Cleveland Clinic

Research Protocol

Title of Proposed Project:

Bupivacaine liposomal injection (Exparel) for postsurgical analgesia in patients undergoing laparoscopic bariatric surgery: a randomized, double-blind, controlled trial

Amendment #1

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Principal Investigator (Name and Title): Dr. Philip R Schauer
Specialty: General Surgery - Bariatric and Metabolic Surgery
Institution/Organization: Cleveland Clinic, Ohio
Mailing Address: 9500 EUCLID AVE - M61
City/State/Zip Code: 44195
E-mail: Schauep@ccf.org
Phone: 216.444.4794
Fax: 216.445.1586

Co-Investigators (Name, Title and Institution):

Surgery Department:

Suriya Punchai, Research Fellow, Cleveland, Ohio
Zubaidah Nor Hanipah, Research Fellow, Cleveland Clinic, Ohio
Ali Aminian, Clinical Scholar, Cleveland Clinic, Ohio

Anesthesia Department:

Karen Steckner, Anesthesiologist, Cleveland Clinic, Ohio
Kamal Maheshwari, Anesthesiologist, Cleveland Clinic, Ohio

Introduction

Despite the increasing use of patient-controlled anesthesia (PCA) for postoperative pain management, efforts are continuing to find effective methods to relieve pain after abdominal surgery. [1-7] Some studies have already suggested that infusion with local anesthetics at the wound site can decrease postoperative pain levels.[2-5] Further, other studies have shown equal amounts of opiate analgesic requirements (administered on patient demand) with placebo and local anesthetic administration.[3-5] However, varying anesthetic administration techniques used in the different studies may explain why the controversy in the literature exists.[1-16]

Although opioid is an effective analgesic but it has opioid related adverse events (ORAEs). Bupivacaine should reduce postoperative pain but it has relatively shorter duration of action. Liposome bupivacaine

(Exparel) has been approved as a single dose infiltration for longer postoperative period analgesic. It provides up to 72 hours analgesia postoperatively; results in lesser opioids usage and reduce the ORAEs.[17]

Transversus abdominis plane (TAP) block is a relatively new regional anesthetic technique that targets blockage of the neural afferent of the lower intercostal, iliohypogastric and ilioinguinal nerves in the neurovascular plane between the internal oblique and the transversus abdominis muscle. TAP blocks have been performed to reduce opioid use and control pain in several laparoscopic surgical procedures, including colorectal resections, cholecystectomy and bariatric surgery.[18]

Efficacy of wound infiltration with or without TAP block using immediate-release bupivacaine HCl for acute postsurgical pain is well established; EXPAREL has been proposed as a method for postoperative pain management. [17-18] Moreover, the administration and the optimal dosage in the bariatric surgical population have not been studied.

The objective of this study is to examine postoperative pain after laparoscopic gastric bypass with TAP block and port sites infiltration using Exparel versus Bupivacaine

Background and significance

Exparel is a FDA approved long-acting, local anesthetic. This is for single-dose infiltration into the surgical site to produce postsurgical analgesia. Exparel offers longer-acting local formulation and can be administered as a single dose.[19] Exparel has a longer duration of action with slower absorption. The mean elimination half-life of local administration of Exparel is approximately 24-34 hours[19-20] versus 2.7 hours for bupivacaine.

Liposomal bupivacaine is for single-dose infiltration and the recommended dose depends on the surgical site but the maximum dose of liposomal bupivacaine is 266 mg and it is injected into soft tissues of the surgical site with frequent aspirations to prevent intravascular injection.

A pooled analysis evaluating the effect of Exparel on pain intensity scores and opioid consumption was published by Dasta et al[21]. This study included 5 surgical procedures (inguinal hernia repair, total knee replacement, hemorrhoidectomy, breast augmentation and bunionectomy) comparing Exparel with bupivacaine HCl, on 912 patients; it showed significantly lower pain score and opioid usage, delayed use of rescue opioid and reduced ORAEs in the Exparel group; as compared to bupivacaine HCL group. *Medication Safet*Liposomal bupivacaine has been classified as a high-alert medication by the Institute of Safe Medication Practices due to its similar appearance to propofol. If liposomal bupivacaine were administered intravenously as if it were propofol, adverse cardiac effects may result. Exparel is available as 13.3 mg/mL (1.3%) solution in a 20-mL single-use vial. It should be refrigerated but may be stored at room temperature for up to 30 days in sealed, unopened vials. Vials should not be re-refrigerated. It can be administered undiluted or diluted up to 0.89 mg/mL (1:14) with preservative-free normal (0.9%) saline for injection.

