INVESTIGATOR STUDY PLAN - REQUIRED

IMPROVING PAIN MANAGEMENT AFTER TOTAL SHOULDER REPLACEMENT USING BUPIVACAINE LIPOSOME
NCT04134442
9/30/201

1. Title
Improving Pain Management after Total Shoulder Replacement using Bupivacaine Liposome – a pilot study

2. External IRB Review History*
N/A

3. Prior Approvals:
Protocol Review Committee approved this study.
MD Anderson approved use of the questionnaires for this study.
Office of Technology management reviewing MD Anderson Contract for Questionnaire use

Conflict of Interest (COI):
The PI and co-investigators are not affiliated with and are not receiving funding from any pharmaceutical or device company.

Pacira, the company producing Bupivacaine Liposome (Exparel), has agreed to supply the medication for the purpose of this initial study, but nobody from Pacira will be involved in study design, the process of the study, data analysis, or result publication.

4. Objectives*
To improve pain control and decrease opioid requirements for subjects undergoing Total Shoulder Replacement.

Hypothesis:
Adding Bupivacaine Liposome (Exparel ™) to Interscalene Nerve block and the current multimodal analgesia regimen will prolong and improve pain control in subjects undergoing Total Shoulder Replacement (TSR) and reverse TSR surgery

5. Background*
Multimodal pain therapy improves pain control after TSR and reverse TSR surgery. Regional anesthesia and interscalene nerve block (ISNB) in particular, are the cornerstone of the multimodal therapy approach[1]. However, ISNB lasts only 10-20 hours (depending on the local anesthetic and additive used), and once it wears off and results in rebound pain on the evening or night of surgery.

Bupivacaine Liposome (BL) has been developed, and can prolong the action of bupivacaine for up to 72 hours[2]. BL has been successfully and safely used for a variety of nerve blocks[3]. BL has been shown to be effective and safe when compared to placebo when used in ISNB for subjects undergoing major shoulder surgery, and was approved by the FDA in April 2018 for ISNB for subjects undergoing major shoulder surgery. One study from Belgium showed that BL combined

1
2
3

with bupivacaine for ISNB in addition to a multimodal analgesia regimen results in improved subject satisfaction scores with pain control.

The studies that looked at using BL alone and compared it to placebo have several limitations. BL does not start to have an effect until 6-8 hours after injection, which means that subjects can have limited relief immediately after surgery. Using a mixture of bupivacaine and BL can result in immediate and prolonged pain relief. The study from Belgium had its own limitations, as subjects had a far lower opioid consumption and pain scores than our subjects at UMASS Memorial Medical Center, and most likely many other areas around the US. Therefore, this study did not show a statistically significant improvement in patients' opioid consumption or pain scores.

Currently, there are no studies comparing the use of bupivacaine liposome and bupivacaine mixture, to bupivacaine alone for ISB for pain control after TSR and reverse TSR surgery, in a population that is comparable to the population at UMASS. We are interested in seeing if there is any significant impact on patients' opioid consumption or pain scores in the days following these major surgeries. Based on our experience at UMASS Memorial Medical Center, patients undergoing TSR and reverse TSR do experience severe range post-surgical pain, and are using much higher amounts of opioids than quoted in existing studies.

In the proposed study, we want to determine the efficacy of adding Bupivacaine Liposome in ISB to the multi-modal pain regimen that we employ for patients undergoing TSR and reverse TSR surgery. As we are not sure where we will see the greatest effect, and how large this effect might be, we would like to first perform a pilot study.

A note on the safety of use of Bupivacaine Liposome and Bupivacaine combination: We will maintain the total dose of Bupivacaine Liposome and Bupivacaine below 3mg/kg which is the limit for toxic dose for bupivacaine. It has been shown safe to mix Bupivacaine Liposome and Bupivacaine, as long as the proportion of each is no less than 2:1 respectively[4].

References

1. Fredrickson MJ, Krishnan S, Chen CY. Postoperative Analgesia for shoulder surgery: a critical appraisal and review of current techniques. *Anesthesia*. 2010; 65:608-624.
2. Chahar P, Cummings KC. *Liposomal bupivacaine: a review of a new bupivacaine formulation.* J Pain Res. 2012; 5:257-264.
3. Ilfeld BM, Viscusi ER, Hadzic A et al; Safety and Side Effect Profile of Liposome Bupivacaine (Exparel) in Peripheral Nerve Blocks. *Reg Anesth and Pain Med.* Sept-Oct 2015. 5: 572-582.
4. Kharitonov V. A review of the compatibility of liposome bupivacaine with other drug products and commonly used implant materials. Postgrad Med. 2014;126(1):129-138.

