Study Title: The effect of an opioid-free anesthetic on post-operative opioid consumption after laparoscopic bariatric surgery: a prospective, single-blinded, randomized controlled trial.

Principal Investigator: Christine Oryhan, MD

Co-Investigators:
Joseph Strunk, MD
Josiah Perez, MD
Lily Chang, MD
Mohan Mallipeddi, MD
Nam Nguyen, MD
Shanley Deal, MD
Angela Hirsh, MD

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A. Specific Aims

To test the hypothesis that an opioid-free anesthetic technique, compared with a more traditional opioid-based technique for laparoscopic gastric bypass surgery, decreases 24 hour post-operative opioid consumption. We propose a study of 196 subjects randomized into two groups. The control group will receive a traditional opioid restrictive general anesthetic. The study group will receive an opioid-free anesthetic technique.

B. Background & Significance

- Obese patients may be sensitive to the respiratory depressant effect of opioids and more likely to require non-invasive ventilatory support to avoid hypoxic episodes. Furthermore, bariatric surgery patients are at high risk for post-operative nausea and vomiting.
- Opioid-related adverse events increase treatment costs, length of stay, and readmission rates.
- Studies have demonstrated benefits of various opioid-free and opioid-sparing techniques on post-operative pain control and opioid requirements. However, many study protocols have utilized high intraoperative opioids, which does not reflect our current practice at

Virginia Mason. We are trying to compare an opioid-free technique to a more traditional opioid-based technique that reflects our relatively more restrictive intraoperative opioid administration.[1,2]

- Data suggests that 6% of all opioid naive patients who are discharged with a prescription for opioids are still using opioids 1 year after surgery.[3,4]
- Few studies have looked at how anesthetic technique can affect the development of persistent post-operative pain, which is difficult and expensive to treat. None of these studies, to our knowledge, have specifically looked into the possibility of an opioid-free anesthetic technique influencing the incidence of persistent post-operative pain in the bariatric surgery population.

C. Preliminary Studies

This study will be the first of its kind to be carried out at Virginia Mason Medical Center. The principal investigator is Dr. Christine Oryhan, a staff anesthesiologist and pain physician, who has considerable knowledge in the evolving topic of opioid-free anesthesia.

D. Research Design and Methods (including data analysis)

Patient selection:
We plan to enroll 196 subjects at VMMC that are undergoing laparoscopic bariatric surgery. Patients who volunteer to be involved in our study will be randomized to either the opioid free or traditional anesthetic arm, with a computer generated arm assignment. They will be blinded from which arm they are randomized to. Group A will receive a traditional opioid restrictive general anesthetic and group B will receive an opioid-free anesthetic technique.

Data will be recorded on human subjects as part of their preoperative workup, the perioperative period, and routine postoperative follow-up as far as three months after surgery. Preoperatively, we will gather routine data on patient age, sex, BMI, and smoking status. We will also gather information from each patient's preoperative routine psychological assessment, including history of depression, history of anxiety, history of substance abuse, PHQ-9 score, and GAD-7 score. Additionally, we will gather information on baseline pain score in patient's abdomen. Perioperatively, we will gather data on ASA classification, type of surgery performed, duration of general anesthesia, volume of intraoperative fluids given, estimated blood loss, duration of PACU stay, intraoperative and PACU hemodynamic modulating medication requirements, lowest intraoperative heart rate, intraoperative and postoperative opioid and antiemetic requirements, hospital length of stay, numeric pain rating scale pain scores, postoperative oxygen requirements, and any complications. After discharge from the hospital, we will gather data taken from the 30-day follow-up phone call, and 3-month follow-up clinic visit that are already part of routine care. These data include Emergency Department visits for abdominal pain, any surgical complications, opioid medication refills, abdominal pain scores, and characteristics of any ongoing opioid use. Patients will be blinded from which anesthetic technique is utilized for the patient's care. All surgical ward nurses, clinic nurses making follow-up phone calls, and bariatric surgeons will be able to identify which patient received with type of

anesthetic care. All of the above data will be recorded and subsequently abstracted from the electronic medical record (EMR).

Subjects will only be enrolled to the study when laparoscopic surgery is planned, as stated in the inclusion criteria. In the event the decision is made intraoperatively for conversion of laparoscopic surgery to open, these subjects will remain on the trial and remaining follow-up data will be collected, however, they will be excluded from the main study group analysis. The anesthetic plan after conversion to open will then be at the discretion of the anesthesiology team.

Statistical Sample Size Calculation:
In order to demonstrate a 40% reduction in 24 hour opioid consumption based on clinical relevance, we first analyzed the typical postoperative opioid consumption from a sample of patients who underwent laparoscopic bariatric surgery at Virginia Mason Hospital in 2018. We found that the mean opioid use in MED for the first 24 hours following laparoscopic bariatric surgery was 134.4mg, with a standard deviation of 106.9mg. Using these numbers, with a significance level of 5% and a power of 90%, our required sample size is 83 subjects per group. We plan on recruiting 98 per group (196 total) to account for inter-subject variability and drop out (15%).

