Liposomal Bupivacaine Versus 0.25% Bupivacaine Hydrochloride for Postoperative Analgesia After Breast Reduction Surgery: A Prospective, Single Blind, Non-randomized Controlled Trial

NCT05891613

23May2023

Liposomal (Exparel) Bupivacaine versus 0.25% Bupivacaine Hydrochloride for Postoperative Analgesia after Breast Reduction Surgery: A Prospective, Single Blind, Non-Randomized Controlled Trial

Breast reduction is a common procedure in plastic surgery that provides symptomatic relief to patients, improves body image, and offers high satisfaction rates. In the United State, according to the American Society of Plastic Surgeons procedure report, 46,340 breast reductions were performed in 2019. (1) Like with other procedures such as thyroid surgery and mastectomy, which were previously required admission to the hospital, there has been a recent trend towards performing breast reduction procedures as a true outpatient or with 24-hour observation. (2) Advances in anesthetic techniques, pre-incision tumescent solution infiltration into the breasts to reduce blood loss, and infusion of local anesthetics with longer half-lives reduce the need for postoperative intravenous analgesia.

Pain has been reported to affect up to 50% of woman undergoing breast surgery. (3) A recent systematic review demonstrated the effectiveness of locoregional anesthesia in reducing pain in the first hour following mastectomy. (3) However, sustained pain control following breast reduction is needed to lower post-operative opioids use and their related adverse effects, increase patient satisfaction scores, reduce hospital admission rates and associated costs. (3)

Liposomal (Exparel) bupivacaine has been advocated to improve post-operative analgesia in plastic surgical procedures. (4) Approved by the U.S. Food and Drug Administration in 2011, liposomal bupivacaine, by design, may provide up to 72 hours of analgesia after a single injection. Systemic plasma levels can persist for 96 hours after administered locally, and 120 hours after administered into the brachial plexus for an interscalene nerve block. Exparel peaks twice. The initial peak is at one hour and the second peak occurs at 12 to 36 hours. Exparel is 95% protein-bound and is metabolized primarily via hepatic conjugation, therefore it should be administered cautiously to patients with hepatic disease. It is excreted via the urine. The elimination half-life is 13-34 hours.

Initial studies have shown it to be superior to conventional bupivacaine in reducing postoperative opioid use, opioid-related adverse effects, and pain scores in patients undergoing breast augmentation, total knee arthroplasty, inguinal hernia repair, hemorrhoidectomy, and bunionectomy. (5)

A recent Cochrane review of 9 studies demonstrated a benefit in liposomal (Exparel) bupivacaine compared to placebo in lowering cumulative pain score between the end of the operation (0 hours) and 72 hours (one study). Compared to bupivacaine hydrochloride, two studies showed no difference for this outcome, however due to differences in the surgical population and surgical procedure (breast augmentation versus knee arthroplasty) a meta-analysis was not performed. (6)

A recent prospective randomized controlled single-blinded trial of wound infiltration with liposomal (Exparel) bupivacaine plus 0.25% bupivacaine (study arm) vs 0.25% bupivacaine (control arm) at a National Cancer Institute-designated tertiary referral cancer center showed that adding liposomal (Exparel) bupivacaine to 0.25% bupivacaine wound infiltration did not decrease the proportion of patients who were opioid-free within 48 hours after surgery. (7) Also,

the addition of liposomal (Exparel) Bupivacaine to 0.25% Bupivacaine did not decrease opioid intake, improve patient's self-reported pain and functional recovery compared with standard bupivacaine. (7)

Similar results were demonstrated in a prospective randomized double-blind trial using bupivacaine vs. liposomal (Exparel) bupivacaine in 30 for patients undergoing augmentation mammoplasty. Although there was a statistically significant decrease in postoperative pain with the use of liposomal (Exparel) bupivacaine, this did not translate to an appreciable clinical benefit that justified the additional cost (bupivacaine costs $1.15 per 20 cc of product vs liposomal (Exparel) bupivacaine, which costs $285 per 20 cc of product). However, one limitation in that study was the instillation of medication into the implant pocket rather than infiltration of the medication into the wound.