Hypothesis

Exparel (1.3%) and 0.5% Bupivacaine usage with infiltration and TAP block decreases opiate usage, nausea and pain at 48 hours as compared to 0.5% Bupivacaine only.

Primary Objective of the study:

To study the opiate usage, pain and nausea post laparoscopic gastric bypass or sleeve gastrectomy using EXPAREL versus Bupivacaine as TAP block and port sites infiltration.

Type of study

This study will be a *double-blind Randomized Controlled Trial*.

Inclusion and exclusion criteria

Patients at our Bariatric Surgery Center of Excellence fulfilling NIH criteria for bariatric surgery and planned operation of laparoscopic Roux-en Y gastric bypass (LRYGB) or laparoscopic sleeve gastrectomy (LSG) as primary bariatric procedure will be evaluated for possible inclusion.

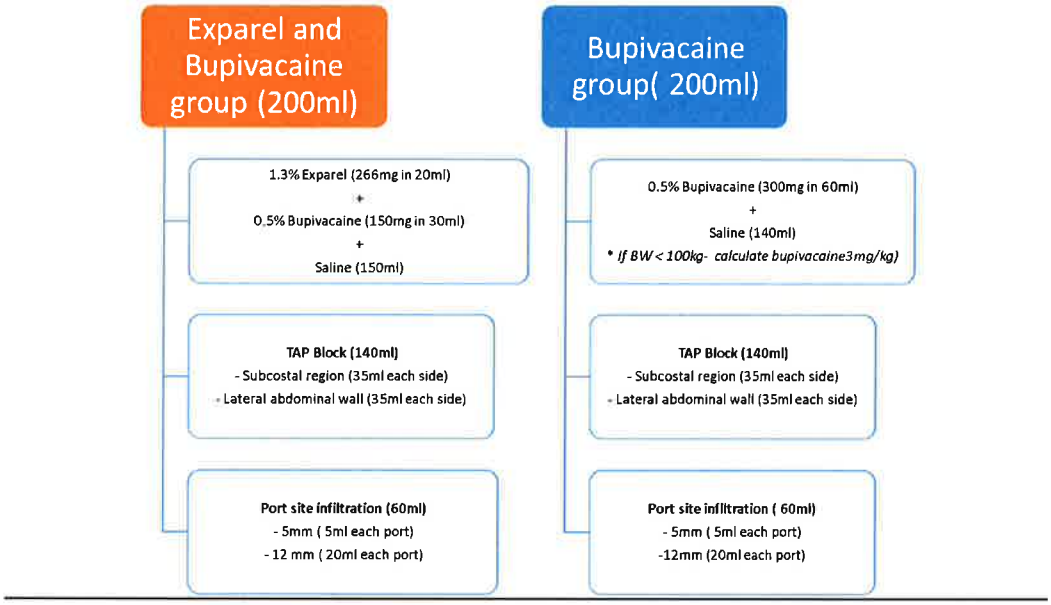
Exclusion criteria include:

1- age <18 or >65
2- BMI <35 and > 60 kg/m^2
3- Inability to walk (bed-bound or wheelchair dependence)
4- previous major abdominal surgery (possible adhesions and longer operation) defined as:
    a. open abdominal surgeries except simple appendectomy and common OB/GYN procedures in the pelvis (hysterectomy, C-section, and oophorectomy, tubal ligation)
    b. laparoscopic bowel or solid organ resection except laparoscopic cholecystectomy
    c. ventral hernia repair with mesh
5- preoperative chronic opiate use for chronic pain defined as opiate usage at least 60 mg/day of morphine equivalent for ≥ 3 months (as defined by *International Association for the Study of Pain*[22]) in the one year period prior to the bariatric surgery
6- the American Society of Anesthesiologists (ASA) score > 3
7- history of hypersensitivity or adverse reaction to bupivacaine or narcotics
8- inability to speak English
9- Concurrent surgical procedure including:
    a. ventral hernia repair
    b. Cholecystectomy
    c. hiatal hernia repair with posterior cruroplasty
    d. extensive lysis of adhesions
    e. other procedures that mandate addition of "trocar(s)" or "feeding tube"
10- Conversion of surgery to hand-assisted or open
11- Intraoperative major complications such as bleeding (> 250ml of blood loss) or leak

Enrollment

After IRB approval, 100 consecutive patients will be enrolled prospectively. Informed consent will be obtained in English in preoperative outpatient visit at bariatric clinic. 100 patients will be randomly assigned into 2 study groups in a double-blinded method. A computer-generated randomization list will be made to assign subjects to their groups. Both the patient and those investigators who assess outcomes are blinded to the study group assignment. The randomization will be allocated to each patient before starting the surgery. Throughout the study, the list is concealed from investigators.

