Preemptive Local Analgesia with Liposomal Bupivacaine in Vaginal Hysterectomy: A Randomized Controlled Study

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Preemptive local analgesia with liposomal bupivacaine in vaginal hysterectomy: A randomized, blinded, controlled study

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INTRODUCTION

Reduction in immediate postsurgical pain is important as it results in less opioid requirements and fewer opioid-related adverse events such as central nervous system and respiratory depression, nausea, vomiting, ileus, and pruritus. Decreased postoperative pain may also result in shorter recovery room and hospital stays, and higher patient satisfaction.

Preemptive analgesia in form of uterosacral ligament injection has been shown to be effective for patients undergoing vaginal hysterectomy. Injection of bupivacaine into the uterosacral ligaments has been associated with significantly reduced pain scores in the first three hours after surgery as well as lower total narcotic use within the first 24 hours following surgery (1). Preemptive analgesia with bupivacaine during vaginal hysterectomy is standard practice at our institution as part of a multi-modal pain management platform.

Liposomal bupivacaine is a novel formation of local bupivacaine designed to provide prolonged postsurgical analgesia. The drug is encapsulated in multivesicular liposomes, thereby allowing prolonged drug release for up to 72 hours. Its safety and side effect profile is similar to bupivacaine HCl and normal saline (2). In 2011, the FDA approved of its use for single-dose local administration into surgical sites.

The efficacy of liposomal bupivacaine has been demonstrated in orthopedic procedures, hernia repairs, hemorrhoidectomy, and breast augmentation. When compared to bupivacaine HCl, studies suggest liposomal bupivacaine may be more efficacious in terms of lower pain scores, longer time to first rescue opioid dose, decreased total opioid consumption postoperatively, and shorter length of hospital stays (3).

There are few studies evaluating liposomal bupivacaine in gynecologic surgery. Hutchins et al demonstrated that patients who received transversus abdominis plane (TAP) blocks with liposomal bupivacaine required 50% less total opioid during the first 72 hours following robotic assisted hysterectomy than patients who received bupivacaine (4). While liposomal bupivacaine is promising for management of postoperative pain, it has not yet been studied in vaginal surgery.

The aim of this study is to compare the effects of preemptive analgesia using liposomal bupivacaine mixed with bupivacaine HCl, versus bupivacaine HCl alone for uterosacral ligament injection in patients undergoing vaginal hysterectomy. We hypothesize that the group receiving a combination of liposomal bupivacaine and bupivacaine HCl will report superior postoperative pain management. Enhancement in pain control should confer a decrease in opioid and other analgesic medication requirements, which may contribute to decreased nausea, vomiting, and higher overall patient satisfaction with pain control.

OBJECTIVES

The primary aim of this study is to compare total post-surgical analgesic medication use in the first 72 hours following surgery completion (all opioids in IV morphine equivalents and total mg use of ibuprofen and/or acetaminophen combined).

Secondary outcome measures include mean PACU VAS (0-10) pain score, VAS pain score at 24, 48, and 72 hours post-surgery completion, nausea and emesis at 24, 48, and 72 hours post-surgery completion, urinary retention, and patient satisfaction with pain management at 72 hours and 7-10 days post op.

DESIGN

This is a prospective randomized, blinded, controlled clinical trial.

STUDY MEDICATION

Liposomal bupivacaine is being used per FDA indication (postsurgical analgesia) at an approved dose and route of administration (surgical site infiltration). It is also being given within the FDA labeled doses of the bupivacaine HCl given concomitantly, which recommends mg dose of bupivacaine HCl to liposomal not to exceed 1:2. Safety and efficacy of concomitant use has been prospectively studied (5). This study does not intend to pursue change to labeling or advertising. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

PARTICIPANTS

We plan to enroll women 18-85 years old who will be undergoing outpatient vaginal hysterectomy with or without concurrent prolapse repair surgeries at the Mayo Clinic Hospital in Arizona. Participants will be recruited during the preoperative visit and consented with a written form.