In our practice, some consultants feel strongly about the benefit of liposomal (Exparel) bupivacaine for post-operative analgesia whereas others don't feel that the costs associated with this medication warrant its use. Given the fact that there is approximately a 100-fold cost difference between liposomal (Exparel) bupivacaine and standard 0.25% bupivacaine, our goal is to investigate whether, in fact, there is an added benefit to liposomal (Exparel) bupivacaine over 0.25% bupivacaine in our patients undergoing breast reduction surgery. This will help in standardization of practices and provide evidence for or against the routine use of liposomal (Exparel) bupivacaine in breast reduction procedures.

Treatment Group (Total of 42 patients):
This is a prospective, multi-surgeon, single blind, non-randomized, controlled trial with breasts allocated to two parallel groups: A mixture of liposomal (Exparel) bupivacaine with plain 0.25% bupivacaine hydrochloride will be used on one side (Treatment side) as local infiltration, and plain 0.25% bupivacaine hydrochloride will be used in the other side. The doses of medication proposed, and study design is based on input from Mayo inpatient pharmacy and anesthesia.

Split breast treatment group (testing efficacy of Liposomal (Exparel) bupivacaine versus bupivacaine hydrochloride): each breast will serve as the control for the other. The study is designed to evaluate early postoperative pain control of each of the products up to 72 hours postoperatively. These treatments are standard of care in our clinical practice.

Informed consent will be obtained by the study team.

Inclusion Criteria:
Adult female patients (18-70 years old) with symptomatic macromastia scheduled for breast reduction using a Wise pattern incision design.

Exclusion Criteria:
Exclusion criteria include inability to provide informed consent, medical or surgical history precluding breast reduction, history of significant chronic pain requiring daily use of opioid or nonopioid analgesics, pregnancy, concomitant non-breast surgical procedure, previous chest wall irradiation, previous breast implant, breast reduction or breast lift surgery, known allergy to

bupivacaine or liposomal bupivacaine, liver or kidney dysfunction at the discretion of the treating investigator, use of antiplatelet or anticoagulation therapy.

The patient will be blinded to which type of local anesthetic was used on which side.

Patients undergoing surgery performed by the principial investigator (Dr. Basel Sharaf) or co-investigators (Dr. Bill Tran, Dr. Christen Harless, Dr. Jorys Martinez, Dr. Vahe Fahradyan, Dr. Aparna Vijayasekaran)

Primary Outcome:

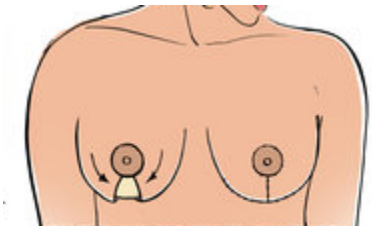
Does Liposomal (Exparel)+ Bupivacaine mix improve pain scores in the first 72 hours post-operatively following breast reduction more than Bupivacaine plain alone?

Methods:

Each patient will receive a total of 40 mL of injectable solution to ensure equal volume of infiltrate being used along the incisions.

Control Side: The control side will receive 20 ml of 0.25% bupivacaine (50 mg) with 20 ml of injectable saline (total of 40 cc) as a subcutaneous infiltration along the inframammary fold incision on one breast.

Treatment Side: The treatment side will receive a mixture of 20 ml of liposomal (Exparel) bupivacaine (266 mg/20 ml) with 20 ml of 0.25% bupivacaine (50 mg) on the **contralateral** side.



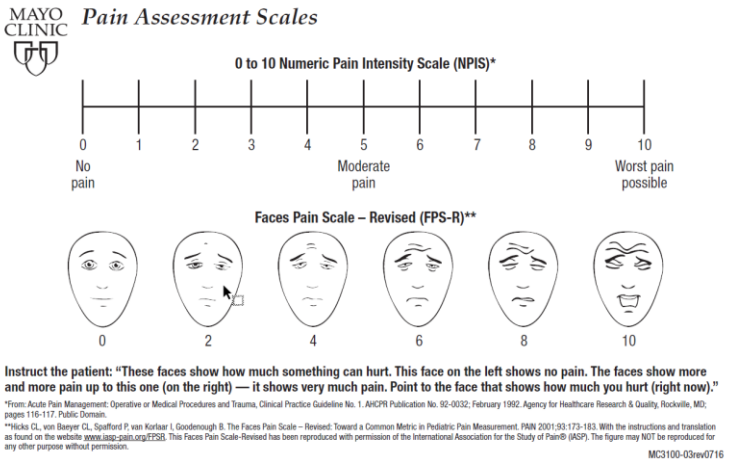
Liposomal (Exparel)/Plain Bupivacaine vs. Plain Bupivacaine

