Date: Sept. 29, 2019

Title: Ketamine Effect on Recovery and Respiratory Outcomes after Laparoscopic Gastric Reduction: A Randomized, Double-Blinded, Placebo Controlled Study

NCT#: 01997515

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Proposed Research Protocol Form
Northwestern University Medical School
Department of Anesthesiology

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Research Aims:

1. **Research Questions(s):** Does Intraoperative Ketamine improve quality of recovery after laparoscopic gastric reduction surgery?
2. **Hypotheses:** Intraoperative ketamine will improve postoperative quality of recovery after laparoscopic gastric reduction.

Research significance:

Background:

Laparoscopic surgery for gastric reduction is frequently associated with high levels of postoperative pain.[1] Postoperative pain is very often treated with opioids. However large doses of opioids can result in respiratory depression with hypoxemia especially in high risk patients with obstructive sleep apnea.[2] Since a large group of patients undergoing surgery for gastric reduction surgery also have obstructive sleep apnea, it is expected that these patients are also at high risk for postoperative respiratory depression and hypoxemia.

Intraoperative ketamine has been used as an effective multimodal agent to reduce postoperative pain.[3] However, ketamine alone has not been examined to improve postoperative pain outcomes in patients undergoing gastric reduction surgery. More importantly, it is unknown if the use of intraoperative ketamine can lead to better overall quality of recovery in the same patient population. In addition, ketamine has been shown to improve ventilation but it remains to be determined if the intraoperative use of ketamine will result in decreased postoperative opioid use and hence less complications such as hypoxic episodes within the first 24 hours after surgery.[4,5]

The main objective of the current investigation is to examine the effect of intraoperative ketamine on postoperative quality of recovery after gastric reduction

surgery. We hypothesize that subjects receiving ketamine will have a greater global quality of recovery score than the ones receiving saline (placebo group). We also seek to determine if intraoperative ketamine would decrease the incidence of postoperative opioid requirements in the same patient population.

Investigational Plan

Study design: Randomized, double blinded placebo controlled clinical trial

Methods:

1. **Primary outcome:** QoR-40 at 24 hours[6]
2. **Size of study groups(s):**
   It would be required to have 36 patients per group in order to achieve 80% power to detect a 10 point difference on the QoR-40 instrument with an estimated standard deviation of 15. To compensate for drop-outs or loss to follow-up, 80 patients will be recruited and randomized.
3. **Secondary outcomes:**
   Postoperative opioid consumption
   Postoperative pain scores
   Length of hospital stay (Hours)
4. **Patient entry, exclusion and dropout criteria:**
   Entry: Age 18-64, surgery: laparoscopic gastric reduction (gastric sleeve or gastric bypass), ASA I, II, III; BMI >35kg/m^2, Fluent in English
   Exclusion: History of allergy to protocol medications, History of chronic opioid use, pregnant patients.
5. **Drop out:** Conversion to an open surgical route, patient or surgeon request.

6. **Protocol specific methods:** Patients will be recruited on the day of surgery. Informed consent will be signed. Participant will complete the preoperative QoR-40 questionnaire (appendix 1) along with the Stop-BANG questionnaire (appendix 2). All medication except for propofol will be dosed based on the adjusted body weight (ABW=Ideal body weight (IBW) + [0.4 X (actual body weight –IBW)][8] Patients will be randomized using a computer generated table of random number to 2 groups: Group K (ketamine) will receive 0.5mg /kg of ketamine bolus followed by an infusion of 0.5 mg/kg/hour of ketamine throughout the intraoperative period. Group P (placebo) will receive the same amount of saline. The investigators will be blinded to study drug. The medication will be prepared by the hospital pharmacy and is not involved with the case or data collection.

   Subjects will be premedicated with midazolam (0.02-0.04 mg/kg IV preoperatively. Routine ASA monitors will be applied. Anesthesia will be induced with remifentanil infusion started at 0.1 mcg/kg/minute titrated to keep blood pressure within 20% of the baseline and propofol 1.5 -2.5 mg/kg. Tracheal intubation will be facilitated with succinylcholine (1-2 mg /kg). Anesthesia will