Procedure:
Control Group A- Opioid-based regimen:

- Preop:
    - Multimodals unless contraindicated (i.e. APAP oral sol & gabapentin)
    - Scopolamine patch
- Induction
    - Fentanyl (50mcg IV)
    - Lidocaine 1.5mg/kg IV bolus using IBW
    - Propofol 2-3mg/kg IV bolus
    - Neuromuscular blockade per Anesthesiology team discretion
- Maintenance
    - Sevoflurane
    - Neuromuscular blockade at the discretion of anesthesiology team
    - May use fentanyl to treat SBP or HR > 20% of baseline
- Emergence
    - Neuromuscular reversal, dosed according to VM protocol
    - May titrate fentanyl per anesthesiology team throughout the case
    - Pt extubated and brought to PACU
- PACU opioid orders per anesthesiology team
- PONV Prophylaxis
    - 4mg dexamethasone, 1mg haloperidol, Scopolamine patch

Experimental Group B- Opioid-free regimen:

- Preop:

    - Multimodals unless contraindicated (i.e. APAP oral sol & gabapentin)
    - Scopolamine patch
- Induction:
    - Dexmedetomidine 1mcg/kg IV bolus over 10 minutes using IBW
    - Lidocaine 1.5mg/kg IV bolus using IBW
    - Propofol 2-3mg/kg IV bolus
    - Neuromuscular blockade per Anesthesiology team discretion
    - Ketamine 0.5mg/kg IV bolus (based on IBW)
- Maintenance
    - Sevoflurane
    - Dexmedetomidine 0.4 mcg/kg/hr IV infusion using IBW (may titrate based on patient response between 0.3-0.5mcg/kg/hr)
    - Lidocaine 2mg/kg/hr IV infusion using IBW
    - May use esmolol as needed to treat SBP or HR > 20% of baseline
    - Neuromuscular blockade at the discretion of anesthesiology team
- Emergence
    - Dexmedetomidine infusion turned off during laparoscopic desufflation
    - Lidocaine infusion turned off at skin closure
    - Neuromuscular reversal, dosed according to VM protocol
    - Pt extubated and brought to PACU
- PACU opioid orders per anesthesiology team
- PONV Prophylaxis
    - 4mg dexamethasone*,* 1mg haloperidol, Scopolamine patch

This is a prospective, single-center, single-blinded, randomized controlled trial comparing the effect of an opioid-free general anesthetic versus a traditional anesthetic with a restricted quantity of opioid on postoperative pain following laparoscopic bariatric surgery. Our primary outcome will be 24-hour opioid consumption after surgery. Secondary outcomes include: numeric pain scores, time from induction to emergence, opioid-related side effects (nausea, vomiting, pruritus, and respiratory depression), time to diet advancement to full liquid diet, time to first bowel movement, 30-day and 3 month pain scores and opioid requirements, cost to OR Pharmacy, time from arrival to PACU to “ready for PACU discharge”, length of hospital stay, 30 day opioid prescription refills after surgery, patient satisfaction, lowest intraoperative heart rate, and intraoperative and postoperative treatment of bradycardia and hypotension.

E. Protection of Human Subjects

1. Risks to the subjects:
    a. Human Subject involvement and characteristics
        i. Human subjects will undergo general anesthesia for elective laparoscopic bariatric surgery according to one of two study protocols
        ii. Human subjects will be adults ≥18 years old, undergoing elective laparoscopic bariatric surgery at Virginia Mason Medical Center, as

deemed appropriate by our bariatric surgeons. We anticipate enrolling 196 human subjects in this study, including patients with ASA class I-III.

2. Consent:
    a. Subjects may provide written consent in surgery clinic after a discussion with their bariatric surgeon. They may also be contacted by telephone prior to the day of surgery by one of the investigators. They will also receive additional explanation and be given the opportunity to provide written consent on the day of surgery if not obtained prior.
    b. Subjects may also be consented over the phone and sign the informed consent form electronically via DocuSign. Their surgeon or one of the investigators will contact the subject by telephone prior to the patient's scheduled surgery. The surgeon and/or investigator will go over the consent, giving detailed description of the study, the procedures to be followed and the risks and benefits of participation. The subject will have adequate time to address any questions or concerns regarding the consent. The subject will then be able to give documented consent. The person obtaining consent will document the consent process in the subject's chart. A copy of the signed consent form will be available to the patient via the DocuSign website.

