Liposomal Bupivacaine Interscalene Nerve Block in Shoulder Arthroplasty: A Single Blinded Prospective Randomized Control Trial

NCT03663283

6/10/2018

Liposomal Bupivacaine Interscalene Nerve Block in Shoulder Arthroplasty: A Single Blinded Prospective Randomized Control Trial

Principle investigator: Dr. Steven Hattrup

Co-investigators: [redacted]

Statistician: [redacted]

Protocol Number (IRBe): 18-005366

Initial version: 5/20/2018 Version **(1.0)**

Table of Contents

1.1 Background 4
1.2 Dose Rationale 4
1.3 Risks and Benefits 5
2 STUDY OBJECTIVES 5
3 STUDY DESIGN 5
3.1 General Description 5
3.2 Number of Subjects 6
3.3 Duration of Participation 6
3.4 Primary Safety Endpoints 7
4 SUBJECT SELECTION ENROLLMENT AND WITHDRAWAL 7
4.1 Inclusion Criteria 7
4.2 Exclusion Criteria 7
4.3 Subject Recruitment, Enrollment and Screening 8
4.4 Early Withdrawal of Subjects 8
5 STUDY DRUG 8
5.1 Description 8
5.2 Treatment Regimen 8
5.3 Method for Assigning Subjects to Treatment Groups 9
5.4 Preparation and Administration of Study Drug 9
5.5 Prior and Concomitant Therapy 9
5.6 Masking/Blinding of Study 10
6 STUDY PROCEDURES 10
6.1 Visit 1 10
6.2 Surgical Stay 10
6.3 Time from discharge to first post-operative visit 11
6.4 First Post-operative Visit (3-weeks post-op) 11
6.5 All Time Points 11
7 STATISTICAL PLAN 12
7.1 Sample Size Determination 12
7.2 Statistical Methods 12
7.3 Subject Population(s) for Analysis 13
8 SAFETY AND ADVERSE EVENTS 13
9 DATA HANDLING AND RECORD KEEPING 14
9.1 Confidentiality 14
9.2 Source Documents 14
9.3 Case Report Forms 15
9.4 Records Retention 15
10 STUDY MONITORING, AUDITING, AND INSPECTING 15

10.1 STUDY MONITORING PLAN 15
10.2 AUDITING AND INSPECTING 15
11 ETHICAL CONSIDERATIONS 16
12 STUDY FINANCES 16
12.1 FUNDING SOURCE 16
13 PUBLICATION PLAN 16
14 REFERENCES 17

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ASES	American Shoulder Elbow Society
CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
INB	Interscalene Nerve Block
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
PROMs	Patient Reported Outcome Measures
SANE	Single Assessment Numeric Evaluation
SST	Simple Shoulder Test
VR-12	Veteran RAND 12 Item Health Survey

Introduction

This document is a protocol for a human research study which will be evaluating the effect of liposomal bupivacaine INB on post-operative pain and narcotic consumption in patients undergoing primary total shoulder arthroplasty. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

The "Opioid Crisis" has been characterized by a significant rise in the prevalence of opioid dependence and drug related deaths. Not only has this placed a substantial strain on the health care economy, but resultant government legislation has led to greater restrictions on narcotic prescriptions. Consequently, there has been increasing interest in the development of multi-modal pain control regiments, particularly, in the post-operative period.

Furthermore, in those patients undergoing orthopedic surgery, adequate pain control is highly important[1]. Patients with poor post-operative pain management in the first 48 hours have an approximate 50 percent chance of achieving long-term satisfactory pain relief[2]. Inadequate pain management has been shown to not only increase hospital length of stay, but increase the risk of thromboembolic events, pulmonary complications[2-4], and chronic pain. Regional analgesia through the use of local anesthetic agents is a commonly employed strategy for pain management. In shoulder surgery, specifically, peripheral nerve block with long acting local anesthetic is a well-established technique for pain control. Typical agents including bupivacaine and ropivacaine, in general, provide a block duration of 12 to 24 hours.

