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Protocol Title: The Effect of Liposomal Bupivacaine on Post Operative Pain and Narcotic Use After Bariatric Surgery

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Synopsis:

This study is prospective, randomized trial in which the efficacy of liposomal bupivacaine (Exparel®) is compared to standard bupivacaine local surgical site injection in reducing total IV and oral morphine equivalents required after laparoscopic bariatric surgery. Exparel® is a 72-hour bupivacaine that is FDA approved for surgical site infiltration and is slowly released from tissue over the course of three days. Having a long acting local anesthetic should provide better pain control than conventional bupivacaine which has a 3.5-hour half-life. Currently, standard surgical site infiltration in laparoscopic bariatric surgery includes bupivacaine but not Exparel®. In some studies, the use of liposomal bupivacaine has been shown to decrease pain and narcotic use after surgery. This has not yet been studied in bariatric patients and the use of liposomal bupivacaine can potentially improve patient post-operative pain control, decrease narcotic use, decrease hospital length of stay and readmission rates and improve patient satisfaction after bariatric surgery.

Hypothesis:

Surgical site infiltration of liposomal bupivacaine compared to standard bupivacaine will reduce in hospital total oral and IV morphine equivalents required after laparoscopic bariatric surgery.

Background:

Although recovery after laparoscopy is brief compared to open laparotomy, pain control from port site incisions can remain challenging. Postoperative pain often involves narcotics and can lead to side effects of nausea, altered gastrointestinal motility such constipation, and potential addiction. Brummett et al found around 6% rate of chronic opioid use after major and minor surgery despite being opioid naïve prior to surgery[1]. In bariatric patients, there is a paucity of literature regarding pain control. Budiansky et al. suggest for patients with morbid obesity that pain management cannot adhere to standard protocols which generally includes administration of opioids. Drugs are typically dosed to weight however the distribution of lean and adipose tissue of a patient with morbid obesity will change the clearance and effect of common medications. In addition, physiologic changes and other co-morbidities relating to obesity including obstructive sleep apnea can limit typical pain regimens or even augment the potential side effects [2]. Minimizing the use of narcotics in bariatric patients is beneficial even in those with chronic opioid use. Bariatric patients with chronic opioid use have an increased prevalence of opioid use several years after bariatric surgery[3]. Therefore, prevention of opioid use after surgery by optimizing intraoperative and postoperative pain control is beneficial.

Currently, standard local injections of bupivacaine at port sites are performed during laparoscopic bariatric surgery. New techniques such as intrathecal opioid administration, bupivacaine continuous catheter infusions or continuous intravenous infusion of dexmedetomidine have been described [4-6]. Recently, the beneficial use of liposomal bupivacaine in pain control has been described in laparoscopic and open colorectal, gynecological and orthopedic surgeries. Exparel® is a 72-hour slowly releasing bupivacaine that is FDA approved for surgical site infiltration. The use of

liposomal bupivacaine in local surgical site injection has been studied in non-bariatric surgeries in improving patient post-operative pain control and decreasing length of hospital stay and improving patient satisfaction [7-9]. However, benefits of liposomal bupivacaine have not been studied in bariatric patients before and not currently routinely used in bariatric surgery.
Liposomal bupivacaine is distributed in a 20 ml single use vial of 13.3 mg/ml of bupivacaine. The Bupivacaine is encapsulated by liposomes and is slowly released from tissues up to 96 hours after injection. Conventional bupivacaine when injected, has a 3.5-hour half-life. When liposomal bupivacaine is combined with bupivacaine, short acting and long acting pain analgesia is provided. Standard post-operative pain control includes patient controlled analgesia and oral narcotics and oral narcotics for discharge. Inadequate pain control has been shown to prolonged recovery, increased narcotic use, and longer hospital stays [10].

Purpose of study:

The purpose of this study is to test the efficacy of liposomal bupivacaine injections compared to standard bupivacaine local surgical site injection in reducing total IV and oral morphine equivalents required after laparoscopic bariatric surgery.
With better pain control, we expect a better recovery, with less narcotic requirements, decreasing hospital length of stay and readmission rates and ultimately patient satisfaction from surgery. Use of liposomal bupivacaine is not standard in bariatric laparoscopic surgeries and can change practice to discontinuing PCA use and decrease or eliminate use of narcotics postoperatively.