be maintained with sevoflurane titrated to a bispectral index (BIS) between 40-60, remifentanil infusion started at 0.1mcg/kg/min titrated to keep blood pressure within 20 % of baseline values, and neuromuscular blockade will be maintained with rocuronium that will be administered at the discretion of the anesthesiologist. Upon termination of the surgery, residual neuromuscular blockade will be antagonized with a combination of neostigmine 0.05mg/kg (to a maximum dose of 5mg) and glycopyrrolate 0.01 mg/kg . Remifentanil will be discontinued at the time of the removal of the laparoscope from the abdomen and hydromorphone 10 mcg/kg IV will be administered. Ondansetron 4 mg IV and dexamethasone 4 mg IV will be administered to prevent postoperative nausea and vomiting. Study drug will be discontinued at the end of the surgical procedure as the dressings are being placed. Normothermia will be maintained intraoperatively using a forced air warming blanket (Bairhugger, Arizant healthcare INC, Eden Prairie, MN). Subjects will receive IV Hydromorphone in divided doses as needed to achieve a verbal rating score for pain <4 out of 10 starting in the operating room following extubation and in PACU. Metoclopramide (10 mg IV) will be used as rescue antiemetic. Patient-controlled analgesia, programmed to deliver 0.2 mg of hydromorphone every 10 minutes, will be instituted before the patient is discharged from the PACU. Before PACU discharge, the LSD ARCI questionnaire[7] (appendix 3) will be completed by the patient to assess for other untoward effects of ketamine. Ketorolac 30 mg every 6 hours for 24 hours will be started when admitted to patient room. SpO2 will be monitored continuously for 24 hours after discharge from PACU. At 24 hours after surgery patients will complete the QoR-40 (appendix 1) instrument. [6]

Risks/Benefits: Participants may not have any direct benefit from taking part in this study. Taking part in this study may help us determine whether the study drug increases 24 hour quality of recovery and decreases opioid requirements within 24 hours of the surgery.

Side effects of ketamine
The common side effects of the study drug ketamine include:

Most Frequent:
Delirium
Hallucinations
Mood changes
Nightmares
Tachyarrhythmia
Tonic- Clonic Epilepsy
Vocalization

Less Frequent:
Bradycardia
Hypotension

Respiratory Depression
Vomiting

Rare:
Anaphylaxis
Anorexia
Conduction disorder of the heat
Diplopia
Injection site
Laryngismus
Nausea
Nystagmus
Obstructive pulmonary disease
Skin inflammation
Skin rash

Normal Saline (placebo):
Hypernatremia

These side effects are uncommon with the lower dose range used in this study.

There is a risk of loss of confidentiality even though there are strict measures in place to prevent occurrence. Answering some of the questionnaires or surveys may make subject feel uncomfortable. The subject may skip to the next question if the question upsets them. There is a very slight risk of skin irritation from the pulse oximeter (Konica Minolta).

Confidentiality: Subjects' identity will be guarded by assigning a numerical code which is only known by the principal investigator and research coordinator. Data will be stored in department computer which is password protected. Each study subject will be assigned a study code number. The code will be used to link study data to patient identification (name) in a separate database. Subject data will be stored on secure computers at Northwestern University. Data access will be password protected and only available to study investigators. The data forms will be de identified after the chart review prior to analysis. 7 years post manuscript completion the data both electronic and paper will be destroyed using current departmental approved methods of destruction.

Literature:

1) Albrecht E, Kirkham KR, Endersby RV, Chan VW, Jackson T, Okrainec A, Penner T, Jin R, Brull R. Ultrasound-Guided Transversus Abdominis Plane (TAP) Block for Laparoscopic Gastric- Bypass Surgery: a Prospective Randomized Controlled Double-Blinded Trial. Obes Surg. 2013 Aug; 23(8); 1309-1314. PMID: 23591549

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7) Haertzen CA, Hickey JE. (1987) Addiction Research Center Inventory (ARCI): measurement of euphoria and other drug effects. Chapter 24. In Bozarth, MA (Ed.), Methods of assessing the reinforcing properties of abused drugs (pp. 389-524). New York: Springer-Verlag.

8) Han PY, Duffull SB, Kirkpatrick CM, Green B. Dosing in obesity: a simple solution to a big problem. Clin Pharmacol Ther. 2007 Nov; 82(5):505-508. PMID: 17952107

9) Myles PS, Weitkamp B, Jones K, Melick J, Hensen S: Validity and reliability of a postoperative quality of recovery score: the QoR – 40. Br J Anaesth 2000 Jan; 84: 11-15. PMID: 10740540

10) Chung F, Abdullah HR, Lao P. STOP-Bang Questionnaire: A Practical Approach to Screen Obstructive Sleep Apnea. Chest. 2016 Mar; 149 (3); 631-638. PMID: 266378880

Appendix 1 QOR-40

Modified Quality of Recovery Survey: MQoR-40 Study Patient Number: _____
Date of Surgery: ___ / ___ / ___

How have you been feeling in the last 24 hours? (please circle one)