In 2011, liposomal bupivacaine (Exparel, Pacira Pharmaceuticals, San Diego, USA) was approved by the US Food and Drug Administration (FDA) for use as a local anesthetic for surgical site infiltration. Liposomal bupivacaine is composed of a phospholipid bilayer that encapsulates bupivacaine, extending drug delivery for up to 72 hours and potentially extending periods of regional analgesia. Early studies evaluating liposomal bupivacaine noted lower subjective pain scores, increased time to first opiate medication, and decreased opiate requirements when compared to placebo[5,6].

Liposomal bupivacaine was FDA-approved for use in interscalene nerve blocks (INB) in the setting of shoulder surgery on April 6, 2018. Despite approval, there is limited data comparing liposomal bupivacaine to traditional agents in this population. The objective of this study is to determine if peripheral nerve block with liposomal bupivacaine in combination with standard bupivacaine will prolong the duration of block, improve pain scores, and decrease opioid utilization in the post-operative period when compared to peripheral nerve block with standard bupivacaine alone.

1.2 Dose Rationale

The FDA approved dosing of liposomal bupivacaine for peripheral nerve block will be utilized (maximum dose of 133 mg). FDA approved dosing ratio of liposomal bupivacaine to

bupivacaine HCl will be utilized, which recommends mg dose of bupivacaine HCl to liposomal not to exceed 1:2.

1.3 Risks and Benefits

The most significant risks associated with this study are directly related to surgery itself.

Risks associated with the nerve block: Block failure, nerve injury, hematoma, infection, and pneumothorax

Serious risks associated with bupivacaine-containing products, while extremely rare, include:

1. *Central nervous system reactions:* persistent anesthesia and paresthesias, excitation and/or depression
2. *Cardiovascular reactions:* dysrhythmias, death
3. *Allergic reactions:* anaphylaxis, angioedema.

Patients who are at highest risk of these complications including patients with severe liver and respiratory disease will be excluded from this study.

Potential benefits from participation in the study include improved post-operative outcomes: diminished post-operative pain, and decreased opioid consumption.

2 Study Objectives

The primary outcome measure will be:

1. Mean difference in patient pain scores over the first 72 hours post-operatively between two groups

Secondary outcomes will include:

1. Total opioid consumption (as measured utilizing morphine intravenous equivalents) in first 72 hours and at 3 weeks
2. Patient perceived duration of block determined as the time patient perceives complete resolution of block
3. Patient satisfaction with pain control at 72 hours, 3 weeks post-operatively and patient reported outcome measures (SANE, SST, ASES, VR-12) at 3 weeks post-operatively

3 Study Design

3.1 General Description

This will be a prospective, single-blinded randomized clinical trial comparing outcomes in patients undergoing total shoulder arthroplasty (anatomic and reverse) who receive a peripheral