Exclusion criteria will include:

- Known history of hepatic disease evidenced by AST or ALT greater than normal values
- Known history of renal disease evidenced by serum Cr greater than normal values
- Known history of prolonged QT ($QT_c >$ than 500 m/s)
- Opiate tolerance noted by daily use of greater than 20 mg morphine daily oral equivalents per day for minimum one month prior to surgery
- Allergy or contraindication to amide local anesthetics, celecoxib, ketorolac, NSAIDS, acetaminophen, gabapentin, sulfa drugs, or ondansetron. Patients allergic to both oxycodone and hydromorphone

- Patients with acute GI bleed in < 6 months of study
- Adults lacking capacity to consent

MATERIALS AND METHODS

Randomization and Blinding:

Redcap software will generate a randomization list in one-to-one ratio to assign patients to either the study group (receiving both liposomal bupivacaine and bupivacaine HCl) or control group (receiving bupivacaine only). All subjects will be recruited and assigned according to their priority at admission. The pharmacist will use this randomization list and dispense the medication sequentially. Patients, care team in recovery, study team members collecting and recording data, and statisticians will be blinded to randomization assignment. The surgical team and pharmacy will be un-blinded. All patients will be documented in EMR as receiving liposomal bupivacaine to ensure the blind is maintained and to ensure that safety features in the EMR for all patients receiving liposomal bupivacaine are activated.

TREATMENT GROUPS

Patients in both groups will be given a total volume of 40ml and dose of 100 mg plain bupivacaine:

- Patients in the study group will receive a mixture of 0.5% bupivacaine HCl and liposomal bupivacaine in 1:1 ratio. 10cc of the mixture will be injected bilaterally into each uterosacral ligament prior to the colpotomy incision. After entry into the posterior cul-de-sac, an additional 10cc will be injected bilaterally into the deeper uterosacral ligaments (diagram attached as appendix 3).

- Patients in the control group will receive 0.25% bupivacaine HCl. 10cc will be injected bilaterally into each uterosacral ligament prior to the colpotomy incision. After entry into the posterior cul-de-sac, an additional 10cc of will be injected bilaterally into the deeper uterosacral ligaments.

We plan to standardize preoperative medication, intraoperative anesthetic regimen, medication, administration in the recovery area, and discharge medication treatment (see appendix 1). Care will include key elements of a validated enhanced recovery protocol (6).

DATA COLLECTION

Demographic data including age, BMI, medical and surgical history, indication for surgery, and degree and type of pelvic organ prolapse will be collected.

Intraoperative fentanyl use will be recorded from the anesthesia record. Immediate postoperative opioid use will be retrieved from the EMR until discharge from PACU. Immediate nausea and emesis will be determined by total dose of antiemetics in PACU. Urinary retention will be determined as post void residual greater than 200 ml on catheterization or bladder scan. Patients will be offered PO opioid analgesics as first line therapy in PACU. Number and percentage of patients receiving intravenous opioids as second line therapy, thus failing PO as first line therapy in PACU will be recorded; however they will remain in the study.

Other intraoperative and immediate postoperative data will include completed procedure, surgery time, estimated blood loss, final pathology, and presence of failed voiding trial, length of stay in recovery, and numbers and reason for any unplanned admissions. Unplanned admission patients' data will be excluded and be recorded as a treatment failure.

All patients will be discharged home with a diary to record analgesic use, VAS pain scores, and presence of nausea and emesis through 72 hours post-surgery (POD 3). Opioid use will be documented as total tablets of 5 mg oxycodone, hydromorphone 2mg, and non-opioid medication use as total tablets of acetaminophen 500 mg and/or ibuprofen 600 mg. VAS (0-10) pain scores will be logged at 6 hour intervals. Nausea and emesis will be documented as how many times patients felt nauseated, how many times they vomited, and total tablets of anti-emetic. Patients will be emailed twice a day with a link to record their documented scores. Those who prefer not to complete the surveys electronically will have the option to complete the paper questionnaire and diary. Those choosing the paper option will receive a daily phone call from study personnel blinded to study groups to remind them to complete their diary and questionnaire. Patient satisfaction for pain control will be assessed as a 0-10 scale question at the 72 hour mark and again at 7 to 10 days postop via telephone.

Allergic reaction to liposomal bupivacaine and local anesthesia toxicity will be assessed immediately on presentation to PACU, prior to discharge, and assessed by telephone and documented up to the 7 to 10^{th} post-operative day. All doses of liposomal bupivacaine are within manufacturer labeling, and this is an FDA "on label" use of the drug (surgical site tissue infiltration). Concomitant bupivacaine HCl with liposomal bupivacaine doses are within manufacturer "on label" recommended ratio of 1:2. Intralipid 20% for local anesthetic toxicity treatment will be immediately available at all times prior to discharge. All data will be entered into HIPAA-compliant REDCap software.