4

6. Inclusion and Exclusion Criteria*

Inclusion Criteria

1. Adult subjects older than 18years old undergoing TSR or reverse TSR surgery
2. Meet criteria for regional nerve block
3. Weight greater than 60kg (safety to keep liposomal bupivacaine and bupivacaine dosing below 3mg/kg)

Exclusion Criteria:

1. Recent drug use
2. Subjects on chronic buprenorphine therapy (either for opioid replacement or pain control)
3. Nerve injury (cervical stenosis, trauma, etc) of the surgical limb
4. Coagulopathy
5. Subjects with significant liver disease (as amide type local anesthetics such as bupivacaine are metabolized by the liver)
6. Infection near or in the area of the nerve block
7. Subject refusal of regional anesthesia
8. Vulnerable populations (prisoners, mental impairment / dementia, etc)
9. Subjects requiring interpreter services (not proficient in English)
10. Subjects with poor cardio-pulmonary reserve who might not tolerate a hemi-diaphragmatic paralysis or hemi-diaphragmatic paresis

Pregnant women are not a study population being focused on in this investigation, as we routinely screen all female patients of childbearing age (unless they have had a hysterectomy) for pregnancy prior to surgery. Patients that test positive for pregnancy do not undergo this elective surgery. Therefore, we do not expect any aspect of the study to have any impact on pregnancy or pregnancy-related issues, so we do not plan to enroll pregnant subjects.

The following vulnerable populations will not be included in the study:

Adults unable to consent for themselves
Pregnant women
Non-adult individuals
Prisoners

7. Study-Wide Number of Subjects*

N/A

8. Study-Wide Recruitment Methods*

N/A

9. Study Timelines*

We expect to be able to enroll all necessary subjects within approximately 1 year of starting the study. It is expected that primary analyses will be completed within 12 weeks of finishing the study. Each patient would be followed while they are in the hospital, or until POD2 (whichever comes first).

10. Study Endpoints*

Primary Outcome:

Morphine equivalent dose (MED) of opioids within the first 24 hours after surgery (including PACU and medications on the floor)

Secondary Outcomes:

1. MED within 24-48 hours
2. Mean VAS pain score in the first 24 hours, and 24-48 hours after surgery
3. Maximum VAS pain score in the first 24 hours, and 24-48 hours after surgery
4. Hospital LOS
5. Brief Pain Inventory Short Form pre-operatively on POD 0, POD 1, and POD 2
6. Cost estimate of each technique
7. Time to administration of the first opioid

11. Procedures Involved*

For the pilot study we will use a total of 20 cases per group.

A HIPAA Waiver will be used for screening purposes. We will be using the electronic medical record system (EPIC) to screen for subjects in the UMass system.

Subjects will be recruited and consented as described later in the study plan.

Subjects will be randomized to the two groups (standard therapy or BL) using a random number generator. The random number with the type of anesthetic will stored in envelopes and will be opened in sequence on each day of the ISNB.

1) Group 1: Standard therapy
    a. Standard pre-operative and post-operative medical regimen including standing acetaminophen 650mg q6hours, gabapentin 300mg q8hours and as needed oxycodone every 4 hours (unless there are contraindications due to liver function, kidney function, or age as currently determined by acute pain service (APS) anesthesiologist)
    b. Preoperative, ultrasound guided ISNB with a bupivacaine mixture: 10ml 0.5% bupivacaine and epinephrine 1:200,000, and 10ml of 0.9% normal saline

2) Group 2: BL
    a. Standard pre-operative and post-operative medical regimen including standing acetaminophen 650mg q6hours, gabapentin 300mg q8hours and as needed oxycodone every 4 hours (unless there are contraindications due to liver function,

kidney function, age, or current therapy as currently determined by APS anesthesiologist)

b. Pre-operative ultrasound guided ISNB with a 20ml mixture consisting of 10ml of 0.5% bupivacaine with epinephrine 1:200,000, and 10ml of BL 1.33%

In accordance with our current practice, all subjects will have premedication with midazolam and fentanyl and general anesthesia (GA) with ETT. Propofol will be used for induction of GA. During surgery, administration of short acting narcotics (fentanyl) will be at the discretion of the anesthesia team.