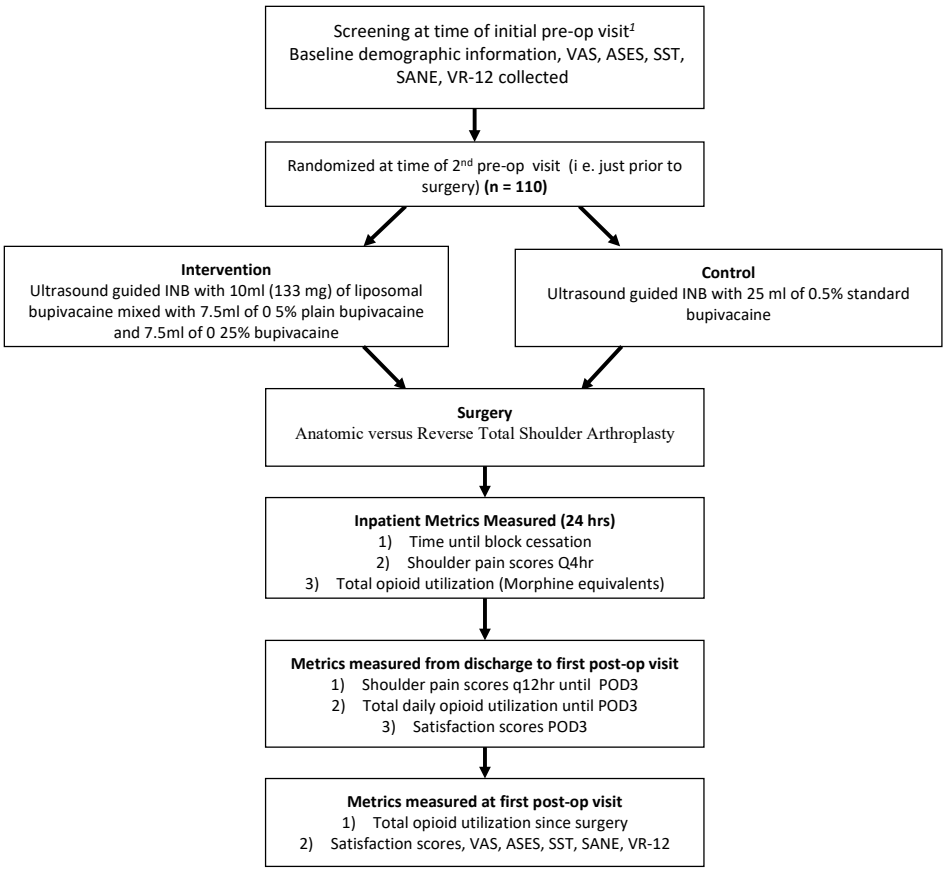
nerve block with liposomal bupivacaine in combination with standard bupivacaine versus standard bupivacaine alone. Subjects will be screened in the outpatient clinic upon initial patient election to proceed with shoulder replacement surgery. Interested and qualified patients meeting all inclusion criteria will be offered the opportunity to participate in this study. Once consent is obtained, baseline characteristics will be recorded and patients will be randomized to intervention or control. Following surgery, patients will be followed until their 3-week post-operative visit.

3.2 Number of Subjects

This study will require a sample size of 50 subjects per group in order to achieve 80% power. The target enrollment will be 110 total subjects in order to combat an expected attrition of 10%.

3.3 Duration of Participation

The duration of time that patients can expect to be directly involved in the study is 3-weeks; i.e. initial surgery up until the first post-operative visit at 3-weeks.



[1]Patient initially elects to proceed with shoulder replacement

3.4 Primary Safety Endpoints

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. In the PACU, vital signs will be obtained every 15 minutes with continuous telemetry and pulse ox, with a minimum 2:1 RN monitoring. Continuous surveillance will be exercised 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. In addition, patients will be monitored for signs of pneumothorax related to the peripheral nerve block including but not limited to: dyspnea, oxygen desaturation, or hemodynamic instability. At discharge, patients will be educated 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.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

- All adult patients (>18 years of age)
- Patients undergoing standard or reverse total shoulder arthroplasty for the primary diagnoses of glenohumeral arthritis or cuff tear arthropathy
- Cognitively intact with the ability to give informed consent as outlined by our institutional review board.
- Patients must be capable of participating in the post-operative electronic survey and / or able to maintain a written diary of events

4.2 Exclusion Criteria

- Non-elective cases
- Infection, tumor, trauma
- Weight < 50 kg
- Patients with any contraindications to regional anesthesia including allergy or hypersensitivity to amide-type local anesthetics
- Patients with allergy to any component of medication regimen e.g. amide-type local anesthetics, oxycodone, hydromorphone, fentanyl
- Chronic pain patients with history of chronic opioid use **(**defined as 20 mg morphine equivalent / day for greater than 30 days pre-operatively
- Concurrent painful physical condition that may require analgesic treatment that is not related to the shoulder surgery (chronic peripheral neuropathy, radiculopathy, or other neurologic disorder)
- Severe hepatic disease defined by clinical evidence of liver disease with abnormal liver function tests.
- Pregnancy

- Respiratory disease that contraindicates interscalene nerve block (elevated contralateral hemidiaphragm, contralateral pneumonectomy, or severe COPD with FEV1 < 50% predicted, and 02 dependence)

4.3 Subject Recruitment, Enrollment and Screening

All patients >18 years of age who present to either the PI's (SJH) or Co-Investigator's (JTT) clinical practices for elective anatomic or reverse total shoulder arthroplasty for the primary diagnoses of glenohumeral arthritis or cuff tear arthropathy and meet the inclusion criteria will be invited to participate in the study.