Design of Study:

Prospective, double blind- randomized controlled clinical trial.

Sample Size:

Approximately 200 patients (100 patients in each arm) are expected to participate in the study. These patients are those that have fulfilled NIH criteria and met preoperative requirements for bariatric surgery. Surgeries and hospital care will be at Fresno Heart and Surgical Hospital (FHSH). Post-operative visits will be at Advanced Laparoscopic Surgical Associates (ALSA).
Methodology used to determine sample size: Utilizing existing data, an estimate was made as to the magnitude of benefit that could be expected for the parameters of interest. Using these estimates, a power analysis was performed to determine the number of patients that would need to be present in each arm for a statistically significant difference at 95% confidence level. Next the estimate of the benefit was reduced to come with the actual number of patients for the study.

Patient Population: Exclusion and Inclusion Criteria

Gender of subjects:
Population breakdown is expected to be similar to that seen in the adult population seeking bariatric surgery.

Age of subjects:

Adults ≥18 years and <65 years.

Racial and ethnic origin:
Population breakdown is expected to be similar to that seen in the adult population seeking bariatric surgery. Patients not able to understand or read English will be excluded.

Inclusion criteria:
- All patients undergoing elective laparoscopic sleeve gastrectomy or Roux-en-Y gastric bypass surgeries.

Exclusion criteria:
- Patients deemed not a candidate for laparoscopic bariatric surgery
- Patients with previous bariatric or gastric surgeries.
- BMI <35 and > 60 kg/m2
- Preoperative inability to ambulate and confined to wheelchair.
- American Society of Anesthesiologist (ASA) score >3
- Not able to understand informed consent, or unwilling to sign consent.
- Not able to understand and read English
- Currently pregnant or lactating.
- Age <18 or >65
- Patients intolerant of opiates, NSAIDS, acetaminophen or local anesthetics.
- Patients requiring opiate use within 30 days prior to time of surgery.
- Patients with reported use of narcotics greater than 2 weeks in preceding year before surgery.
- Patients with history of substance abuse, alcohol addiction
- Patients with diagnosis of chronic pain, history of fibromyalgia, chronic regional pain syndrome (dystrophic pain syndrome).
- Bupivacaine use within 96 hours before operation
- Prisoners
- Patients with renal failure or hepatic failure.

Intraoperative Exclusion criteria:
- Bariatric surgery operation >3 hours.
- More than 5 laparoscopic incision sites used during surgery, conversion to open operation, placement of a feeding tube or drain.
- Concurrent ventral hernia repair, large hiatal hernia repair or intraoperative extensive lysis of adhesions
- Concurrent cholecystectomy, subtotal gastrectomy, or fundoplication

Study Methods and Procedures:

Treatment Arm: Liposomal bupivacaine 20mL of injectable saline diluted with 60 ml of 0.25% Marcaine and 20 ml of saline for a total of 100 ml. After induction of anesthesia, the patients will receive a 20 ml mixture locally infiltrated at each trocar incision site (5 sites).

- Other names: Exparel®

Control Arm: 60 milliliters (ml) of 0.25% bupivacaine diluted with 40 ml of saline for a total of 100 ml. After induction of anesthesia, the patients will receive 20 ml mixture locally infiltrated at each trocar incision site (5 sites).

- Other Names: Marcaine

Patients who have been deemed appropriate candidates for elective bariatric surgery specifically laparoscopic Roux-en-Y gastric bypass (RYGB) or vertical sleeve gastrectomy (VSG) with Dr. Kelvin Higa, Dr. Keith Boone, Dr. Daniel Swartz, Dr. Ariel Shuchleib Cung, Dr. Ikemefuna Akusoba, and Dr. Pearl Ma (sub-investigators and principal investigator) will be offered participation in the study. These patients have already met preoperative qualifications and workup for bariatric surgery. There are no advertisements to recruit patients for the study. The patients will be introduced to the study and be offered participation at the preoperative visit which occurs within a week of their planned scheduled elective surgery. No additional laboratory testing or imaging will be required to participate in the study.

