conversation with potential participants, individuals will not be publicly identified or embarrassed).

Privacy will be ensured at all times. Conversations with potential participants will be conducted privately, usually in an exam room with a closed door to prevent others from overhearing the conversation. Individuals will not be publicly identified or embarrassed.

22. Procedures to Maintain Confidentiality

a. Describe the manner and method for storing research data and maintaining confidentiality. If data will be stored electronically anywhere other than a server maintained centrally by UAB, identify the departmental and all computer systems used to store protocol-related data, and describe how access to that data will be limited to those with a need to know.

Participant data will be stored on a password-protected computer system maintained for human subjects research purposes by the UAB Department of Anesthesiology. Access to this particular system is restricted to only certain members of the research team, based on their need to know. The list of patients participating in the study, including their medical record numbers and dates of surgery, will be kept separately and securely and will be destroyed after final data analysis. Any original paper records may be scanned and stored on the above mentioned departmental server and then shredded after they have been transferred to the password-protected computer system.

b. Will any information derived from this study be given to any person, including the subject, or any group, including coordinating centers and sponsors? ☐Yes ☒No

If Yes, complete i-iii.

i. To whom will the information be given? _____

ii. What is the nature of the information? _____

iii. How will the information be identified, coded, etc.? _____

23. Additional Information

In the space below, provide any additional information that you believe may help the IRB review the proposed research, or enter "None."

This study was originally closed on May 28, 2014. The PI is now requesting to re-open this protocol. The PI understands that it has been over a year and will have to re-submit the protocol. You will find attached the originally approved HSP. A few personnel were added and removed along with changes to the patient population (now focusing on patients undergoing general ENT or Orthopedic surgery).