4.4 Early Withdrawal of Subjects

Should patient wish to withdraw from the study due to any major adverse events i.e. from the surgery, intervention, or the inpatient stay, he or she may do so without any penalty and we will monitor and treat any adverse event.

If patient decides he or she would like to withdraw from the study for any reason whatsoever, he or she may do so without any penalty even after data collection has begun.

5 Study Drug

5.1 Description

Liposomal bupivacaine (Exparel, Pacira Pharmaceuticals, San Diego, USA) was approved by the US Food and Drug Administration (FDA) for use as a local anesthetic for surgical site infiltration. Liposomal bupivacaine is composed of a phospholipid bilayer that encapsulates bupivacaine, extending drug delivery for up to 72 hours and potentially extending periods of regional analgesia. It is administered in a liquid form. On April 6th, 2018 Exparel was FDA-approved for use in INB to produce postsurgical regional anesthesia.

In this study, liposomal bupivacaine will be utilized in peripheral nerve block for the purposes of postsurgical regional anesthesia in patients undergoing shoulder arthroplasty.

5.2 Treatment Regimen

Liposomal Bupivacaine Group:

In this group, all INBs will be administered utilizing ultrasound guidance by an attending anesthesiologist experienced in the technique, or experienced anesthesiology resident with direct attending supervision and assistance. Study patients will receive 10ml (133 mg) of liposomal bupivacaine mixed with 7.5ml of 0.5% plain bupivacaine and 7.5ml of 0.25% bupivacaine. Further, 8 mg (2 ml) IV dexamethasone will be administered concomitantly at the time of the block

Control Group:

In this group, all peripheral nerve blocks will be performed with ultrasound guidance by an attending anesthesiologist experienced in the technique, or experienced anesthesiology

resident with direct attending supervision and assistance. Standard bupivacaine will be utilized. 25 ml of 0.5% bupivacaine for peripheral nerve block will be utilized. Further, 8 mg (2 ml) IV dexamethasone will be administered concomitantly at the time of the block.

5.3 Method for Assigning Subjects to Treatment Groups

Our 110 participants will be equally randomized to one of two treatment arms using a randomized block strategy with varying block sizes[7]. The randomization list will be created in SAS v9.4 (SAS Institute; Cary, NC) and will be uploaded into the REDCap randomization module.

The pharmacy team, the study coordinator, and the statistician will have access to the randomization module with the pharmacy team serving as the primary randomizers and the study coordinator and statistician serving as back-ups. Only the statistician will have knowledge of how the randomization list was built and will be the only one that has seen it.

5.4 Preparation and Administration of Study Drug

The pharmacist will prepare, and dispense the medication sequentially. Medication syringes will be blinded utilizing black tape. Patients will then undergo peripheral nerve block under ultra sound guidance and receive either the study group medication or the control group medication.

5.5 Prior and Concomitant Therapy

All patients will receive no more than 4 mg of midazolam for sedation at the time of the block. All patients will undergo general endotracheal anesthesia using propofol, fentanyl, rocuronium or succinylcholine, sevoflurane in air-oxygen, and ondansetron. Fentanyl will be limited to 250 micrograms intraoperatively. Reversal of muscle relaxant will be with either neostigmine and glycopyrollate or suggamadex. Block success will be assessed pre-operatively with shoulder abductor weakness and re-assessed on arrival to PACU. Patients will receive a standardized post-operative pain management regimen for 24 hours from PACU arrival.

