BIOMEDICAL RESEARCH PROTOCOL
UNIVERSITY OF MISSOURI

Project Title: A randomized controlled trial of the effect liposomal bupivacaine (Exparel) when compared to saline control in reducing opioid utilization for pain management in postoperative lumbar spine surgeries.
IRB Number: 2037544
Version Number: 3
Version Date: 04/25/2022
Principal Investigator: Theodore Choma, MD
Funding Source: TIGERS Grant – University of Missouri School of Medicine

Clinical Trial Phase: Phase IV
Clinicaltrials.gov Number: MCT04644796
Study Drug/Study Device: Liposomal Bupivacaine (Exparel)

I. Research Objectives/Background

1. Primary Objective:
    a. Establish a relationship between liposomal bupivacaine surgical site injection and postop opioid utilization.
2. Secondary Objectives:
    a. How does self-reported pain (11 point visual analog pain scale) differ in patients given liposomal bupivacaine compared to patients in the control group?
    b. Is there a difference in length of hospital stay between the liposomal bupivacaine group compared to the control group.
3. Background:
    a. Lumbar spine fusions utilizing a posterior approach are major surgeries that generally entail a significant amount dissection, even with minimally invasive spine techniques. Despite efforts to utilize multimodal approaches to combat postop spine pain, most patients will still require some form of opioid pain medication for a period of time.
    b. Multiple studies have shown that people who are taking opioids for acute pain have a greater likelihood of long-term opioid use. Furthermore, the greater the initial opioid exposure, the greater the risk of long-term use, abuse, and overdose. Studies have shown that patients who are given doses of opioids exceeding 90 morphine milligram equivalents per day increases the risk of death from an overdose by 10-fold.
    c. Many efforts have been made to reduce postop pain and opioid use, including developments in incisional site injections of local anesthetics, continuous incisional site anesthetic pain pumps, as well as multimodal comprehensive pain management, yet patients undergoing lumbar spine surgeries continue to depend on opioids for relief.
    d. Liposomal bupivacaine (LB) is a novel formulation of long-acting bupivacaine, lasting for up to 72 hours following injection. LB has been shown to be

efficacious in reducing postop pain and opioid utilization in several different surgical settings, however its utility in spine surgeries has still yet to be established.

e. For the past 5 years, one of our spine surgeons has been using liposomal bupivacaine for incisional site infusion, targeting the paraspinal muscles. Retrospective data was collected in a historic chart review between 2014 – 2019 and analysis of this data showed clear benefit to using LB to reduce opioid use within the first 72 hours postop.
f. Given our promising results from an observational study, it is our goal to advance our study to a double blind, randomized trial to determine the efficacy of liposomal bupivacaine in lumbar spine surgeries in reducing opioid utilization.

II. Drugs/Biologics/Devices

1. Liposomal bupivacaine (Exparel) 266mg/20mL, Intramuscular, single dose intraoperatively.
2. Liposomal bupivacaine is a long-acting local anesthetic, lasting for up to 72 hours, that has been FDA approved for the indication of surgical site local analgesia. We chose to use this product for this study because it has the benefit of providing long-acting analgesia, which especially beneficial in studying the immediate postoperative period for pain relief. 266mg/20mL is considered to be the maximum safe dose administered IM, without diluting the solution with saline.
3. The standard reference therapy will be a saline placebo. There is currently no local anesthetic utilized upon surgical site closure as a standard of care for lumbar spine patients. For this reason, we want to determine if the use of liposomal bupivacaine is superior in reducing opioid utilization post-op compared to no liposomal bupivacaine.
4. Include justification and safety information.
5. Liposomal bupivacaine can be differentiated visually from normal saline. In order to blind the surgeons from treatment vs control, the syringes containing the medication or saline will be sheathed by the investigational drug study department.

III. Recruitment Process

1. Patients will be recruited from *The Missouri Orthopedic Institute* (MOI) during routine outpatient clinic evaluations for lumbar spine procedures. Surgical procedures will be performed either at MOI or University of Missouri Hospital.
2. Both male and female patients will be considered for this study. Any patient over the age of 18 years old and having an isolated lumbar spine procedure that requires a posterior surgical approach for therapeutic spine purposes will be considered.
3. Standard safety precautions according to University of Missouri Hospital System guidelines will be taken by research staff. These precautions include wearing appropriate PPE (approved masks and eyewear) and social distancing 6 feet apart whenever possible.
4. All patients will be screened for COVID-19 prior to surgery within 14 days of the day of surgery, in accordance with University of Missouri Guidelines.

