PROTOCOL TITLE: Prospective Randomized controlled trial comparing liposomal bupivacaine to bupivacaine Interscalene blocks for total shoulder arthroplasty surgery

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Prospective Randomized controlled trial comparing liposomal bupivacaine to bupivacaine Interscalene blocks for total shoulder arthroplasty surgery

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VERSION NUMBER/DATE:

1 3/20/2018

2 5/22/2018

3 6/27/2018

4 7/22/2019

5 12/4/2019

6 3/19/2020

7 6/3/2020

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	5/22/18	Updated recruitment procedures	No
2	6/27/18	Edited for IRB response	Yes
3	7/22/19	Updated recruitment numbers	No
4	12/4/2019	Decreased discharge opioid amount	Yes
5	3/19/2020	Group size clarification	Yes
6	6/3/2020	e-consent addition	No

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ABBREVIATIONS/DEFINITIONS

- LB/ liposomal bupivacaine
- TSA/total shoulder arthroplasty
- QOR/Quality of Recovery
- RCR/rotator cuff repair
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STUDY SUMMARY

Study Title	Prospective Evaluation of Liposomal bupivacaine in Total Shoulder Surgery
Study Design	Prospective randomized double blind
Primary Objective	Total opioids in 72 hours
Secondary Objective(s)	Pain scores within 72 hours, QOR at 72 hours and 14 days, Number of phone calls to surgeon, adverse events, time to discharge
Research Intervention(s)/Investigational Agents	Liposomal bupivacaine and bupivacaine vs bupivacaine
Scientific Assessment	HRPP facilitated scientific assessment
IND/IDE # (if applicable)	Study Medication has been approved for use in shoulder surgery April 6, 2018
IND/IDE Holder	Pacira Pharmaceuticals
Investigational Drug Services # (if applicable)	N/A
Study Population	Adult patients aged 18 and older who are undergoing total shoulder arthroplasty
Local Sample Size (number of participants recruited locally)	90

1.0 Objectives

Purpose: To determine if LB plus bupivacaine provides superior pain control compared to bupivacaine alone when injected in an interscalene block for patients undergoing total shoulder arthroplasty surgery.

2.0 Background

Significance of Research Question/Purpose: Liposomal Bupivacaine (LB) has not been adequately studied in peripheral nerve blocks and has yet to be studied for use in interscalene blocks for Total Shoulder Arthroplasty (TSA) patients. It has been studied in Rotator Cuff Repairs (RCR) surgery and showed superior analgesia compared to bupivacaine.

Preliminary Data: It is our standard of care to use this medication in an interscalene block at the U of MN for patients undergoing TSA. A retrospective study performed showed superior analgesia and less opioids in those having LB plus bupivacaine vs bupivacaine or ropivacaine only blocks.

Existing Literature: Vandepitte et al showed that LB plus bupivacaine was superior to bupivacaine when used in interscalene nerve block for patients undergoing major shoulder surgery (both RCR and TSA).

3.0 Study Endpoints/Events/Outcomes

Primary Endpoint/Event/Outcome: To determine if LB plus bupivacaine in an interscalene block results in less opioid use over 72 hours compared to bupivacaine only for TSA surgery.

Secondary Endpoint(s)/Event(s)/Outcome(s):

- To determine if LB plus bupivacaine in an interscalene block results in less pain over 72 hours as compared to bupivacaine only in an interscalene block for TSA surgery. Assessed via total pain scores (Use of Visual Analog Scale)

- To determine if LB plus bupivacaine in an interscalene block results in improved (Quality of Recovery) QOR at 72 hours and 14 days as compared to bupivacaine only in an interscalene block for TSA surgery. Assessed via QOR 15 patient survey.

- To determine if LB plus bupivacaine in an interscalene block results in fewer phone calls to the surgeon within 72 hours as compared to bupivacaine only in an interscalene block for TSA surgery.

- To determine if LB plus bupivacaine in an interscalene block hastens readiness for hospital discharge compared to bupivacaine only in an interscalene block for TSA surgery.