3. Inclusion/Exclusion Criteria
    a. Inclusion criteria: Adult (≥18 years old) patients undergoing planned elective laparoscopic gastric bariatric surgery (i.e. laparoscopic roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy), able to provide informed consent.
    b. Exclusion criteria: Any opioid use within 4 weeks prior to surgery, chronic antiemetic use, hypersensitivity or contraindication to any study drug, ASA class IV, , patients unable to provide post-operative pain scores, pregnancy or lactating, <18 years old, refusal or inability to provide informed consent.
    c. Ethnic / Racial Category: Will not be assessed.

4. Sources of Materials:
    a. All research material obtained from living humans involved in the project will be collected as they normally would according to current standard work at Virginia Mason's Bariatric Surgery Program. During initial surgical consultation and any other necessary preoperative clinic visits, patients will undergo routine laboratory workup. This will include a blood draw, from which we will measure, as a part of normal standard of care, patient HbA1c.
    b. Data will be recorded on human subjects as part of their preoperative workup, the perioperative period, and routine postoperative follow-up as far as three months after surgery. Specific data to be collected is listed under section D.
    c. All blood samples, records, and data will be collected as part of standard of care at Virginia Mason.
    d. Limited PHI linking the subject to the data will be maintained to assure source documentation is accurate and study is conducted per protocol and regulations.

No data will be linked directly to the subject and the randomization envelope will contain a unique study subject number. Access to collected data will be limited to key study personnel. All data will be kept on password protected computers.

5. Potential Risks:
    a. There are risks associated with any general anesthetic. Side effects can occur with different medications. All of the below listed medications involved in the general anesthetic techniques are commonly used in surgical patients intraoperatively, subjects will not have an undue burden of risk associated with their participation in this study. Risks associated with dexmedetomidine use include bradycardia and hypotension requiring pharmacologic treatment, transient hypertension during loading, atrial fibrillation, sinus arrest, nausea, and fever. The dexmedetomidine as an adjuvant during surgery is an “off label,” but well-established use. Additional risks associated with lidocaine include CNS effects (tinnitus, perioral tingling, metallic taste, restlessness, vertigo, and seizures), and cardiovascular effects (hypotension, PR prolongation, QRS widening, and dysrhythmias). Additional risks associated with ketamine include delirium, diplopia, nystagmus, tachycardia, hypertension, hypersalivation, nausea, vomiting, nightmares, and hallucinations. However these risks occur at anesthetic doses, and only subanesthetic doses will be used during this study. Risks associated with intraoperative opioids include postoperative nausea and vomiting, delirium, delayed return of bowel function and respiratory depression.

6. Adequacy Of Protection Against Risks
    a. Recruitment and Informed Consent: Potential study participants will be asked by the bariatric surgeon if they would like to be involved in the study during their preoperative visit, whether it be initial consultation or any subsequent preoperative visit. If time allows, the surgeon themselves will discuss the study, and obtain informed consent. If clinic time does not allow, then patients will be given an information packet containing details of the planned study, and will later receive a phone call during which informed consent can be obtained. If this is the case, then all informed consent will be documented on the day of surgery. The investigators will answer any questions the subjects have.
    b. Protection against Risk: All data will be recorded and abstracted from the electronic medical record. As such, this data will be protected by all HIPPA rules. All abstracted data will be coded and recorded in password protected spreadsheets on the Virginia Mason Medical Center G-Drive. This plan should be as effective at minimizing risks to confidentiality as the electronic medical record and Virginia Mason server themselves. Even if our data on the G-drive is breached, the data will be de-identified to the degree that no persons or sensitive information should be identifiable.
    c. Subjects will have access to any and all medical care if an adverse event were to occur. We can ensure necessary medical or professional intervention in the event of adverse effects to the subjects.

7. Potential Benefits Of the Proposed Research To The Subjects And Others
    a. This study has the potential to help answer important questions regarding post-operative pain control, decreasing postoperative opioid consumption, and modulating the incidence of persistent postoperative pain in our bariatric surgery patients. Namely, we can potentially demonstrate our hypothesis that an opioid-free anesthetic helps decrease postoperative opioid consumption and the incidence of persistent postoperative pain. The bariatric surgery population is being specifically studied in the case because as it currently stands, they are most accurately being tracked with excellent postoperative follow-up.
    b. We believe the risks are reasonable in relation to the anticipated benefits because prior studies have already demonstrated the safety profile of the drugs as administered during a general anesthetic. Furthermore, all of the study drugs in our treatment arm will be administered in relatively low doses, and are already part of standard of care at other institutions[1]. Patients in the experimental treatment arm will also benefit from avoiding known adverse side effects of intraoperative opioids, as outlined above.

8. Importance Of The Knowledge To Be Gained
    a. This study aims to provide an evidence-based strategy for reducing postoperative opioid consumption, which has important implications in the setting of our national opioid epidemic. Additionally, our study hopes to provide a cost-analysis of this strategy, now that dexmedetomidine is available in generic forms.