Surgical technique



6 trocars are placed to perform LRYGB or LSG: two 12 mm trocars and four 5 mm trocars. Either Exparel or Bupivacaine will be injected at port sites. For standardization of the technique, we consider the following details:

1-We will use

- ***"60ml of 0.5% Bupivacaine + 140 ml of Saline" for control arm***
- ***"20 ml of 1.3% Exparel + 30 ml of 0.5% Bupivacaine + 150 ml of Saline" for experimental arm***

2-Above Local anesthetics have a similar total volume of *200 ml* for each patient (diluted by normal saline)

3-We will use 16G spinal needles for administration of local anesthetics

4-All the solution will be injected at the beginning of the surgery

5-Port site infiltration:

By multiple injections, we make a circular bulge (with a diameter of 2 cm) around each port site. Infiltrate with either EXPAREL or Bupivacaine:

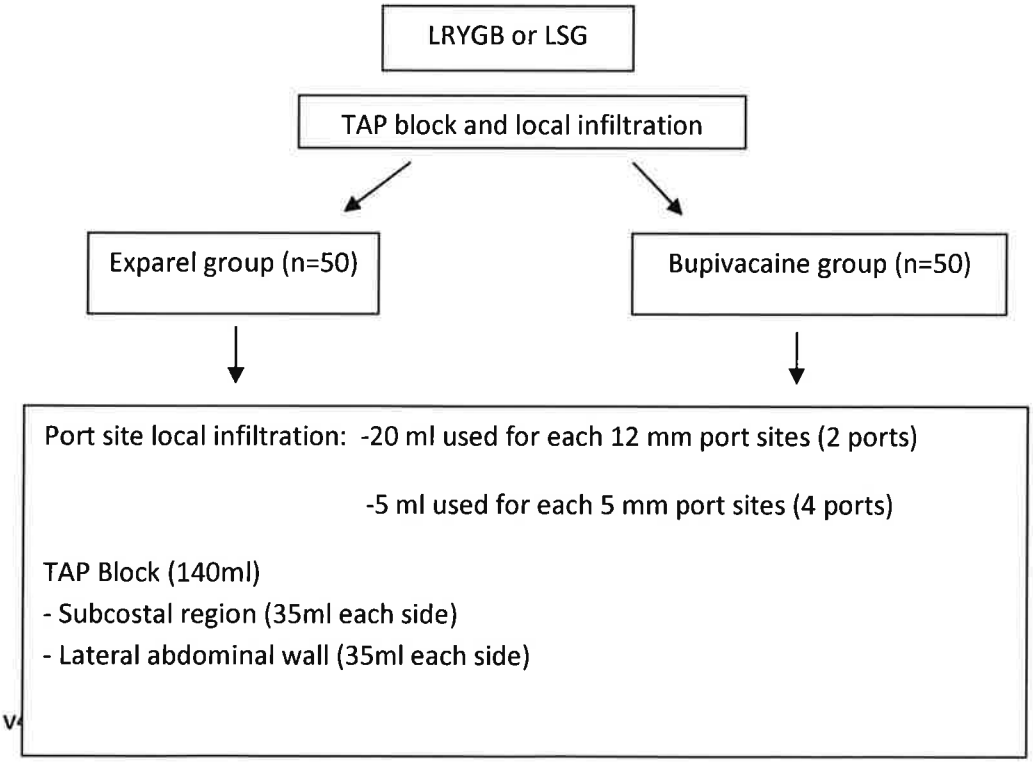
- 20 ml of infiltration will be used for each 12 mm port site.
- 5 ml of infiltration will be used for each 5 mm port site.

6- TAP block:

The TAP blocks [18] will be performed with laparoscopic guidance just after pneumoperitoneum is created. A 35 ml of either Exparel or Bupivacaine solution will be infiltrated at both sides along the anterior axillary line up to the iliac crest and also both sides of the subcostal region in the TAP plane. An insulated needle [16G spinal needle] will be passed through the skin and then continued until two distinct "pops" are felt. These "pops" indicated that the needle had passed through each of the two fascial layers (the external oblique and internal oblique aponeurosis) leaving the needle between the internal oblique and the transversus abdominis muscles. The laparoscope will be used to confirm that the needle tip is not subperitoneal. If the injection is in the correct plane, a smooth bulge could be seen raised by the fluid, with the injectate covered by the transversus abdominis. The procedure will be performed at both sides of the abdomen.