4.0 Study Interventions/Investigational Agent(s)

Description: LB is a long acting local anesthetic. It is liposome encapsulated bupivacaine which allows for prolonged release of bupivacaine over a 72-hour period. Bupivacaine is a medium acting local anesthetic which provides between 6 and 24 hours of analgesia when used in a peripheral nerve block. Both medications are standard of care for use in interscalene blocks here at the U of MN. Acetaminophen is a medication used to treat pain, gabapentin is a gabapentinoid which is used to treat postoperative pain, and Celebrex is a selective COX-2 inhibitor also used to treat pain.

Drug/Device Handling: The LB will be stored in a locked pyxis fridge in a box labeled Liposomal Bupivacaine. The anesthesiologists in charge of regional anesthesia the day the procedure will be informed will write the order for dispensing the medication and the block per standard of care. It will be retrieved by the PI and sub I's for use in the interscalene blocks.

Biosafety: Per standard of care

Stem Cells: N/A

5.0 Procedures Involved

Study Design: Level I randomized prospective outcomes study comparing two groups of patients. Patients will be assigned either to Liposomal Bupivacaine plus bupivacaine for an interscalene block or they will receive bupivacaine for an interscalene block injection.

Study Procedures: After consenting to the study (either in clinic or the PAC clinic) and completion of the preoperative process (per standard of care), a randomization scheme from a random number generator will be followed to ensure equal likelihood of group assignment. The patient will be placed in the supine position with the head of the bed elevated 30 degrees with standard ASA monitors applied. Sedation will be provided with midazolam 0-2mg and propofol 0-50 mg. The interscalene groove will be identified with the ultrasound. Using sterile technique, a 21g Nerve block needle will then be inserted and advanced under ultrasound guidance until it is in the interscalene groove. Once in the interscalene groove, 20 mL of local anesthetic will be injected, with 10mL deposited at the top of the brachial plexus and 10mL at the bottom. In the study group, 5 mL of each 0.5% bupivacaine and LB will be injected at each location.

The control group with have 20mL of 0.5% bupivacaine divided between the injection sites. Patients would be required to take a dose of acetaminophen 975 mg oral, gabapentin 300 mg oral, and Celebrex 400 mg oral prior to surgery (per standard of care). The patient will be monitored (vital signs, respiratory status and oxygen saturation) in the preoperative area until he/she is brought into the operating room for their procedure. A working block prior to surgery will be confirmed via sensory testing of the shoulder.

All patients will undergo a standard induction with propofol 1.5-3.0 mg/kg, lidocaine 60-100 mg, ondansetron 4 mg, dexamethasone 10 mg and ketamine 0.25 mg/kg. An LMA or ETT will be placed and an opioid sparing technique will occur. Standardized maintenance will be a propofol infusion without neuromuscular blockers. 25-50 mcg of IV Fentanyl will be utilized for increases in heart rate greater than 20% or increases in systolic blood pressure above baseline.

Once in the operating room the surgeon will use 10 mL of 0.25% bupivacaine for skin, subcutaneous, and intraarticular injection.

When the operation is complete, the patient will be brought to the post-operative care unit (PACU). The patient will receive IV fentanyl for a pain score of greater than 5 on the visual analog scale. If more than 200 mcg of fentanyl is given and pain still remains above a 5 then IV hydromorphone will be used. A dose of 5-10 mg of oral oxycodone (or 2-4 mg of oral hydromorphone) will be given as soon as the patient is able to tolerate oral medication per standard protocol: If their pain score is 4-6 (on the Visual Analog Scale) then 5mg oral oxycodone (2 mg hydromorphone) can be administered, if their pain is between 7 to 10 then 10 mg of oxycodone (or 4 mg of hydromorphone) can be administered. The patient will either be discharged to a hotel or brought to the ward where each day a member of the research team will evaluate (if in the hospital) or call (if discharged to hotel) the patient for signs of complications and ask the patient their maximum pain score, total opioids and non-opioid pain medication used, and length of stay. If patients have met criteria for discharge to home including pain <4/10, independence of intravenous analgesia, and medical stability for discharge but are awaiting placement, the time of discharge for the purposes of the study will be the day they have met such criteria as opposed to the actual time of discharge as this can vary depending on patient placement.