In the pre-operative office visit prior to surgery, the clinical investigators or sub investigators will inform the patient of the opportunity to participate in the research study. The clinical investigators or sub investigators will consent the patient at the preoperative visit.
The patients will undergo standard enhanced recovery after surgery (ERAS) protocol which has a standard preoperative and postoperative pain protocol.

Randomization:
If the patient chooses to participate, they will be randomized to 2 arms of either liposomal bupivacaine also known as Exparel® group, or bupivacaine only group on the day of surgery before anesthesia induction in the operating room.
The randomization will be in a 1:1 ratio. The patient and operating surgeon will not be notified which arm the patient is in. The randomization will be done by choosing an envelope in a stack that is previously randomized in a 1:1 ratio by computer program generator. The card in the envelope will state the assigned treatment arm. This will be relayed only to the operating room surgical tech. The randomized card will have an attached patient label and be placed into a locked container for later retrieval by study coordinator and entered into database by end of the operating day. The study coordinator will have access to decode each patient in the study for medical necessity.

The operating room surgical techs and nurses will then prepare the medications and cover the syringes containing the medications with colored sterile tape. Surgical techs and nurses responsible for preparing the medications will verify the medications and doses with one another before covering the syringe with sterile tape. This will impede the surgeon from guessing medication type as liposomal bupivacaine is slightly opaque. All syringes and containers containing study medications will be labeled appropriately with either 1.3% bupivacaine and/or 0.25% bupivacaine and normal saline.
The Surgical techs and nurses will announce the medications as “study medications” when delivered to the surgeon and during “Time-Out” procedures. This is in compliance

with CMC Operating Room Policy and Procedure Number 11142.

Once medications are mixed and placed into masked syringes, the surgeon may enter the operating room. At the beginning of the surgery, the patient will be administered local surgical site injections of the assigned medications.
A total of 100 milliliters (mL) mixture of either liposomal bupivacaine (Exparel®) mixed with bupivacaine and saline or bupivacaine mixed with saline will be injected into the surgical incision site at the beginning of surgery. Each surgical site will receive 20 ml of the medication mixture. If in the treatment arm, they will receive 20mL of liposomal bupivacaine diluted with 60 ml of 0.25% Marcaine and 20 ml of saline for a total of 100 ml. If in the bupivacaine only (control) arm, they will receive 60 ml of 0.25% bupivacaine diluted with 40 ml of saline for a total of 100 ml. Dosing is within safety parameters as confirmed with FHSH pharmacy (See attached letter). Additional intraoperative exclusion criteria is outlined above and study coordinator will track patients based on EMR data.

As part of routine post-operative care, the patient will be taken to the recovery unit (PACU) after the operation. The recovery room staff and nursing floor staff, and remaining clinical team not present during randomization in the operating room will be blinded to the type of local anesthetic given. The clinical team including residents, fellows, and remaining surgeons including sub investigator will primarily manage the patient's post-operative care including pain and nausea medications under standard routine ERAS protocol. Management of additional pain and nausea medications will be routinely determined by the non-operating surgeon (other sub-investigators). All patients in the study will receive a standard CMC patient identification wristband and Exparel wristband with warning printed that they should not receive additional bupivacaine for 96 hours after the operation. A study contact number will be added to Exparel wristband for non-Fresno Heart clinicians to call if additional pain medications are to be administered. Per CMC guidelines, Exparel wristbands are not required to be placed as a medical precaution. They have routinely been placed to aid in identifying patients who have received Exparel to aid in ERAS protocols. If patients require return to the operating room within 96 hours after the operation, then liposomal bupivacaine without additional bupivacaine will be administered and study coordinator will be notified of the event.

After discharge, patients will receive a questionnaire to rate daily pain score, daily nausea score, and number of narcotics taken each day. At the first post-operative visit (generally around post-operative day 7), they will be seen by a clinical investigator to review medications, questionnaires, and if any complications relating to surgery or medications administered. Questionnaires and patient journals pertaining to the study will only be limited up until the first post-operative visit.

Patients will be followed as part of standard post-operative bariatric surgery protocol where visits in the office will occur one week post operatively, three weeks post operatively, then routinely every 3-4 months afterwards routinely or more often depending patient routine needs after bariatric surgery**.** Routinely, patients are then

seen annually in the office as part of their routine health care. There are no additional follow up requirements because patients were involved in the study.