	None of the time	Some of the time	Usually	Most of the time	All of the time
COMFORT					
Able to breathe easily	1	2	3	4	5
Have had a good sleep	1	2	3	4	5
Able to enjoy food	1	2	3	4	5
Feel rested	1	2	3	4	5
EMOTIONS					
Have a feeling of general well-being	1	2	3	4	5
Feel in control	1	2	3	4	5
Feel comfortable	1	2	3	4	5
PHYSICAL INDEPENDENCE					
Have normal speech	1	2	3	4	5
Able to wash, brush teeth, shave	1	2	3	4	5
Able to look after your own appearance	1	2	3	4	5
Able to write	1	2	3	4	5
Able to return to work/usual home activities	1	2	3	4	5
PATIENT SUPPORT					
Been able to communicate with MD	1	2	3	4	5
Able to communicate with family / friends	1	2	3	4	5
Able to communicate with visiting healthcare worker	1	2	3	4	5
Have support from family / friends	1	2	3	4	5
Have support from visiting healthcare worker	1	2	3	4	5
Able to understand instructions and advice	1	2	3	4	5

Have you had any of the following in the last <u>24 hours</u>? (please circle one)

	None of the time	Some of the time	Usually	Most of the time	All of the time
COMFORT					
Nausea	5	4	3	2	1
Vomiting	5	4	3	2	1
Retching	5	4	3	2	1
Feeling restless	5	4	3	2	1
Shaking / twitching	5	4	3	2	1
Shivering	5	4	3	2	1
Feeling cold	5	4	3	2	1
Feeling dizzy	5	4	3	2	1
EMOTIONS					
Had bad dreams	5	4	3	2	1
Feeling anxious	5	4	3	2	1
Feeling angry	5	4	3	2	1
Feeling depressed	5	4	3	2	1
Feeling alone	5	4	3	2	1
Had difficulty falling asleep	5	4	3	2	1
PATIENT SUPPORT					
Feeling Confused	5	4	3	2	1

	None of the time	Some of the time	Usually	Most of the time	All of the time
PAIN					
Moderate pain	5	4	3	2	1
Severe pain	5	4	3	2	1
Headache	5	4	3	2	1
Muscle pains	5	4	3	2	1
Backache	5	4	3	2	1
Sore throat	5	4	3	2	1
Sore mouth	5	4	3	2	1

Please check that all questions have been answered.

Thank you for your assistance.

Date: ___ / ___ / ___ Time: _____ AM / PM

Appendix 2 (STOP-Bang Questionnaire)

STOP-Bang Questionnaire

	YES	NO
Snoring: Do you snore loudly (loud enough to be heard through closed doors)?		
Tired: Do you often feel tired, fatigued, or sleepy during daytime?		
Observed: Has anyone observed you stop breathing during your sleep?		
Blood pressure: Do you have or are you being treated for high blood pressure?		
BMI: more than 35 kg m^{-2}?		
Age: over 50 year old?		
Neck circumference: >40 cm?		
Gender: Male?		
Total Score		
PACU Desaturation		

High risk of OSA: Yes to ≥3 questions.

Low risk of OSA: Yes to <3 questions.

Chung F, et al: BJA 2012; 108: 768-75

Appendix 3 (LSD ARCI) [7]

LSD_ARCI Questionnaire

Question	True	False
My hands feel clumsy		
I have a weird feeling		
I have an unusual weakness of my muscles		
Some parts of my body are tingling		
I feel anxious and upset		
I have a disturbance in my stomach		
A thrill has gone through me one or more times since I started the test		
I notice my hand shakes when I try to write		
I feel an increasing awareness of my bodily sensations		
It seems I'm spending longer than I should on each of these questions		

Appendix 3 QOR-40

Modified Quality of Recovery Survey: MQoR-40 Study Patient Number: _____
Date of Surgery: ___ / ___ / ___

How have you been feeling in the last 24 hours? (please circle one)

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COMFORT					
Able to breathe easily	1	2	3	4	5
Have had a good sleep	1	2	3	4	5
Able to enjoy food	1	2	3	4	5
Feel rested	1	2	3	4	5
EMOTIONS					
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Had bad dreams	5	4	3	2	1
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Feeling angry	5	4	3	2	1
Feeling depressed	5	4	3	2	1
Feeling alone	5	4	3	2	1
Had difficulty falling asleep	5	4	3	2	1
PATIENT SUPPORT					
Feeling Confused	5	4	3	2	1

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Please check that all questions have been answered.

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Date: ___ / ___ / ___ Time: _____ AM / PM