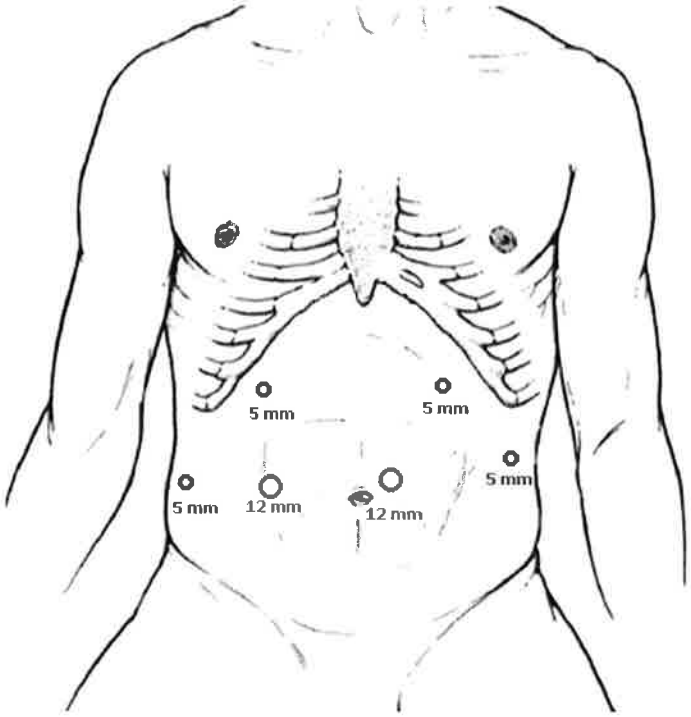
TAP block with either EXPAREL or Bupivacaine:

- 35 ml will be used at each subcostal and at lateral abdomen at both side of the abdomen.



Exparel v

LRYGB or LSG
Port Sites Illustration



Anesthesia Protocol

All patients will be pre-medicated with oral or intravenous midazolam as necessary. Patients will be monitored according to standards (ECG, noninvasive blood pressure, oxygen saturation, temperature). An arterial line will be placed if clinically indicated. If clinically indicated, a central venous catheter will be inserted.

Anesthetic management will be standardized. Etomidate (0.2-0.3 mg/kg) or propofol (1-2 mg/kg), rocuronium (0.6 mg/kg), and fentanyl (1-2 μg/kg) will be used for induction. Anesthesia subsequently will be maintained with sevoflurane (up to 1.5 MAC) in a carrier gas of 50-80% inspired oxygen and air. Sevoflurane administration will be adjusted by the attending anesthesiologists with the goal of maintaining arterial blood pressure within 20% more or less of baseline values.

Fentanyl will be administered according to patient's requirements. Additional muscle relaxant will be given as necessary to maintain 1-2 mechanical twitches in response to supra-maximal stimulation (Train-of-four stimulation) of the ulnar nerve at the wrist. Ventilation will be mechanically controlled to maintain end-tidal carbon dioxide tension near 35 mmHg. Tidal volume will be set between 8 and 10 ml per kilogram lean body weight to keep the peak inspiratory pressure below 30 mmHg and a positive end expiratory pressure of 5 mmHg or higher according to patient's requirements will be administered. Temperature will be monitored, and normothermia (core temperature > 36 degrees Celsius) will be maintained with forced-air warming.

Postoperative pain management

The pain management will be using the multimodal pain regimen as below:

Preoperative (1-2 hours prior to surgery):

1. Tylenol 1000 mg PO
2. Celebrex 400 mg PO unless patient has chronic kidney disease (CKD) or coronary artery disease
3. Gabapentin 600 mg PO

Intraoperative:

1. Decadron upon induction unless the patient is diabetic

Postoperative (starting form POD 0):

1. Scheduled Tylenol 650 mg PO q6h
2. Scheduled Toradol 15 mg IV q6h unless CKD or acute kidney injury (AKI) or surgeon discretion
3. Oxycodone elixir (Roxicodone) 5-10 mg PO q4h PRN pain
4. Dilaudid 0.5 mg IV q4h PRN breakthrough pain

All administered medications will be recorded (inpatient medications by the nurses, and outpatient usage by the patient). In case of drug allergies/intolerance to either dilaudid or oxycodone, an appropriate alternative will be used.