On the post-operative floor the pain regimen will be standardized according to department protocol as follows:

- Acetaminophen 1000mg Q8 hours scheduled
- Tramadol 50mg Q6 hours PRN pain scale 4-6 with repeat dose
- Tramadol 100mg Q6 hours PRN pain scale 7-10 with repeat dose
- Oxycodone 5mg Q4 hours PRN pain scale 4-6 with repeat dose for pain not controlled with tramadol
- Oxycodone 10mg Q4 hours PRN pain scale 7-10 for pain not controlled with tramadol
- IV Fentanyl 25 mcg Q2hr PRN pain scale 7-10 with repeat dose for pain not controlled with above

Discharge medications will include one of the following options:

1. Oxycodone 5 or 10 mg Q4 hrs PRN for moderate (5-6) to severe (7-10) pain
2. Oxycodone-acetaminophen 5/325 or 10/325 Q4 hrs PRN for moderate (5-6) to severe (7-10) pain, not to exceed 8/day
3. Hydrocodone-acetaminophen 5/325 or 10/325 Q4 hrs PRN for moderate (5-6) to severe (7-10) pain, not to exceed 8/day
4. Tramadol 50 mg or 100 mg Q6 hrs PRN for moderate (5-6) to severe (7-10) pain, not to exceed 6/day
5. Tylenol 1000 mg q6hr PRN pain moderate to severe pain, total dose not to exceed 4000 mg/day

5.6 Masking/Blinding of Study

Patients, care team in recovery, study team members collecting and recording data, and statisticians will be blinded to randomization assignment. The administering anesthesiologist and pharmacy will be unblinded. 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. Further, all additional standard precautionary measures (e.g. wrist band) will be similarly implemented for both patient groups.

6 Study Procedures

6.1 Visit 1

This will be the initial visit when patient elects to undergo total shoulder replacement surgery. Patients who meet inclusion criteria will be given the opportunity to be enrolled in the study if they so choose. A brief survey will be performed by the research assistant to determine if any exclusion criteria are met. Should they elect to partake, they will be consented and assigned to specific treatment groups. Patient pain scales (VAS) and patient reported outcome measures (ASES, SST, SANE, VR-12) will be measured at the pre-operative visit. All patient demographic information and medical history will be obtained as is routine during the pre-operative visit.

6.2 Surgical Stay

Patient reported pain will be measured utilizing visual analogue scales – VAS at 4 hour intervals during the duration of their inpatient hospitalization following surgery. Further, time until cessation of the nerve blockade as quantified as time to patient reported cessation of the nerve blockade, and time until first opioid rescue will be noted. Patients and nursing staff will be educated on how to accurately quantify time to patient reported cessation of the nerve blockade as follows: pain scores of 3 or greater at surgical site will be considered as time of cessation of nerve block.

Furthermore, all narcotic utilization during the hospitalization will be recorded. All values will be presented as morphine equivalents[8].

Operative time, laterality of surgery, length of stay, and disposition at discharge from the hospital will additionally be collected.

6.3 Time from discharge to first post-operative visit

At discharge, pain scores will be measured utilizing electronically managed surveys that will be e-mailed to each patient on a twice daily basis (upon waking the AM and just prior to bedtime) after discharge for the first 72 hours following surgery. Finally, patient satisfaction scores (Likert scores) will be emailed to the subjects at 72 hours.

Total opioid consumption will similarly be measured based off of electronically managed surveys or a written diary on a daily basis following discharge for the first 72 hours. All values will be presented as morphine equivalents.

6.4 First Post-operative Visit (3-weeks post-op)

During the first follow-up visit, total opioid consumption during their post-operative course will be measured, and pain scales and satisfaction scores will be obtained including ASES, SST, SANE, VR-12. Total opioid consumption will be quantified by the number of narcotic prescription pills remaining. Opioid consumption will be standardized to morphine equivalents. All diaries will be collected at this time.

6.5 All Time Points

If patient non-compliance with electronic surveys is identified, the study coordinator will attempt to contact non-compliant patient to either encourage him/her to either complete the surveys, or to directly obtain respective data points from them. Further, patients who are given diaries will receive daily reminder phone calls from the study coordinator in the 72 hours following discharge.