The reason for including bupivacaine plain on both sides is to ensure equal early post-op analgesia as Exparel is a controlled released medication with bimodal peak onset of action (1 hour and 12 hours). The 1 hour onset of Exparel is due to the 3% extra liposomal bupivacaine present in Exparel mixtures and is unlikely to be sufficient for early post-op analgesia. The consultant will perform or supervise the proper infiltration of these medications along the entire length of the incisions (Horizontal limb of Wise pattern and along the lateral chest wall) using a 22-gauge needle on a 20 cc syringe.

	Liposomal Exparel + Bupivacaine 40 ml	Bupivacaine + Saline 40 ml
Liposomal (Exparel) component	266 mg/20 mL	0 mL
Bupivacaine 0.25%	50mg/20 mL	50 mg/20 mL
Saline	0 mL	20 mL
Total volume	40 mL	40 mL

The maximum allowed dose of plain bupivacaine for infiltration is 2.5 mg/kg up to 175 mg, which is also the maximum dose for a 70 kg patient (i.e. 2.5 mg/kg = 175 mg). Liposomal (Exparel's) 266 mg is equivalent to 300 mg bupivacaine, but released predominately over the first 24-48 hours making an exact conversion to equivalent dose of plain Bupivacaine difficult. Based on the release kinetics of liposomal (Exparel) and what previous studies have used for comparator doses, the plain bupivacaine side will receive 50 mg. To ensure safety, we will preferentially use 50 mg of bupivacaine Plain on the contralateral size, which is our current practice. We have not experienced overdosing of these medications. To provide immediate analgesic effect on the Exparel side, we will also expand liposomal (Exparel) with additional plain bupivacaine, a practice that is already in use by several of our consultants in plastic surgery.

The study is designed to evaluate early postoperative pain control of each of the infiltrates up to 72 h postoperatively. On post-operative day 1, 2, and 3 each patient will be contacted by a clinical team member or a research team member to document pain level in each breast. The pain score for each side will be documented using the validated Numerical Pain Rating Scale (NPIS). (10)



The primary outcome is the cumulative post-operative 3-day pain scores on each treated side.

The pain score will be documented in the Redcap system twice per day, once in the am and once in the pm.

Our power analysis indicates that 25 subjects are necessary to achieve an expected power level >80%. This was calculated using the Power and Sample Size program from the Department of Biostatistics, Mayo Clinic. This was based on a beta value of 0.8 and a clinically significant difference in pain scores on a scale of 0-10 to be two points with a standard deviation of one.

Statistical Analysis:

Descriptive summaries will be reported as mean (standard deviation) or median (minimum, maximum) for continuous variables and using frequencies and percentages for categorical variables. The treatment group will receive intervention where one breast will be treated with Bupivacaine and other will be treated with Liposomal (Exparel) + Bupivacaine. This group will be referred as split breast treatment group. Within patient comparison of continuous ~~outcomes such as~~ pain ratings score over 72 hrs, between the breast treated with Bupivacaine Plain Vs. Liposomal (Exparel) + Bupivacaine among split breast treatment group will be performed using paired t-test or Wilcoxon signed rank test. Categorical outcomes such as complications (at a breast level) will be compared using McNemar's test as a test of paired proportions. For comparisons between the treated breasts, we will first take an average of pain ratings from both treated breast per patient within split breast treatment group. Statistical analysis will be performed using SAS version 9.4 software (SAS Inc. Cary, NC). All tests will be two sided and p-values <0.05 will be considered statistically significant.

Sample Size and Power Calculations:
This study includes paired comparison among the patients in split breast treatment group (i.e. comparison at a breast level). Sample size calculation reflects the within patient comparison of pain ratings between breasts Pain rating scale ranges from 0-10. Based on normal distribution assumption, we estimate the standard deviation to be approximately 1.67 (i.e. 10/6) units, if patients utilize the entire pain range of 10 points.

At a 5% level of significance, a standard deviation of 1.67 points, with a paired t test with 80% power and 24 patients enrolled, a difference in pain score of 1 point could be detected between treated breasts, within a patient. Accounting for a dropout rate of 40% we will enroll a total of 42 patients to this study.

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