Data will then be analyzed to determine if liposomal bupivacaine has decreased number of total morphine equivalents and has a beneficial effect on surgical care, post-operative nausea, hospital length of stay and readmissions.

Data Collection:

Patient demographics, medical history, medications, use of narcotic pain medication within 30 days of surgery, hospital course and post-operative course including narcotics, antiemetic use, complications relating to bariatric surgery, follow up compliance, and weight loss after surgery.

1. Daily assessments while in hospital:
    a. Analog pain score (rating scale from 0 to 10 with 0 being no pain and 10 being the worst possible pain on numeric pain intensity scale
    b. Total IV and oral morphine equivalents administered including use of patient controlled analgesia and breakthrough narcotics.
    c. Presence of nausea and antiemetic medications administered.
2. Hospital course:
    a. Length of stay, complications requiring interventions or reoperations relating to bariatric surgery, readmission.
3. Immediate post-discharge follow-up:
    a. Analog pain score (rating scale from 0 to 10 with 0 being no pain and 10 being the worst possible pain on numeric pain intensity scale with patient documenting daily pain scores.
    b. Daily documentation of number of prescription narcotics taken.
    c. First post-operative visit questionnaire review of pain score, nausea score, and daily requirement of narcotics.
    d. Assessment of operative complications.

Study Procedures

There are no research-related procedures to be performed on patients consenting for participation in this research study other than the various tests and procedures performed per protocol for the evaluation and care of patients with higher BMI undergoing gastric bypass surgery in the program.

Risks of Study Medications:

Bupivacaine:

Likely (>20%) risks of bupivacaine injection during surgery: none reported

Less Likely (10-20%) risks of bupivacaine injection during surgery: none reported

Rare but Serious (<10%) risks of bupivacaine injection during surgery:

- The common adverse reactions can occur (incidence greater than or equal to 2% to less than 10%) following administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.
- Nervous system toxicity includes restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness
- Cardiovascular toxicity includes arrhythmias, heart blocks, decreased myocardial (heart) contractions, low blood pressures and potential cardiac arrest.
- Allergic-type reactions are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptoms (including severe hypotension).
- Patients with liver disease may be at higher risk for developing toxicities as the medication is cleared by the liver.
- The less common/rare adverse reactions (incidence less than 2%) following administration were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, hyperhidrosis, cold sweat, urticaria, bradycardia, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.

Liposomal bupivacaine 266 mg/20 ml:

Likely (>20%) risks of liposomal bupivacaine injection during surgery: none reported

Less Likely (10-20%) liposomal risks of bupivacaine injection during surgery: none reported

Rare but Serious (<10%) risks of liposomal bupivacaine injection during surgery:

- The most common side effects were nausea, constipation, and vomiting.
- The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia

postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

- The less common/rare adverse reactions (incidence less than 2%) following administration were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, hyperhidrosis, cold sweat, urticaria, bradycardia, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.
- Nervous system toxicity includes restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness
- Cardiovascular toxicity includes depressed cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure

Statistical Analysis:

Descriptive statistics will be performed on all patients and the demographic data will be examined and compared. Poisson Regression, student's t-test, and non-parametric testing will be used for the analysis of continuous variables. Chi-square analysis will be used for categorical data.

This interventional study is designed to test the null hypothesis that the rate of morphine equivalent units utilized by patients who were administered liposomal bupivacaine (Exparel®) during a primary bariatric surgery is greater than or equal to the rate of patients who were administered Marcaine, versus the alternative hypothesis that the rate of morphine equivalent units utilized by liposomal bupivacaine (Exparel®) during patients is lower than that of bupivacaine only patients. Testing of this hypothesis will be performed for the time period of the inpatient stay, as well as for the period of 7-10 postoperative days.

The sample size selected for this study was chosen to allow for a power of 0.90, an alpha of 0.05, and the ability to detect a rate change of as low as 10% or a 11 unit difference in average daily morphine equivalent units utilized. NCSS/PASS was the statistical software package used for the sample size calculations.

A combination of NCSS and RStudio will be used for the statistical analysis of this study.