SAMPLE SIZE

We plan to enroll and randomize 104 patients with the goal of obtaining complete data on at least 96 (47 per group) assuming a 10% loss to follow up. With a sample of 96, we achieve 80% power to detect a 30% difference in total opioid use at the 72 hour mark corresponding to an effect size of 0.6 at an alpha 0.05.

DATA ANALYSIS

Statistical summary descriptives such as mean, median, standard deviation, first quartile, third quartile and range for quantitative data, and frequency and proportions for categorical data will be provided. The objectives of the study comprise the group comparisons between combination liposomal bupivacaine/bupivacaine HCl vs. bupivacaine HCl only for total opioid use in morphine equivalents, total non-opioid use, VAS pain scores, episodes of emesis, total antiemetic use, and patient satisfaction. The normality assumptions will be checked and the appropriate parametric tests such as the two independent sample t-test or non-parametric tests such as the Wilcoxon rank sum test will be used. Group associations with categorical variables will be tested using the Chi-square or Fishers' exact test. The significance level is at 0.05.

SAFETY MONITORING

All patients will be continuously monitored for local anesthetic toxicity or other reaction to liposomal bupivacaine for the entire surgical scope of care. During surgery standard ASA monitors will be in place and in recovery vital signs every 15 minutes with continuous telemetry and pulse ox, with a minimum 2:1 RN monitoring. They will remain in recovery a minimum of 4 hours post op. Continuous surveillance for medication reaction or local anesthetic toxicity including but not limited to tinnitus, perioral numbness, mental status changes, cardiac arrhythmia, respiratory compromise, rash, or hives. 20% intralipid for treatment of toxicity will be available at all times. Patients will also be discharged with specific education regarding signs and symptoms for local anesthetic toxicity and instructions to call the on call physician with mild symptoms and present to the ED if moderate or severe symptoms.

ADVERSE EVENTS

The investigator/study team will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

An adverse event is defined as an untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject. All adverse events that are considered related to the direct use of liposomal bupivacaine will be defined, collected, and reported.

The principal investigator will be responsible for determining whether an event is related to the direct use of liposomal bupivacaine. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the standard of care procedure or in the package insert for liposomal bupivacaine.

All study-related AEs will be followed until stabilization or resolution.

ADVERSE EVENT REPORTING PERIOD

For this study, the study treatment follow-up period is defined as *7-10* days after the procedure when they are contacted by the study team.

MEDICAL MONITORING

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan Medical monitoring will include a regular assessment of the number and type of serious adverse events.

FUNDING

Pacira Pharmaceuticals, Inc. is funding the study. Pacira Pharmaceuticals, Inc. will pay the institution to cover costs related to running the study; however, they will have no role in randomization, patient care, assessment of data, or development of conclusions. Attempts will be made to publish the results independent of outcome, even for a negative study.

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APPENDIX I

DATA COLLECTION

I. Demographic data
   a. Age/date of birth
   b. BMI

II. Preoperative data
   a. Indication for surgery
   b. Medical history
   c. Surgical history

III. Operative data
   a. Surgery performed
   b. Operative time
   c. Pathologic diagnosis
   d. Total fentanyl dose in mcg during surgery
   e. Complications during surgery; anesthetic and surgical

IV. Immediate postoperative data (PACU until discharge)
   a. Total opioid use in mg morphine IV equivalents
   b. Antiemetic use as total doses IV antiemetics
   c. VAS pain scores: cumulative in PACU until discharge
   d. Urinary retention: determined as post void residual greater than 200 ml on catheterization or bladder scan.