Once the patient meets discharge criteria, they will be discharged home where each day they will fill out a pain diary. Additionally, a member of the research team will call the patient for signs of complications and ask the patient their current pain score, total opioid pills taken and non-opioid pain medication taken

at 24, 48, and 72 hours postoperatively. Additionally, they will perform a Quality of Recovery Score survey at 72 hours, and 14 days postoperatively.

While in the hospital all patients will receive a standardized multimodal pain medication regimen. Acetaminophen 975 mg q6 hours, ibuprofen 600mg q6 hours and prn oxycodone 5-10 mg q4 hours or 2-4 mg hydromorphone oral every 4 hours. All patients will be discharged with 30-40 pills of 5 mg oxycodone or 30-40 pills of hydromorphone 2 mg with instructions to take 5-10 mg oxycodone for severe pain every 4 hours as needed or 2-4 mg every 4 hours hydromorphone as needed for severe pain. Patients will be instructed to start with the lower dose, but can repeat the dose if needed up to 10mg oxycodone or 4mg hydromorphone every 4 hours if needed.

Assessments: Post-operatively patients will be evaluated at 2 and 6 hours post-operatively by a blinded research staff. This person will not be aware of the patient's mode of analgesia. The patients will be contacted via in person assessment or via telephone at 24, 48, and 72 hours +/- 5 hours. Patients will be asked to rate their pain on scale of 0-10. The amount of opioids used by the patient will be recorded by study personnel as will any other adjuvant pain medication used. The time in phase 1 and phase 2 of PACU will be recorded. The patients will be asked at 72 hours post-injection if they would undergo an interscalene block with their medication again or if they would choose a different form of pain management (ex: higher doses of pain medications). Patients will fill out a Quality of Recovery Survey at 72 hours and 14 days, and be assessed for block related complications at this time. As part of the research, patients also will undergo diagnostic ultrasound of their diaphragm on POD 1. All complications will be recorded including:

- Failure of the block
- Wound infections
- Subsequent procedures
- Complications related to placement of the interscalene block including nerve injury, prolonged sensory loss greater than three days, prolonged arm weakness greater than three days
- Opioid related side effects of nausea and/or vomiting
- Local anesthetic toxicity as evidenced by seizures or cardiovascular collapse without other reasonable etiology

All data will be recorded on the Clinical Diagnostic Sheet and will then be given to the research coordinator for manual data entry. Data collection will continue until POD #14. At that time study participation will be terminated. Should patients be re-admitted to the hospital in the next two weeks (Up to POD 30) for pain, a notation will be made in study records.

An analysis of the total cost of analgesics will be tabulated at the conclusion of the study to determine the most cost effective treatment option as this will be

added into the cost of hospitalization including the number of days each patient spent in the hospital.

Blinding Procedure: A random number generator will be used to determine if the patient will have LB plus bupivacaine or bupivacaine for their interscalene block. The primary investigator will access the number generator in the pre-op area immediately prior to block placement. The website www.random.org will be used as the random number generator.

The research assistant in this study will be blinded to the method of analgesia for the patient. This person will not be responsible for any clinical testing and will record all data in the protected database daily. They will not have any access to the patients' clinical records or chart. **Any questions from the patient will be referred to the on-call resident or staff on call.**

Study Duration: We anticipate the study to take approximately 1 year from the date of enrollment of the first patient. Patients will be in the study for 14 days and then their chart monitored for up to 30 days post surgery. The data analysis should take one month after full enrollment of the study.

Individually Identifiable Health Information: This study involves the use of individually identifiable health information. Please see attached HIPAA authorization form.