Data Safety Monitoring and Reporting Plan:

Analysis: An interim analysis of results shall be performed at midpoint of the study (100 patients randomized). The final analysis will be performed once 100 evaluable patients have been enrolled in the study.

The Primary Investigator or Study Coordinator will monitor the research clinical study in a manner consistent with the applicable health authority regulations and the clinical standards adopted by the investigators.
The scope of the Primary Investigator or designated Study Coordinator's responsibilities include:

- Working with each Investigator and office staff to assure that the protocol, responsibilities and record keeping requirements are understood prior to initiation of the study
- Maintaining close contact with the investigators concerning the progress of the study
- Monitoring the study progress on a regular basis, semi-annually or more frequently
- Handle data entry and/or analysis
- Report Adverse Events in a timely manner

The reporting and monitoring process will be assisted by the following tools:

- A Study Data File for each patient will be created to maintain the information for each patient enrolled in the study. It will include copy of signed/dated Informed Consents and any adverse event reports.
- All submitted clinical data will go through quality assurance review, data entry and statistical analysis.

A Data and Safety Monitor (DSM) will be designated as Julie Carlock, RN, CNOR, RNFA, CBN who will meet with study coordinator and Principal investigator following enrollment of 100 subjects and will have access to the de-identified data. The role of the DSM will be to:

- Evaluate the collected data for participant safety, study conduct and progress
- Make recommendations concerning continuation, modification, or termination of the trial.

The study may be stopped for one or more of the following reasons:

- Study aims met at the first analysis
- A finding of no significant differences between therapeutic groups
- The DSM determines there are significant safety issues

Confidentiality and Privacy:

Currently all data for patients undergoing bariatric surgery are kept confidential
The data will be collected from electronic medical records from Advanced Laparoscopic Surgical Associates (ALSA) surgical group and through EPIC.

Data Security:

All data will be maintained on a firewall and password protected shared drive maintained by investigators, sub investigators, and clinical staff. Patients assigned to randomized treatment group will have patient identifier label and entered into secure

database by study coordinator. Patient label and study assignment will be placed into a secure locked box and collected at end of each operating day. The information will be entered by the study coordinator or study staff and the patient label and randomization cards will be placed in secure CMC vendor approved shredding boxes immediately afterwards. This will be completed daily and by 1-2 assigned study staff who will maintain chain of custody of patient information. Patient questionnaires and dairies will also be collected and stored following HIPAA regulation and locked in secure room.

Data collection, information from patient diaries and questionnaires from ALSA and data collection from CMC electronic health records will be placed on password protected file on Fresno Heart and Surgical hospital server drive with limited rights access. All patient information will be de-identified prior to analysis. The data safety monitoring monitor (DSM) will meet (in person or via conference call) following enrollment of 100 subjects and will have access to only de-identified data.

All data collected during the study that contains any patient identifiers will be destroyed upon completing the publications relevant to this study. Data that is stored electronically will be erased from all electronic storage locations. Any paper records that are collected will be destroyed via shredding using a CMC approved vendor.

Transition from research participation:
All subjects will continue to receive standard of care.

Adverse Reaction and Adverse Event Reporting:
Throughout the course of the study, all efforts will be made to remain alert to possible adverse experiences or unanticipated findings. If adverse experiences occur, the first concern will be the safety and welfare of the patient, and appropriate medical intervention will be made. Any adverse reactions observed by the Investigator or reported by the patient, regardless of severity, will be recorded in the patient's case file and reported to the IRB.

Any patients who are discontinued from the study due to adverse experiences will be followed until their medical outcome is determined, and written reports will be provided to the IRB by the Investigator.

Funding Section:
No outside source of funding is available to support healthcare expenditures for patients participating in this research study. Coverage for health care expenditures will be sought from each patient's health insurance carrier as per current practice for bariatric. Liposomal bupivacaine (Exparel®) and bupivacaine are FDA approved medications for surgical site infiltration and are included in the bundled cost for bariatric surgery. No extra costs will be charged to the patient. There are no specific costs related to research and therefore no extra funding is required for participation in this study. No additional laboratory testing or imaging will be required to participate in the study. The

investigators and clinical staff involved in the study have no relevant financial disclosures to provide.

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