Outcome variables

Demographic and baseline variables:

1- Age
2- Gender
3- BMI
4- Weight
5- ASA class

6- Operation time
7- Anesthesia time

Dependent variables:

1- Cumulative postoperative opiate requirements at 48 hours **[Primary outcome]**
2- Pain score (NRS), early postop in the recovery unit
3- Highest Pain score (NRS) per shift both *at rest and during movement* (10 meter of walking distance)every 8 hours during hospitalization and at 1 week
4- Nausea score (NRS) per shift every 8 hours during hospitalization.
5- Cumulative opiate requirements in the first week after discharge.
6- OBAS Score (The overall benefit of analgesic questionnaire) obtained on POD 1 and every day while in the hospital.
7- Q Quality of life score using SDS survey [24] (post op day 1, post-op visit at 1 week and 30 days)
8- Number of antiemetic administration in the hospital for Postoperative nausea vomiting (PONV)
9- Postop complication including postoperative nausea and vomiting and required antiemetic administration, cardiopulmonary complications, wound complications (e.g., infection, hematoma), systemic toxicity from regional anesthetics
10- Post-operative ORAEs (constipation, pyrexia, dizziness, pruritus, headache, peripheral edema, insomnia, muscle spasm, back pain, pain in extremity, chills, hypoesthesia, tachycardia, hypotension, anemia, hypokalemia)
11-

Outcome Assessment

Pain and nausea scores are measured every 8 hours using a standard Numerical Rating Scale (NRS) until discharge. A rating of 10 indicated the most severe pain and a rating of 0 indicated no pain. A blinded nurse will instruct subjects to rate their pain. The total amount of narcotics used will be recorded from the nurse chart. Daily assessment of common postoperative symptoms is performed and included postoperative nausea and vomiting and required antiemetic administration, cardiopulmonary complications, wound complications (e.g., infection, hematoma), systemic toxicity from regional anesthetics and length of hospital stay. Wound complications will be assessed in the first clinic visit in 7-10 days.

Sample size calculation

Assuming an 80% power for the study (β=0.20), a type I error at 5% (α=0.05), we hypothesize our effect size to be at least a 20% reduction in the opioid usage in the Exparel arm compared to the control arm. The chosen effect size is a conservative estimate when looking at the data from the article by Dasta et al.[21] where an effect size of 25% reduction in opioid use was demonstrated when Exparel was used compared to the bupivacaine alone.

A sample of patients who underwent a routine primary LRYGB or LSG at the Cleveland clinic and received only the bupivacaine were used to generate the mean and standard deviation for the morphine equivalent usage of narcotic analgesia postoperatively (161.01 ± 63.03mg). Given the above a priori values, the sample size needed for each arm is estimated to be 43. Moreover, we plan to have at least 50 patients in each arm, to account for the attrition rate.

Confidentiality of data

The data obtained will be stored on a RED Cap database developed by the PI, research fellows, and the bariatric research support staff at the Cleveland Clinic. Only researchers listed on the protocol will have access to the data. The data provided to investigators outside of the protocol will be provided without identifying information in order to protect the patient's identity and remain de-identified. The data will be maintained throughout the approved duration of the project. If personnel changes occur before the completion of this study, data will remain secure and encrypted and transferred to the care of the PI.

Human subjects, adverse events, and data monitoring committee

The adverse events and unanticipated problems related to the procedural interventions (i.e. injection of liposomal bupivacaine) will be reviewed by the principal and co-investigators. Any event or problem that has not been previously reported will be reported to the IRB immediately. Any event that has been reported but is more severe will be reported immediately to the IRB. A DMC is not planned for the study.

The patient will be asked to notify the physician and/or research nurse of any side effects, adverse effects, and unanticipated problems. They will be encouraged to call to report these. Patients will also be seen several times postoperatively. An interim analysis will also be performed after ½ of the patients have completed their follow up.

The IRB will be notified of adverse events that are serious, unexpected, related or possibly related to participation in the study. We will also report any adverse events that, regardless of severity, may warrant review and revision of the study protocol. Deaths will be reported to the IRB as per IRB institution policy.

Consent

As patients are evaluated for possible inclusion and subsequently meet the criteria for the study. The written consent will be obtained in the bariatric surgery clinic during the preoperative visit. There should be no vulnerable subjects in this study. Please see proposed consent document.

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