Complications will be recorded. These include cardiac arrest, acute respiratory failure, venous thromboembolism event, ileus, SSI, deep infections, urinary tract infection, nerve injury, pneumothorax.

Schedule of Events

Study Activity	Pre-op Visit	Surgical Stay	Time from discharge to first post-op visit	Post-op Visit
Study Agent Administration		X		
Informed consent	X			
Randomization		X[a]		
Demographics	X			
History / Physical Exam	X			
Concurrent Meds	X			
Pain Scores	X	X	X	X
PROMs[b]	X			X
Satisfaction Scores[c]			X	X
Opioid Use		X	X	X
Adverse Event Evaluation		X	X	

a: In pre-op, will be performed by pharmacy
b: ASES, SANE, SST, VR-12 scores
c: Obtained at 72 hrs post-op and at 1st post-op visit

7 Statistical Plan

7.1 Sample Size Determination

Using an equal-variance t-test with a multiplicity-adjusted alpha of 0.0167 (0.05/3), we need 55 subjects per group in order to achieve 80% power to detect a true effect size of 0.66 or larger. The total sample size of 110 includes 10 additional patients to protect against an estimated attrition rate of 10%. The effect size was estimated using an established MCID of 2[9] for VAS pain scales and a standard deviation of 3.

7.2 Statistical Methods

Descriptive Statistics

Univariate descriptive statistics for categorical variables will include frequency and percent and for numerical variables will include mean, standard deviation, median, and range (minimum value, maximum value). Univariate tests of these variables with the treatment variable will be performed with either the Chi-Square test or two sample t-test in order to identify potential confounders.

Handling of Missing Data

Initial descriptive statistics will be performed to quantify univariate missingness and distribution of variables. Observed values that appear to be extreme will be verified with the research staff for accuracy. If extreme values do not appear to exhibit undue influence on the statistical methods they will be kept in the analysis. Otherwise they will be removed. Extreme values found to be erroneous will be corrected.

Missing values for outcomes (e.g. VAS, opioid consumption, etc) will be imputed using the last observation carried forward method. Since we expect downward trends in these observations as time from procedure increases, this method will provide a conservative between-treatment estimate of the effect (assuming the observations are missing at random and are roughly missing with equal frequency within each treatment group).

These results will be compared to the results of a linear mixed-model which doesn't require that every patient has data for every measure at every point in time. Instead, it all information recorded and only excludes those time points at which data is missing. For example, if a patient is missing data at 48 hours, then the linear mixed-model will only include the data at 24 hours and 72 hours. In contrast, the last observation carried forward method would use the observed value from 24 hours for the 48 hour value and then all three time points will be included.
In both cases, the baseline values for VAS and opioid consumption must be known for the patient to be included in the analysis.

Multiplicity

There is only one primary hypothesis so we will not adjust for multiplicity at the highest level. However, if the linear mixed-model shows that the time by treatment interaction term is statistically significant and we perform post-hoc pairwise comparisons, the Tukey-Kramer

method will be used to adjust for multiple comparisons. There are several secondary aims that we consider exploratory analyses and as such will not adjust for multiple comparisons.

Primary Hypothesis: The average post-op pain score, adjusted for baseline pain scores, over the 72 hours post-op will be significantly lower in the liposomal bupivacaine group.

The difference in post-operative numeric pain scores between the treatment groups over time will be analyzed using a linear mixed-model with an interaction term for time and treatment and will adjust for the baseline (pre-op) scores.

Secondary Hypothesis 1: The average post-op satisfaction score over the 72 hours post-op will be significantly lower in the liposomal bupivacaine group.

The difference in post-operative numeric satisfaction scores between the treatment groups over time will be analyzed using a linear mixed-model with an interaction term for time and treatment.

Secondary Hypothesis 2: Time to block cessation will be longer in the liposomal bupivacaine group than the standard bupivacaine group.

The difference in time to block cessation will be analyzed between treatment groups using a two sample t-test if necessary model assumptions are met or the Wilcoxon Rank-Sum test if assumptions are not met.

