**TITLE:** Vaginal Cuff infiltration with liposomal bupivacaine for pain relief: A double blind, randomized controlled trial

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## INTRODUCTION

Laparoscopic mode of surgery for full tubal ligation is preferred due to better cosmetic results, faster recovery and decrease in pain. The goal of treating pain at an earlier stage is to decrease opioid use and increase patient's satisfaction. Various modes of pain relief are used to achieve better quality of pain relief for enhanced post op recovery. These various options of pain control include pain medications that belong to different classes, and have different route of administration. The options include oral, intravenous, local and anesthetic analgesia. The local infiltration can be given intraoperatively that can provide pain relief in immediate post op period and decrease opioid usage that has side effects like nausea, constipation, dizziness and obstipation. Exparel is liposomal bupivacaine. Liposomal drug containing formulations provide controlled drug release over an extended period of time approximately 72 hours. Few studies have been done that show decrease in pain score and opioid use with paracervical block and uterosacral ligament infiltration. There is only one study done in which vaginal cuff infiltration was performed with Ropivacaine. Our hypothesis is that vaginal cuff infiltration with Exparel (bupivacaine with liposome) will decrease post op pain score, and opioid use. The primary outcome will be NRS score assessment at predetermined times in post op recovery unit and at home with pain diary. Secondary outcome will be amount of opioid use, operative time, weight of specimen, method of extraction, EBL and any other complications.

## STUDY OBJECTIVES

The goal of the study is to access whether 10 ml Exparel (liposomal bupivacaine) used with 10 ml bupivacaine decreases pain in comparison with just 20 ml of bupivacaine if given into the vaginal cuff right before making the incision in vaginal cuff in the minimally invasive (robotic-assisted or laparoscopic) total hysterectomy. A reduction in pain after the surgery would result in decrease in opioid usage, fewer opioid-related adverse events, and increased satisfaction in patients.

## HYPOTHESIS

Our hypothesis is Exparel in vaginal cuff reduces postsurgical cumulative pain scores, reduces overall opioid consumption, increases the proportion of patients who will not receive opioids, delays time to first opioid rescue dose, and will be associated with significantly higher rates of patient satisfaction compared with placebo.

## STUDY DESIGN

We are basing the design of our study on Kilpio et al. and Radke et al. studies. It will be a double blind, placebo based, randomized control Intervention arm (40) will get 10ml of Exparel diluted with 10 ml of bupivacaine around 2,4, 8 and 10 o' clock in vaginal cuff. Placebo group (40) will receive 20 ml of bupivacaine in vaginal cuff. A set supply of bupivacaine and exparel will be purchased from the Maimonides Medical Center Pharmacy. The Pharmacy will store the medications and distribute the drugs to study team on the day of procedure. All women >18 years age scheduled for Laparoscopic and robotic hysterectomies

with Bilateral salpingectomy or bilateral salpingo-oophorectomy will be assessed for eligibility. Women should have lab values that are not twice the upper normal limit, able to provide consent, follow up and complete all assessments and language-based questionnaires. All will be interviewed at preoperative visit and screened for eligibility.

**Subjects:**

**Eligibility Criteria:** Include inclusion and exclusion criteria.

Inclusion Criteria:
Any patient age > 18 years who is having minimally invasive robotic or laparoscopic total hysterectomy for any indication without any anesthetic block.

Exclusion criteria includes:

1) Use of any of the following medications within the times specified before surgery: a. opioid, SSRI, tricyclic antidepressant, gabapentin, pregabalin within three days of surgery. b. Use of acetaminophen within 24 hours of surgery
2) Concurrent painful physical condition or concurrent surgery that may require analgesic treatment (such as NSAID, opioid, SSRI, tricyclic antidepressant, gabapentin, pregabalin) in the postoperative period for pain that is not strictly related to the minimally invasive supracervical hysterectomy procedure and may confound the postoperative assessments (e.g., rheumatoid arthritis, chronic neuropathic pain.
3) Chronic user of analgesic medications, including taking opioid medications for more than 14 days in the last 3 months, or nonopioid pain medications more than 5 times per week.
4) Current use of systemic glucocorticosteroids (e.g. Decadron) or use of glucocorticoids within one month of enrollment into this study.
5) History of hepatitis (other than hepatitis A).
6) History of hypersensitivity or idiosyncratic reactions to amide type local anesthetics, opioids, or propofol.
7) Administration of an investigational drug within 30 days prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
8) Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, may interfere with study assessments or compliance.
9) Significant medical conditions or laboratory results that, in the opinion of the Investigator indicate an increased vulnerability to study drug and procedures, and expose subjects to an unreasonable risk as a result of participating in this clinical trial.
10) Any clinically significant event or condition uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postoperative course.
11) women with endometriosis