Use of Radiation: N/A

Use of Center for Magnetic Resonance Research: N/A

6.0 Data and Specimen Banking

Storage and Access: All study data will be stored on excel spreadsheets stored in Box. Only the PI and members of the research team will have access to the data.

Data: The data from this study will be collected both from Epic and directly from the patient. The data collected includes: demographic data, age, weight, ASA class, duration of surgery, length of stay in recovery room both phase 1 and 2, length of hospital stay, amount of opioids given intraoperatively and post-operatively, non-opioid pain medication, pain score (0-10) at 2, 6, 24, 48, and 72 hours, satisfaction with treatment, Quality of Recovery survey at 72 hours and 14 days, and any adverse events.

Release/Sharing: N/A

7.0 Sharing of Results with Participants

Results will not be shared with participants.

8.0 Study Population

Inclusion Criteria: All adult patients aged greater than 18 years of age that are undergoing total or reverse total shoulder arthroplasty

Exclusion Criteria: Patients with allergy to local anesthetics, daily use of opioids for more than 3 weeks prior to surgery, patient refusal and those who have opted out of research, patients with coagulopathy, non-english speaking patients, and those who do not have access to a telephone.

Screening: Patients will be screened at their preoperative visit either in the surgeon's office, pre assessment center, or preoperative area.

9.0 Vulnerable Populations

Vulnerable Populations: No vulnerable populations will be included in the study.

10.0 Local Number of Participants

Local Number of Participants to be consented: 90 patients as we expect a drop out or loss to follow up of 20%.

11.0 Local Recruitment Methods

Recruitment Process: Patients will be recruited from the group of adult surgical patients at the University of Minnesota undergoing TSA and receiving an interscalene block. Patients will be approached at the preoperative assessment clinic at the Clinic and Surgery Center if possible by a research staff member to determine their interest in participation. If they decide to be a participant they will be consented and given a copy of their consent form for their records and a consent will be scanned and placed into EPIC. If they need additional time to consider enrollment, they will be asked if we can reach out to them by phone the night before surgery or if we should revisit the study with them on the day of surgery. If the patient is unable to be consented prior to day of surgery, the research staff will approach them in the preoperative surgical area. These patients will have significant time to review the study with research staff as well as the physicians performing the procedure due to the fact they arrive several hours prior to their scheduled surgery. All subjects will have enough time to ask questions about the study and the potential risks involved regardless of which venue they

are consented. Any patient that refuses to participate in the study at any time point will be placed on a secured list to avoid duplicate attempts to recruit them.

Identification of Potential Participants: Patients will be identified by members of the treatment team in either the surgeon's clinic, pre-assessment clinic, or preoperative area. Patients who have opted out of research will not be asked to participate in the study. Patients will be approached to consent for the study by a surgeon, anesthesiologist, or member of the research team. Patients who agree to participate in the study will sign both a study consent and HIPAA authorization allowing the use of specified information contained in medical records for research purposes.

Recruitment Materials: N/A

Payment: No payment will be provided to patients.

12.0 Withdrawal of Participants

Withdrawal Circumstances:. Subjects who have consented prior to the day of surgery and for some reason choose not to participate will be withdrawn and a notation will be made in the study records and these people will be considered screen failures. The surgeon may choose to withdraw the patient from the study prior to surgery for any medical reason or if they suffer a major life threatening adverse event.

Withdrawal Procedures: If the patient is withdrawn from study prior to the procedure, they will be noted in study records as screen failures. If they undergo the procedure and they decide they no longer want to be a part of the study or withdrawn by the physician, they will be withdrawn and no further data will be collected. This will also be noted in the study documentation.

Termination Procedures: If the study is terminated for any reason, or there is more than 5 % major adverse events the data that is already collected will be stored in a secure location only accessible to research personnel on this study. No further data will be collected if the study is terminated.