As BL will be used, no additional local anesthetics will be used during surgery (i.e. lidocaine for induction or maintenance of anesthesia, or local anesthetics for infiltration in the surgical field). Ketamine will not be used as an anesthetic / analgesic adjunct

After this, all patients will remain on our standard protocols. In the PACU, subjects will receive IV hydromorphone for pain control. Once on the post- operative floor, subjects pain will be managed with oxycodone as needed every 4 hours (5mg for moderate pain, 10mg for severe pain) and 0.4 mg IV hydromorphone for breakthrough pain.
Subject's postoperative opioid consumption and pain scores will be obtained from their charts. Subjects will fill out a Brief Pain Inventory Short Form on POD 0 pre-operatively, on POD 1, and POD 2 (if the patients have not been discharged from the hospital).

Blinding
In this study, we will work with the Investigational Drug Pharmacy, who will store the medications, and supply medications on the day of surgery. Subjects will be blinded, as all subjects will receive an ISNB. The surgeon, anesthesiology team, PACU and floor nurses will also be unaware of group assignment, and will use their clinical judgement and subjects' reporting when administering medications and recording pain scores. Surveys about subjects' satisfaction with pain control, as well as data collection from subjects' records will be done by study investigators that are not involved in performing injections.

The Anesthesiologists performing the nerve block will not be blinded (as the Bupivacaine Liposome solution is a suspension and is white, whereas bupivacaine solution is clear), but will not participate in further evaluations of the subjects or data collection.

12. Data and Specimen Banking*

Once the data will be collected, it will be de-identified for analysis and future use. We hope to use the results of this study to perform a power analysis for a larger study looking at any improvements in pain control associated with the addition of BL to bupivacaine for ISB in patients undergoing TSR and reverse TSR surgery.

13. Data Analysis and Management*
There are no data available for use of bupivacaine liposome and bupivacaine solution vs bupivacaine alone for ISNB for subjects undergoing TSR or reverse TSR surgery in a center where subjects have high pain scores and high opioid use; thus, there is no way for us to perform

an accurate power analysis. Consequently, we are performing this pilot study to estimate the means and standard deviations of the two groups' use of opioid medications within the first 24 hours in order to calculate a robust power analysis in anticipation of performing a larger study.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects*

Each subject will be monitored for any complications - paresthesias, nerve damage, nausea and vomiting. ISNB is a standard form of therapy and both bupivacaine and BL are standard FDA approved local anesthetics that are used for ISNB. Standard clinical postoperative follow-up by the anesthesia team and APS team will be followed to discern any complications related to the ISNB as they would for any clinical subject not involved in the study.

15. Withdrawal of Subjects Without Their Consent*

N/A

16. Risks to Subjects*

Bupivacaine Liposome can extend the action of the nerve block. Typically, bupivacaine liposome causes a sensory blockade (loss of sensation) for up to 72 hours but does not cause a motor blockade. However, theoretically this can occur.

More than 10% of subjects who have received Bupivacaine Liposome for ISB have reported the following side effects: nausea, vomiting, constipation, and pyrexia.

All other risks would be the same as all the other medications and procedures are part of our standard therapy for subjects undergoing TSR and reverse TSR surgery

Risks of Bupivacaine containing medications:

- Central Nervous System (CNS) Reactions: There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesia. CNS reactions are characterized by excitation and/or depression
- Cardiovascular System Reactions: Toxic blood concentrations depress cardiac conductivity and excitability which may lead to dysrhythmias, sometimes leading to death
- Allergic Reactions: Allergic-type reactions (eg, anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients.

17. Potential <u>Direct</u> Benefits to Subjects*

The potential benefit will be that use of Bupivacaine Liposome will provide prolonged analgesia the pain control from the nerve block. This should also reduce the amount of opioid medications used by subjects, thereby reducing side-effects of nausea, vomiting, sedation, hallucinations, confusion, itching. Furthermore, with better and longer pain control, subjects may be able to eat quicker and leave the hospital sooner.

18. Vulnerable Populations*

The study does not intend to include any vulnerable subjects.

19. Multi-Site Research*

N/A

20. Community-Based Participatory Research*

N/A

21. Sharing of Research Results with Subjects*

If patients are interested about group assignment, they can contact the study PI after POD2 or their discharge from the hospital whichever comes first (upon completion of the study).
N/A

22. Setting

Facilities:

The research will take place at UMass Memorial Medical Center at the Memorial Campus. All areas in the clinics and PACU have access to the electronic charting system allowing access to the research subject's data required by the study protocol.

Where research procedures will be performed:

Subjects will be seen in the outpatient clinic rooms and inpatient rooms at the Memorial Campus. Study visits will occur in the Memorial Campus orthopedic clinic, pre-operative holding area, operating room, PACU and inpatient rooms. The post-study interviews may take place on the inpatient floor.