Secondary Hypothesis 3: Total opioid consumption will be significantly lower in the liposomal bupivacaine group.

The distribution of total opioid consumption for the two groups will be compared using a multiple linear regression model with a term to adjust for baseline opioid consumption.

Interim Analysis
Our study does not entail any sequential or adaptive trial designs and as such requires no interim analyses.

7.3 Subject Population(s) for Analysis

Only patients who are randomized into the study and have necessary baseline values for primary and secondary outcomes will be included in the analyses.

8 Safety and Adverse Events

8.1 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.

8.2 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.

8.3 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.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

The study coordinator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject. Source documents are defined as documentation of the observations and activities of a clinical study. Source documents may include, but are not limited to, study progress notes, e-mail, correspondence, subject quality of life surveys, subject diaries, computer printouts, laboratory data, and recorded data from automated instruments. All source documents for this study will be maintained by the

investigator in accordance with ICH GCP and applicable regional or national regulations. The official signed informed consent form (ICF) for each subject will be maintained as a source document, and a copy provided to the subject.

When paper source documents are used, ICH GCP and applicable regional or national regulations documentation guidelines will be followed. For example, incorrect entries should be crossed out with a single pen stroke. Corrections must be made adjacent to the item to be altered, initialed and dated with the reason for the correction if necessary by the investigator or designee. Overwriting of data or use of a liquid correction is not allowed.

Designated study personnel will enter data from source documents corresponding to a subject's visit into the protocol specific redcap database. Subjects will not be identified by name in the study database, but will be identified by a subject number.

9.3 Case Report Forms

Subject data will be entered into a RedCap database. Each field in the RedCap database will be filled out completely by the investigator or designee as stated in the Delegation of Authority Log. All data entry in RedCap will have corresponding source documentation filed in the subject study record.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for as outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy"

All data will be stored in a locked office and will be maintained for at least 5 years after the completion of the project. Any data containing patient personal information will be destroyed once the study is complete and final report written.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator

will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

This study will not include any vulnerable subjects.

12 Study Finances

12.1 Funding Source

This study will be independently funded by the respective departments. Additional, a Mayo Small Grant application is currently in submission.

13 Publication Plan

The primary responsibility for publication of the results of this study will be held by the PI (SJH). Approval must first be obtained from the PI prior to any dissemination of study results to any third parties.

14 References

1. Hamilton DF, Lane J V, Gaston P, et al. What determines patient satisfaction with surgery? A prospective cohort study of 4709 patients following total joint replacement. *BMJ Open*. 2013;3(4). doi:10.1136/bmjopen-2012-002525.

2. Wells N, Pasero C, Mccaffery M. Chapter 17 . Improving the Quality of Care Through Pain Assessment and Management. *Patient Saf Qual An Evidence-Based Handb Nurses Vol 1*. 2004.

3. American Society of Anesthesiologists Task Force on Acute Pain Management. 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. *Anesthesiology*. 2012;116(2):248-273. doi:10.1097/ALN.0b013e31823c1030.

4. Wu CL, Naqibuddin M, Rowlingson AJ, Lietman SA, Jermyn RM, Fleisher LA. The effect of pain on health-related quality of life in the immediate postoperative period. *Anesth Analg*. 2003;97(4):1078-1085, table of contents.

5. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of depofoam?? bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. *Adv Ther*. 2011;28(9):776-788. doi:10.1007/s12325-011-0052-y.

6. Gorfine SR, Onel E, Patou G, Krivokapic Z V. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. *Dis Colon Rectum*. 2011;54(12):1552-1559. doi:10.1097/DCR.0b013e318232d4c1.

7. Efird J. Blocked randomization with randomly selected block sizes. Int J Environ Res Public Health. 2011;8:15–20. doi: 10.3390/ijerph8010015

8. Opioid Oral Moprhine Milligram Equivalent (MME) Conversion Factors. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf. Accessed July 11, 2018.

9. Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. *J Orthop Surg Res* 2015;10:24.