V. Postoperative data to 72 hour (POD 3)
   a. Total opioid use in mg morphine IV equivalents
   b. Non-opioid medication use in total tablets of 600 mg ibuprofen and 500 mg acetaminophen
   c. VAS pain scores: mean of cumulative in PACU until discharge, day of discharge at home, 24 hours (POD 1), 48 hours (POD 2), 72 hours (POD 3). Home VAS scores will be mean of 6 hour intervals each day
   d. Times patients felt nauseated: day of discharge at home, 24 hours (POD 1), 48 hours (POD 2), 72 hours (POD 3).
   e. Episodes of emesis: day of discharge at home, 24 hours (POD 1), 48 hours (POD 2), 72 hours (POD 3).
   f. Antiemetic medication use: day of discharge at home, 24 hours (POD 1), 48 hours (POD 2), 72 hours (POD 3).
   g. Indication for admission (if applicable)
   h. Patient satisfaction with postoperative pain control (0-10; 0=unsatisfied, 10=very satisfied)
      i. 72 hours
      ii. 7-10 days post op

ANESTHESIA PROTOCOL

I. Preoperative:
   a. Up to 4 mg Midazolam at providers discretion on transport to OR
   b. Celecoxib 400mg PO (Gyn service order)
      i. For patients 18-64 years old
   c. Acetaminophen 1000mg PO (Gyn service order)
   d. Decadron 4mg (Gyn service order)
   e. Gabapentin 300-600mg PO (Gyn service order)
      i. For patients 18-59 years old, order 600mg
      ii. For patients 60-69 years old, order 300 mg
      iii. Do not give if >70 years old

II. Intraoperative:
   a. Study group: (OR nurse to retrieve, surgeon to inject)
      i. Mix 20cc 0.5% bupivacaine HCl and 20 cc liposomal bupivacaine in 1:1 ratio
      ii. Inject 10c of mixture into each uterosacral ligament prior to colpotomy
      iii. After entry into posterior cul-de-sac, inject additional 10cc of mixture into deeper uterosacral ligaments

iv. Total injection = 40 ml

b. Control group: (OR nurse to retrieve, surgeon to inject)
   i. Inject 10cc of 0.25% bupivacaine into each uterosacral ligament prior to colpotomy
   ii. After entry into posterior cul-de-sac, inject additional 10cc of 0.25% bupivacaine into deeper uterosacral ligaments bilaterally
   iii. Total injection = 40ml

c. Anesthesia:
   i. All patients will receive general endotracheal anesthesia
   ii. Induction with Fentanyl 1-2 mcg/kg, Propofol/lidocaine, succinylcholine/rocuronium
   iii. Maintenance with Sevoflurane in air oxygen mixture, and fentanyl prn to a case maximum of 400 mcg, no additional opioids
   iv. Background propofol infusion (25-75 mcg/kg/min)
   v. No ketamine
   vi. Prophylactic antibiotic prior to incision
   vii. Reversal at provider's discretion with glycopyrrolate/neostigmine, or sugammadex
   viii. Ketorolac 15mg IV during wound closure
   ix. Ondansetron 4mg IV during wound closure

III. Recovery:

a. PACU
   i. First line: IV Tylenol, PO Oxycodone 5-10 mg or PO hydromorphone 2 - 4 mg mild (VAS 0-4), moderate (5-6), or severe (7-10) pain (Gyn service order)
   ii. Second line: Fentanyl 25 mcg q 5 min prn to max of 200 mcg for severe pain (7-10) (Gyn service order)
   iii. Third line: hydromorphone 0.2 mg IV q 5 min to max of 2 mg for severe pain (7-10) refractory to fentanyl (Gyn service order)
   iv. Ondansetron 4 mg IV PRN up to 2 doses (Gyn service order)
   v. Promethazine 6.25 mg IV PRN one dose for refractory nausea up to 2 doses (Gyn service order)
   vi. May give other anti-emetics as needed.

b. Discharge Medications
   i. Acetaminophen 1000 (2 OTC 500 mg strength) mg Q8 hrs PRN mild (0-4) to moderate (5-6) pain

ii. Ibuprofen 600 (prescription 600 mg strength) mg Q8 hours PRN mild (0-4) to moderate (5-6) pain
iii. Oxycodone 5 or 10 mg Q4 hrs PRN for moderate (5-6) to severe (7-10) pain. Patients will be discharged with two prescriptions: the first to be filled for 10 tablets, the second for additional 20 tablets if needed.
iv. Hydromorphone 2 or 4 mg Q4 hrs PRN for moderate (5-6) to severe (7-10) pain. Patients will be discharged with two prescriptions: the first to be filled for 10 tablets, the second for additional 20 tablets if needed.
v. Ondansetron 4 mg PO Q6 hours PRN for nausea
vi. Prochlorperazine 10 mg PO Q8 hours PRN for nausea

APPENDIX 2