23. Resources Available

Time that will be devoted to conduct and complete the research:

Adequate time has been allocated for enrollment, collection of subject data, history, demographics, and analyzed data. The PI, research staff and sub investigators will work the necessary hours to complete the project.

The staff involved in the research project:

This study includes the PI, sub-investigators, and research (including nurse) coordinators. This staff consists of physicians, research nurses, and research coordinators. Collectively, the staff has over 40 years of clinical research experience at UMMS. The roles of each research staff member are listed below:

Principal Investigator:

This position requires advanced training in Anesthesiology, in the subspecialty of regional anesthesia, and experience with research design and laboratory methods. The PI is responsible for ensuring that all team members have current CITI training, appropriate training for their respective roles, including knowledge of the study protocol and procedures for maintaining confidentiality. The PI may consent subjects, discuss potential subjects with the attending physician, data analysis and performing any other study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

Sub-investigators:

- This position requires advanced training in the Anesthesiology and/or orthopedic surgery. Sub-investigators may be responsible for consenting subjects, data analysis and performing any other study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

Research Nurse (Coordinator)

- This position requires a registered nurse with advanced training in the critical care area. Research nurses may be responsible for handling IRB submissions, overseeing regulatory responsibilities, screening and consenting subjects, data analysis and performing any other study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures. They will have completed all JCAHO required annual competencies to practice in the hospital.

Research Coordinator

- This position requires a specialized research professional working with and under the direction of the clinical Principal Investigator (PI). Research coordinators support, facilitate and coordinate the daily clinical trial activities and play a critical role in the conduct of the study. They responsibilities include: maintaining records, handling IRB submissions, data management, and performing any other study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

A trained and experienced research coordinator, research nurse or sub-investigator will perform various tasks required by the study at various time points. A trained and experienced research coordinator, research nurse or sub-investigator will enter subject data into the CRF, and perform regulatory functions required by the study.

Process to ensure that all persons assisting with the research are adequately informed about the protocol:

All research personnel that are involved in the protocol will be trained at the initiation visit. If they are unable to attend the initiation visit, the PI or a person they feel is appropriately knowledgeable will provide training including: the flow of the research study, procedures required by the protocol, the researcher's duties and functions. A signature log of all those trained will be kept in the Regulatory Binder of the study. The binder is kept in a secure location with minimal access to unauthorized personnel (in the critical care research office). The clinical staff caring for the subject will be in-serviced regarding the research protocol and any procedure that they are authorized to complete.

24. Local Recruitment Methods

Identify potential subjects:

HIPAA waiver is necessary for screening purposes at UMass Memorial Medical Center. Subjects will be screened for eligibility based on the inclusion criteria and exclusion criteria, adult subjects undergoing total shoulder or reverse total shoulder replacement surgery. The subject's medical record number will be the identifier used to track the subject records.

Screening: The orthopedic surgeon (Dr. Aaron) will be asked to identify potential study subjects. After screening the subject and confirming whether the subject meets eligibility criteria and are interested in participating, Dr Aaron will introduce the study to the subject, and ask if they would like to participate in it. If so, Dr. Aaron will go over the consent and the study, and give a copy of the consent form will be given to the subject to take home and review.

Only subjects that have agreed to participate in the study with Dr. Aaron will be seen on the day of surgery. On the day of surgery, someone from the study team will approach the patient to answer any final questions and briefly go over the consent again prior to obtaining written consent.

25. Local Number of Subjects

Twenty subjects will be needed in each group. We expect to screen much more (double or triple this number) because of the potential for the subject refusal or ineligibility based on the inclusion and exclusion criteria. We will stop screening once the study number is reached.

Dr. Aaron completes 110-130 Total Shoulder Replacements and reverse Total Shoulder Replacement surgeries per year.

26. Confidentiality

Local procedures for maintenance of confidentiality: The subject's research records will be confidential to the extent possible. In all records, the subject will be identified by a code number and their name will be known only to the researchers. The subject's name will not be used in any reports or publications of this study. The U.S. Food and Drug Administration (FDA), and the UMMS Institutional Review Board and/or their representatives may inspect the subject's medical records that pertain to this research study. They will not be allowed to copy down any parts of the subject's identifiable information or take any of the subject's identifiable information from our office.

A Screening log will be kept on a password protected research drive only accessed by research staff listed on the protocol. PHI included on the log will be the subject's initials and Medical Record Number. At the end of the study, the Screening log will be deleted.

Where and how will data or specimens be stored locally: The source data will be stored in the critical care research office. The Critical Care Research office is secured with a keypad lock. The combination is known only to authorized individuals. The electronic data is protected in a database that is password protected and encrypted.