13.0 Risks to Participants

Foreseeable Risks: The study has the following risks:

- infection (< 1%)
- bleeding (< 1%)
- nerve injury (< 1%)
- cardiac arrhythmias (irregular heartbeat) (< 1%)
- respiratory complications (<1 %)

These complications all fall within the standard risks of surgery and the performance of the interscalene injection. Any intervention being provided as a part of this study falls within the standard of care as both medication options are within the standard treatments for post-operative pain and are currently used as analgesic options at UMMC.

EXPAREL contains bupivacaine. Serious side effects related to bupivacaine are not common, but may occur if too much is given or if it is accidentally injected into a blood vessel. When given incorrectly, side effects may involve the brain or the heart.

The effects on the brain and central nervous system may include:

- Restlessness (< 2%)
- Anxiety (<2%)
- Dizziness (<2%)
- Tinnitus (ringing in the ears) (<2%)
- Blurred vision (<2%)
- Tremors (shaking) possibly proceeding to convulsions (<2%).

The effects on the heart appear when too much bupivacaine is given or when bupivacaine is injected in a blood vessel by accident. These effects cause a decrease of the heart function, including low heart rate or abnormal heart rhythm, decreased blood flow, low blood pressure, and, in extreme cases, heart attack. (<2%)

The numbing sensation caused by bupivacaine may be persistent, with slow, incomplete, or no recovery. Sometimes a tingling sensation may appear in the area treated with bupivacaine. When injected next to a large nerve, bupivacaine may cause weakness or paralysis.

Allergic reactions are rare, but may include rash, itching and redness of the skin, sneezing, nausea, vomiting, dizziness, fainting, sweating, fever, and low blood pressure.

Other side effects of liposomal bupivacaine when given into the wound include:

- Nausea (22.6%)
- Constipation (8.7%)
- Vomiting (6%)
- High temperature (5.5%)
- Dizziness (<2%)
- Swelling (<1%)
- Low blood pressure (<2%)

- Anemia (<1%)
- Itching (2.4%)
- High heart rate (1.3%)
- Headache (5%)

Reproduction Risks:

If the patient were pregnant we would not perform the study on them. If they were to become pregnant there are no known risks to the patient.

Risks to Others: N/A

14.0 Potential Benefits to Participants

Potential Benefits: The potential benefits of participating in this study include reduced pain following shoulder surgery and shortened hospital stay.

15.0 Statistical Considerations

Data Analysis Plan: We plan to collect our data using excel, which will be maintained in box. When the study is completed and ready for statistical analysis the data will be shared with our staff statistician.

Power Analysis: Following the pilot study of 30 patients, it was determined that 40 additional patients (for a total of 70 patients, 35 per group) would need to be enrolled to reach 80% power.

Statistical Analysis: This study will be analyzed by our staff biostatistician. The data will be deidentified and shared with him in box. The statistician will be provided the protocol so they are able to analyze for primary and secondary objectives.

Data Integrity: All patients will be assigned a unique patient identifier. The data that will be sent to the statistician will be deidentified.

16.0 Confidentiality

Data Security: All paper documents and consent forms will be stored in a locked cabinet in the anesthesia research office in B573 Mayo. All study data will be stored electronically in Box and only the PI and members of the research team will have access to the data.

17.0 Provisions to Monitor the Data to Ensure the Safety of Participants

Data Integrity Monitoring.

The PI, co-investigators, and research assistants will all have access to the study data stored in the University's Box storage system. All the research assistants have experience collecting pain scores and other relevant study information. The PI of the study will periodically review the study data to ensure accuracy and completeness of study data.

Data Safety Monitoring: The Department of Anesthesiology has established a Data and Safety Monitoring Committee consisting of several staff anesthesiologists which include persons who are board certified as pain specialists. Data will be transmitted in box to persons on the board on a monthly basis for review. If there are patterns of adverse events, the board will meet as needed and provide recommendations.

All safety data will be collected on a case report form and transferred into an excel spread sheet that will be stored in box. Also, all phone call data will be collected on a case report form and transferred into excel in box.

All data will be collected by research assistants on a daily basis. Subjects are monitored at several intervals on day of surgery and daily up to 72 hours. If the patient is discharged prior to 72 hours they will Who will review the data.