IV. Consent Process

1. Patients will be given a short survey to determine eligibility for the study.
2. For patients who are eligible to be enrolled in the study, consent will be obtained from the authorized clinical research staff.
3. Recruitment is completely voluntary, and it is the patient's right to revoke consent at any point in time during the study if they no longer wish to participate.

V. Inclusion/Exclusion Criteria

1. Inclusion criteria:
    a. Patients undergoing isolated lumbar spine procedures using a posterior approach.
    b. Surgical spine procedures include:
        i. Single-level lumbar spine surgeries with or without fusion
        ii. Multi-level lumbar spine surgeries with or without fusion
2. Exclusion criteria:
    a. Procedures involving intrathecal space
    b. Patients with documented allergy to local anesthetics (bupivacaine, lidocaine, procaine, benzocaine).
    c. Acute lumbar trauma that requires immediate spine stabilization
    d. Revision of failed back surgeries (including nonunion and malunion)
    e. Revision of wound or hardware
    f. Contraindication to regional anesthesia
    g. Patients with chronic use of opioid medications
    h. Liver dysfunction (INR > 1.5, albumin <2.8g/dl, bilirubin >2mg/dl)
    i. Renal dysfunction (eGFR < 60ml/min/1.73m^2)
    j. Severe COPD requiring continuous oxygen supplementation
    k. Unable to give informed consent (including prisoners and mentally disabled)
    l. Pregnant patients

VI. Number of Subjects

1. Using data taken from Tomov et al 2018, a power analysis was conducted to test differences in mean total opioid use between the liposomal bupivacaine group and the control group at 72 hours post-op. Equal group sizes were considered with power at least 0.80, two-sided Type I error set at 0.05, and equal variances between the two groups were assumed using a two-sample independent t-test framework. Using a treatment mean total opioid use (in morphine equivalent mg) of 231.4mg and control mean of 273.9mg, with pooled standard deviation of 40.0mg, at least 15 subjects per treatment group are required (30 total). As follow-up for this study is shortly after surgery (and all during LOS), an adjustments were made for study attrition to allow for enrollment up to 50 to account for those that may be consented but not have surgery or those that do not fill out the VAS and medication log post-op.

VII. Study Procedures/ Design/Treatment Plan

1. Randomization of study group vs control group will be done independently by investigational drug study personnel. Vials of the medication vs sterile saline will be blinded with labels that are able to be scanned into the system so that only investigational drug study personnel know which patients belong to each arm. In order to blind the surgeon, the syringes will be shielded due to the ability to visually differentiate the two treatments.
2. All patients will be screened for COVID-19 per University of Missouri Hospital and Clinic's protocol (<14 days from day of surgery).
3. All patients will undergo a standard induction and maintenance of general anesthesia balanced according to institutional protocols based on ASA guidelines:
    a. ***Anesthesia protocol (standard of care)*** – All surgery will be performed with standard general anesthesia. Induction will be achieved, and general anesthesia maintained based on the following protocol (Doses vary based on patient specifics such as age, weight and comorbid disease):
        i. Lidocaine 50 – 100mg
        ii. Fentanyl 50 – 100mcg
        iii. Propofol 100 – 200 mg
        iv. Rocuronium 50 – 100mg
    b. Intraoperative (standard of care)
        i. Sevoflurane 1 – 2% or desflurane 4 – 6%
        ii. Fentanyl, hydromorphone, ketorolac and / or ketamine IV as needed on suspicion of pain.
        iii. antibiotics were given intravenously 2g of cefazolin or 900mg of clindamycin.
4. All patients will receive the standard of care for indicated lumbar spine procedures.
5. Patients in the study group will receive liposomal bupivacaine at the end of the procedure (following fascial closure, but prior to superficial closure). LB should be injected slowly and deeply, infusing ~1-2 mL according to manufacture guidelines for infiltration. According to these guidelines, injection should utilize a moving needle technique (ie, inject while withdrawing the needle) at multiple locations surrounding the incision(s) to achieve maximal effect. Care will be taken to aspirate prior to injection to minimize the risk of intravascular injection of medication.
6. Patients in the control group will utilize the same technique of injecting as the study group, however, with normal saline.
7. If necessary, patients will be given additional pain medications to facilitate extubating following surgery.
8. All patients will receive a standardized inpatient pain protocol based on ASA guidelines for acute pain management in the post-op period.
    a. MILD PAIN (score 1-4)
        i. Acetaminophen 1000mg PO q6hr PRN
        ii. Ibuprofen 800mg PO q4hr PRN
        iii. Acetaminophen-codeine 1 Tablet PO q4h PRN
        iv. Acetaminophen-Hydrocodone 325mg-5mg PO q4h PRN
        v. Acetaminophen-Oxycodone 325mg-5mg PO q4h PRN