How long will data or specimens be stored locally: The study documents may be retained in the files of the responsible investigator for 2 years. However, these documents should be retained for a longer period if required by the applicable legal requirements. After that period of time the documents may be destroyed, subject to local regulations (shredded).

Who will have access to the data or specimens stored locally: The research nurses, the investigators and sub-investigators, the IRB, and the FDA.

Who is responsible for receipt or transmission of the data or specimens locally: The research nurses/coordinators and the investigators.

How will data and specimens be transported locally: Data collected will be collected on source documents and then transcribed to an electronic format (RedCap). Each subject will be issued a numeric identifier for this study that will correspond with the information listed on the Data Collection Form.

27. Provisions to Protect the Privacy Interests of Subjects
A HIPAA waiver of authorization will be used to screen any subjects.

At enrollment the subject will sign an Informed Consent Form which describes the protected health information that will be used and disclosed for research purposes. The subjects will be given information to withdraw the right to use any new information if they feel they do not want to continue in the research study.

Only research personnel involved in the research study and trained to conduct the study related procedures will be involved with the subjects.

The data will be entered into REDcap and accessed and stored safely on a secured drive.

28. Compensation for Research-Related Injury
The University of Massachusetts Medical School does not provide funds for the treatment of research-related injury. If the subject is injured as a result of their participation in this study, treatment will be provided. The subject or their insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

29. Economic Burden to Subjects
Subjects will not incur any additional cost from being in the study.

30. Consent Process
Where will the consent process take place: The consent process will take place in the clinic or holding area of the hospital, an area that provides privacy to the subject.

Any waiting period available between informing the prospective subject and obtaining consent: The subject will be given as much time as possible to decide whether they would like to participate in the research study. All questions will be discussed. If the subject is not comfortable making a decision, the subject will not be enrolled.

Informed Consent Process: The principal investigator will ensure that informed consent is obtained in accordance with the SOP: HRP-802 INVESTIGATOR GUIDANCE: Informed Consent". Those obtaining informed consent from the subject will be a PI, sub investigator, research nurse, research nurse manager or research coordinator who has been properly trained by

the principal investigator, is knowledgeable about the study and able to answer any questions the potential subject may ask.

After discussing the study in detail (risks, procedures, follow-up) the subject will be given the informed consent form to review. The subject will be asked if they understand what has been explained. All questions will be discussed. If they are uncomfortable or hesitant about participating in the research, the consent process will be stopped. If the subject is willing to participate in the research, they will sign and date the informed consent form. The research staff personnel obtaining consent will sign and date the forms where appropriate. A copy of the ICF form will be given to the subject. The original ICF will be placed in the regulatory binder for the research study. A copy of the ICF form will be placed in the subject's medical record.

A note will be placed in the subject's electronic medical record noting the following:

- The date and time that the informed consent form was signed
- Discussion of the study and questions answered
- That the subject met all study entry criteria

31. Process to Document Consent in Writing

We will be following the "HRP-803 INVESTIGATOR GUIDANCE: Documentation of Consent."

32. Drugs or Devices

Study drug will be shipped by the Pharmaceutical company and/or their representatives according to federal guidelines to the Investigational Pharmacy in the ACC building at UMass Memorial Medical Center. The drug will be stored according to protocol guidelines by the staff of the Investigational Pharmacy (IP). The investigator or other designated individual (Investigational Pharmacist) will maintain records of the product's delivery to this clinical trial site, the inventory at this site, the use by each subject, and the return to the Sponsor or alternative disposition of unused products. These records include dates, quantities, batch or serial numbers, and expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial subjects.

When a subject is enrolled into the study, a copy of the completed signature page of the informed consent form and a "research study order sheet/prescription" will be faxed to the Investigational Pharmacy. The research study order sheet/ prescription, a copy of the signed informed consent/HIPAA form will be sent to Health Information Management to be scanned into their medical record. The research order sheet contains information regarding the study drug dosage, route, times to be administered and any special instructions involved with the administration of the drug. The order sheet/prescription with the subject's information (medical record number, name, date of birth, allergies, subject ID#, Study Visit #, assigned study kits and address). The order sheet/prescription is signed by the PI or a MD/NP sub investigator.

The study medication will be administered by a licensed professional who is appropriately knowledgeable in the administration of the study drug. The anesthesiology team and nursing staff caring for the subject will be in-serviced when a subject has been enrolled into the research study. The study rationale will be explained and the procedures that will be required while the subject in on the study will be reviewed. The first dose of study drug will be administered by the research team.