9. Subject Safety And Minimizing Risks
    a. All risks pertinent to this study design are anticipated to be encountered in the intraoperative and immediate postoperative period, during which all study participants will be directly cared for by an anesthesiologist, anesthesiology resident, nurse anesthetist, and/or PACU nurse. Intraoperatively, all vital signs including heart rate and blood pressure will be monitored continuously throughout the duration of the operation in accordance with American Society of Anesthesiology standards. All episodes of bradycardia and/or hypotension will be treated appropriately and the treatment recorded in the anesthetic record. Postoperatively, patient vital signs, mental status, pain, and nausea will all be continuously monitored by PACU nurses as part of standard of care. All assessments and treatments will be recorded in the electronic medical record.
    b. Study endpoints regarding these risks will include intraoperative and postoperative blood pressure and heart rate, and any pharmacologic interventions made to maintain hemodynamic stability (MAP > 65mmHg and heart rate/MAP no greater than 20% above baseline before induction).

10. Quality Assurance - Site Monitoring
    a. An independent review of the records will be conducted by the Benaroya Research Institute's Regulatory Compliance and Education Department. The

Compliance Department shall assist the investigator(s) in the maintenance of complete, accurate, legible, and well-organized clinical study data. In addition the study monitors will explain, interpret, and ensure the investigator's continued understanding of all applicable regulations concerning the proper execution of the protocol and the investigator's reporting responsibilities. The data collection forms will be monitored periodically for accuracy, completeness, and adherence to the protocol, regulatory compliance, and the maintenance of comprehensive clinical records. These data will be checked against medical records to verify completeness and accuracy.

11. Audit and Inspection
    a. Internal quality audits may be performed pre-, throughout or post-study by the Compliance Department. Furthermore, the Investigator agrees to inform the Regulatory Compliance Department immediately of any known or suspected inspection by authorities and agrees to provide access to the required subject records and other study documentation.

12. Data Collection
    a. All records associated with the study will be maintained for approximately 10-15 years. Those documents may include the following:
        i. Subject files including the completed data collection form, supporting source documentation and the informed consent.
        ii. The protocol with all amendments, the investigator brochure or package insert (if applicable),
        iii. Copies of all regulatory documentation, e.g., Delegation of Authority Log,
        iv. All correspondence with the IRB, Scientific Merit, Data Safety Monitoring and regulatory authority.
        v. The database and any statistical analyses conducted for the study.

13. Subject Confidentiality
    a. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SID's only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the OHRP or designee.

14. Institutional Review Board
    a. Institutional Review Board (IRB) Review and Informed Consent: This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the BRI IRB. A signed consent form will be obtained from each subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the signed consent form will be given to the subject.

b. Study Modifications/Discontinuation: The study may be modified or discontinued at any time by the IRB, Sponsor, OHRP, FDA, or other Government agencies, as part of their duties to ensure that research subjects are protected.
c. Adherence to Protocol: Revisions to the protocol will only be made when changes have been approved by the principal investigator, sponsor and regulatory authority, as applicable. Changes must also be approved by the IRB of record, preferably, before implementation unless subject safety is at risk. Protocol deviations (minor items that do not impact subject safety or data integrity) will be avoided, but if necessary, they should be approved by the principal investigator and acknowledged by the IRB of record prior to their occurrence. If consistent deviations are noted, the PI will determine if a preventative action plan is necessary, working or whether another solution will be sought. Protocol violations (impact subject safety or data integrity) should be avoided, but if they occur, must be reported to the PI within 24-48 hours of learning of the event. Prompt reporting to the IRB of record is also mandatory.

F. Reference/Literature Citations

1. Mauermann E, Ruppen W, Bandschapp O. Different protocols used today to achieve total opioid-free general anesthesia without locoregional blocks. Best Pract Res Clin Anesthesiol 2017;31:533-45.
2. Hoehn RS, Seitz AP, Singer KE, et al. Enhanced recovery protocol for laparoscopic sleeve gastrectomy: Are narcotics necessary? J Gastrointest Surg 2019 Jan 28; epub ahead of print.
3. Raebel MA, Newcomer SR, Bayliss EA, et al. Chronic opioid use emerging after bariatric surgery. Pharmacoepidemiology and Drug Safety 2014;23:1247-1257.
4. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surg. 2017;152(6):e170504.

G. Consultants

All investigators work in the Department of Anesthesiology or Department of Surgery at Virginia Mason Medical Center and will be actively involved in subject recruitment, study design, and analysis.

H. Facilities Available

Following the standard work at VMMC, all general anesthetics will be performed in the operating room at Virginia Mason Medical Center.

J. Appendix- none