vi. Oxycodone IR 5mg PO q4hr PRN
vii. Morphine 2mg IV q4h PRN mild breakthrough pain
viii. Hydromorphone 0.5mg IV q4h PRN mild breakthrough pain

b. MODERATE PAIN (5-7)
i. Acetaminophen-codeine 2 Tablets PO q4h PRN
ii. Acetaminophen-Hydrocodone 325mg-5mg PO, 2 tablets, q4h PRN
iii. Acetaminophen-Oxycodone 325mg-5mg PO, 2 tablets, q4h PRN
iv. Oxycodone IR 5mg PO, 2 tablets, q4hr PRN
v. Ketorolac 15mg IV q8h PRN
vi. Morphine 2mg IV q4h PRN moderate breakthrough pain
vii. Hydromorphone 0.5mg IV q4h PRN moderate breakthrough pain

c. SEVERE PAIN (8-10)
i. Acetaminophen-Hydrocodone 325mg-5mg PO, 2 tablets, q4h PRN
ii. Ketorolac 30mg IV q8hr PRN
iii. Oxycodone IR 5mg PO, 2 tablets, q4hr PRN
iv. Morphine 4mg IV q2h PRN severe breakthrough pain
v. Hydromorphone 1mg IV q4h PRN severe breakthrough pain

9. Data collection:
   a. Inpatient opioid utilization will be obtained from the patient chart from authorized research staff. Outpatient opioid utilization will be obtained by patient pain log. Patients who are discharged will be contacted by research personnel every other day to ensure adequate follow-up and compliance to study protocol. Opioids will be quantified by post-op day and converted to standard morphine milliequivalents (MME) for comparison.
   b. Visual analog pain scales will be collected from inpatients every hour for the first 6 hours postop, then every 4 hours for the duration of the hospital stay to determine appropriateness of PRN medications.
   c. Outpatient VAS and pain medication log will be utilized each day until the first post-operative clinic visit, about 2 weeks post-op. Patients who are discharged will be contacted by research personnel every other day to ensure adequate follow-up and compliance to study protocol.
   d. Patient length of hospital stay will be obtained by authorized research staff from the patient chart.
   e. Additionally, data for time in the operating room, time spent in the PACU, intraoperative complications (fracture, vascular injury, and anesthesia-related), acute postoperative complications (medical, nerve injury, dislocation, hematoma, and wound complications), opioid complications (nausea, hypoxia, increased O2 requirement, post-op ileus), and cost of local infiltrates will be collected from patient charts.
10. Data analysis:
   a. Opiate consumption, pain scores, and hospital length of stay will be analyzed comparing the study and control groups. The study and control groups will then be subdivided based on the type of procedure (single-level lumbar spine without fusion, single-level lumbar spine with fusion, multi-level lumbar spine without fusion, multi-level lumbar spine with

fusion). Study and control patients will be analyzed using either unpaired t-test or Mann-Whitney U test depending on the data normality.
    b. Categorical data will be compared using chi-square test or Fisher's Exact test.
    c. Data will be analyzed by our team of biostatisticians within the department of Orthopedic Surgery.
    d. Primary outcome: Opiate utilization
    e. Secondary outcomes: Visual analog pain score and hospital length of stay
11. Patient removal criteria will include:
    a. Need to convert surgery to involve intradural space.
    b. Unintentional breach of intradural space.
    c. Patients with neurologic impairment following surgery, of which was not present prior to operation.
    d. Patient fails to comply with post-op instructions and limitations.
12. The study will be ended prematurely if an obvious superiority of treatment group over control submerges during data analysis.

VIII. Potential Risks/Adverse Events

1. Risks for surgery in both groups are no different from patients who are not enrolled in the study.
2. General risks for lumbar spine surgery include the risk of bleeding, infection, wound dehiscence, injury to surrounding structures, and lower extremity paresthesia or paralysis.
3. Foreseeable discomfort will be no different from patients undergoing the same procedure who are not enrolled in the study. There will be foreseeable discomfort in perioperative pain, which will be minimized based on techniques outlined in the study procedures.
4. Risk to patients given liposomal bupivacaine include nausea, vomiting, constipation, unintentional intravascular injection which could result in dysrhythmias and depressed cardiac conductivity, in rare cases leading to death. Great care is taken during injection of the medication to aspirate the injection site to avoid intravascular infiltration. Methemoglobinemia has been reported with use of local anesthetic. It's important to note, however, that these rare, yet potentially life-threatening, complications are not unique to liposomal bupivacaine, rather these are risks associated with the drug class as a whole.
5. If serious complications occur (cardiac, respiratory, neurologic, hypoxemias, or other unanticipated serious complications), that are suspected by the physician to be related to the use of liposomal bupivacaine, these events will be reported to the PI within 24 hours of the event occurrence. The PI will then report this complication to the IRB within 5 days of becoming aware of the event.