12) contraindications to any medication used in the study (acetaminophen, NSAID or opioid).

**Data Collection Procedures:**

The severity of pain will be assessed preoperatively in the holding area, at the time 1hr, 12, 24, 48 and 72hrs postoperatively using a VAS from 0 to 10 with 10 being the worst pain the patient has ever experienced. The first 3 assessments will be performed in the hospital by the principal investigators and the remaining assessments will happen through a phone conversation with the patient after discharge from hospital at the 72 hour mark. The VAS has been found to be a simple scale.
The data will also be collected through chart review and. this data will include age, VAS score reporting by nurses in PACU, BMI, previous abdominal surgery, previous vaginal delivery and parity.

Pain inquiries will assess low pelvic/suprapubic area and lower abdominal pain, type of pain (dull, achy, sharp, stabbing, etc.) and radiation of pain to a surrounding area. Other endpoints will include number of patients who required break through (additional) opioid analgesic medications, median time to first break through opioid use, total opioid analgesic requirement. The time, day and number of requests for break-through (additional) analgesia will be noted by gynecologic surgery team (Research assistant) participating in this study.

When the patient is home she will have a Pain Medication Diary, and VAS score sheet that we will provide for her prior to discharge. Patient will be contacted over phone to get the data from her log sheet.

Secondary outcome that will be assessed include total oxycodone use, operative time, weight of specimen, method of extraction, EBL and any other complications.

**Data Analysis:** Explain how data will be analyzed.

All analyses will be performed using SPSS software, version 20 (IBM SPSS Inc., IL, USA). Data will be presented as medians and interquartile ranges (IQRs) or n (%). Differences in continuous variables were analyzed using the Mann–Whitney U-test for skewed data. Chi-square or Fisher's exact tests were used for independent nominal data where appropriate. Statistical significance was defined as $p<0.05$. The 95% Confidence Interval (CI) for differences of proportions were calculated using Newcombe's method.

**Sample Size:** Explain sample size.
Previous studies have reported 40% reduction in VAS score and in absolute numbers pain decreased from 5.9-2.3. We are using 25% reduction is pain score, assuming VAS score 6 with

standard deviation of +/- 3 from previous studies. With decrease of 25% in pain score with 80% power and alpha of 0.05, we will need sample size of 70, but with dropout rate of 15% we will increase our sample size by 80.

1) If a subject experiences an adverse event that render her incapable of continuing with the remaining study assessments, a final evaluation visit will be performed, so that the subject's study participation could be terminated in a safe and orderly manner.
2) Subjects are free to discontinue from the study at any time, without prejudice to future treatment.
3) A subject may be discontinued from the study if she refuses either study drug administration or to comply with study procedures. Reasons for discontinuation from the study will be documented.
4) A subject could be discontinued from the study by the Investigator, if it was considered to be in the best interest of the subject. If the discontinuation
occurs after administration of the study drug, a final evaluation visit will be performed, so that the subject could be terminated in a safe and orderly
manner.
5) Participants who do not withdraw from study they will have their regular follow up visit their operating physician in 2 weeks of the procedure.
6) Participants who withdraw will need to have their regular 2 weeks post visit with their operating physician, but no data will be collected from them as they will be accounted for in the dropout group and the reason will be documented.

**Expected Outcomes:** Explain what you hope the study will determine.
Intervention group will have decrease in VAS Score than control group. Secondary outcome expected is decrease in opioid use in intervention group compared to placebo group.

## REFERENCES


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