The data will be reviewed on a regular basis (weekly) by the PI and research staff. If there are consistent complications noted a meeting will be convened by the DSMB for recommendations.

The statistical tests for analyzing the safety data to determine whether harm is occurring.

The statistician uses R or SAS for analysis. Most likely a regression analysis will be performed to see which event is most likely the contributor for the complications Also a chi-square analysis can be performed. All is very dependent on data variability.

A fatal or serious adverse event that is attributable to either the delivery or the study medication itself.

18.0 Provisions to Protect the Privacy Interests of Participants

Protecting Privacy:

Patients will be asked if this is a good time to answer questions. All patients will have the right to refuse to answer questions when called. All calls will be done in a secure office and the data is deidentified when entered. It will be stored using a unique study identifier.

Access to Participants:

All patients are required to sign a consent that states their privacy of the data being collected. In addition, they are required to sign a HIPAA consent that further describes the data being collected. It also describes that all data is deidentified and stored in a secure database. They will be informed that data is stored and reviewed in box which is HIPAA compliant and that only study personnel have accesss.

19.0 Compensation for Research-Related Injury

Compensation for Research-Related Injury:

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to the patient and/or insurance company.

Contract Language: N/A

20.0 Consent Process

Consent Process (when consent will be obtained): Patients will be identified in the pre-operative time period by the surgeons and if possible will be consented by the research coordinator or research assistant. If patients have more questions and do not want to sign at their clinic will be asked if it is allowable for a study staff member to contact them prior to surgery via phone to clarify if they have any questions. On the day of surgery, if the patient has not already signed consent and is still interested in participating in the study they will be presented with consent and Health and Insurance Portability and Accountability Act (HIPAA) forms. The patient will review the forms with the surgeon, research staff, or anesthesiologist, with the REDCap e-consent process being preferentially used. Subjects will be reminded that participation is completely voluntary, and that they may stop participation at any time without question or penalty. The surgeon, research staff, or anesthesiologist will answer any questions that the subjects may have about the study. If the patient decides to participate, they will be asked to sign the consent and HIPAA forms. One copy will be saved for study records, and the subject will be provided with a copy of the forms for their own records.

Waiver or Alteration of Consent Process: N/A

Non-English Speaking Participants: N/A- No Non-English speaking patients will be enrolled in this study.

Participants Who Are Not Yet Adults: N/A

Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

Adults Unable to Consent: N/A

21.0 Setting

Research Sites: Patients will be consented in the surgeon's clinic, pre assessment clinic, or preoperative area. The surgical procedures will take place at the M health Ambulatory Surgery Center or Fairview Riverside campus.

International Research: N/A

22.0 Multi-Site Research N/A

23.0 Resources Available

Resources Available:

Research assistants are available to aid in consent and data acquisition. All research assistants will be familiar with the study protocol and have experience working with similar studies.

We plan to enroll 70 subjects. The plan is to screen 90 subjects to research this target population. This center performs approximately 300 TSAs annually. We plan to conduct this study over 3 months. Enrollment and data collection will be completed at this time. Statistical Analysis will take approximately two months to complete.

All procedures will be performed in the clinical facilities at the MHealth Clinics and Surgery Center and at the west and East Bank. Data storage and analysis will be done using desktop equipment which is available at the Research Office B573 Mayo.

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed.

Care for such injuries will be billed in the ordinary manner, to the patient and/or insurance company.

All study personnel will be adequately trained by the Principle Investigator on the study protocol and study conduct. A log will be maintained to track which personnel are trained. A delegation of authority log will also be maintained to track which personnel are responsible for specific duties.

24.0 References

1. Vandepitte C, Kuroda M, Witvrouw R et al. Addition of liposome bupivacaine to bupivacaine HCl versus bupivacaine HCl alone for interscalene brachial plexus block in patients having major shoulder surgery. *Reg Anesth Pain Med*. 2017;42:334-341.