IX. Anticipated Benefits

1. Anticipated benefits to the patient will be potentially:
    a. less or equivalent post-operative pain
    b. Less need for opioid pain medications, decreasing individual risk of developing tolerance, chronic need for opioid pain medication, and risk of developing opioid use disorder.

2. Anticipated benefit to society:
    a. Providing a long-acting postoperative pain modality to potentially reduce patient need for opioids.
    b. Less need for providers to prescribe opioids for acute postop pain management will potentially lead to less opioid diversion on a societal level.
    c. Less post-operative pain leads to earlier time to ambulation and shorter hospital stays, ultimately moving lumbar spine procedures closer to the goal of moving toward same-day outpatient procedures.

X. Compensation

1. N/A

XI. Costs

1. Cost of liposomal bupivacaine and sterile normal saline
2. Cost of research personnel
3. Cost of statistician services
4. Cost of investigational drug study services

XII. Data Safety Monitoring Plan

The PI will be responsible for maintaining safety of the data. The PI will monitor the data to ensure study protocol is being followed. Both the patient master list and coded data will be monitored by the PI.

All procedures involved in this study will be conducted with the same degree of privacy consideration used for standard of care with these procedures. All data will be collected and stored in electronic format. Study data will be coded and stored separately from the patient master list. The electronic data will be stored on a secure MU network and password protected. Data will be monitored and curated by the involved approved research staff as designated by the IRB for this project. Data will be deidentified and analyzed via statistical software once the data has been gathered per the study protocol.

The patient is at no greater than minimal risk due to the data being collected. To minimize the risk of the use of private records, only members of the research staff will have access to any of these records. The data will be stored for a minimum of 7 years per MU policy. Any electronic data will be stored on a secure server. They will be deleted appropriately at the end of the storage period. Any breach in data security will be immediately reported to the IRB within five days of detection.

XIII. Multiple Sites

1. This study will be performed at a single site.

2. The University of Missouri Hospital and Missouri Orthopaedic Institute will be utilized according to attending physician schedule and availability
3. Both institutions have all required approvals necessary to participate in the proposed study

XIV. References/Appendices

1. Postoperative Pain and Length of Stay Lowered by Use of Exparel in Immediate, Implant-Based Breast Reconstruction
2. Daniel R Butz 1, Deana S Shenaq 1, Veronica L M Rundell 1, Brittany Kepler 1, Eric Liederbach 1, Jeff Thiel 1, Catherine Pesce 1, Glenn S Murphy 1, Mark Sisco 1, Michael A Howard 1
3. Postoperative Pain Management after Spinal Fusion Surgery: An Analysis of the Efficacy of Continuous Infusion of Local Anesthetics. Richard A. K. Reynolds,1 Julie E. Legakis,1 Jillian Tweedie,2 YoungKey Chung,3 Emily J. Ren,4 Patricia A. BeVier,2 Ronald L. Thomas,5 and Suresh T. Thomas2
4. A Novel Liposomal Bupivacaine Formulation to Produce Ultralong-Acting Analgesia Gilbert J. Grant, M.D.,* Yechezkel Barenholz, Ph.D.,† Elijah M. Bolotin, Ph.D.,‡ Mylarrao Bansinath, Ph.D.,§ Herman Turndorf, M.D., Boris Piskoun, B.S.,# Elyad M. Davidson, M.D.**
5. The Use of Exparel (Liposomal Bupivacaine) to Manage Postoperative Pain in Unilateral Total Knee Arthroplasty Patients Jonathan W. Surdam, MD, David J. Licini, MD , Nathan T. Baynes, PA-C, Britney R. Arce, BSN, RN, CRRN
6. Practice Guidelines for Acute Pain Management in the Perioperative Setting: An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management. https://pubs.asahq.org/anesthesiology/article/116/2/248/12956/Practice-Guidelines-for-Acute-Pain-Management-in
7. https://www.cdc.gov/drugoverdose/epidemic/index.html
8. https://www.exparel.com/hcp/about-exparel/dosing-and-administration