

Prospective, randomized
clinical trial comparing
analgesic efficacy of single
injection vs. continuous
interscalene blockade vs. local
infiltration analgesia for
patients undergoing primary
total shoulder arthroplasty

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List of Abbreviations**LIST OF ABBREVIATIONS**

AE	Adverse Event/Adverse Experience
ASA	American Society of Anesthesiologists
ASES	American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form
CISB	Continuous Interscalene Nerve Block
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
LAST	Local Anesthetic Systemic Toxicity
LIA	Local Infiltration Analgesia
NRS	Numeric Rating Scale
OBAS	Overall Benefit of Analgesia Score
PHI	Protected Health Information
PI	Principal Investigator
POD	Postoperative Day
RASS	Richmond Agitation-Sedation Scale
SAE	Serious Adverse Event/Serious Adverse Experience
SF-12	Medical Outcomes Study 12-Item Short Form
SF-36	Medical Outcomes Study 36-Item Short Form
SISB	Single injection interscalene blockade
SOP	Standard Operating Procedure
TSA	Total Shoulder Arthroplasty

Study Summary

Title	Prospective, randomized controlled trial comparing analgesic efficacy of single injection vs. continuous interscalene blockade vs. local infiltration analgesia for patients undergoing primary total shoulder arthroplasty
Running Title	SISB vs CISB vs LIA
Protocol Number	15-009646
Phase	Phase IV
Methodology	Single-center, unblinded, randomized control trial with three intervention arms
Overall Study Duration	18 Months (time when data collected for last patient)
Subject Participation Duration	16 weeks
Single or Multi-Site	Single Site
Objectives	Primary objective is to assess analgesia efficacy between single injection interscalene blockade vs. continuous interscalene nerve block vs. local infiltration analgesia for patients undergoing primary total shoulder arthroplasty. Secondary objectives include pain scores and opioid consumption at pre-defined time intervals, peripheral nerve block complications, length of hospital stay, and postoperative follow up at 12-16 weeks.
Number of Subjects	One hundred and twenty-nine patients will be randomized to one of three interventions: single injection interscalene blockade, continuous interscalene nerve block, or local infiltration analgesia
Diagnosis and Main Inclusion Criteria	Patients presenting for unilateral primary total shoulder arthroplasty (includes anatomic and reverse total shoulder arthroplasty), who are able to provide to consent, older than 18 years of age, and have American Society of Anesthesiologists (ASA) physiological status I-III
Study Product, Dose, Route, Regimen	Ropivacaine weight base dose mixed with epinephrine, ketorolac, and normal saline 0.9% injected once in the periarticular structures of the shoulder joint by the surgeon
Duration of Administration	One time injection
Reference therapy	Interscalene brachial plexus block utilizing bupivacaine hydrochloride
Statistical Methodology	Randomization of each patient to a study arm will occur in a 1:1:1 allocation utilizing randomization schedule which will be created by the Division of Biomedical Statistics and Informatics. Subgroup analysis will be performed evaluating reverse total shoulder arthroplasty vs anatomic total shoulder arthroplasty, and patients who received allocated treatment per planned protocol

Introduction

This document is a clinical research protocol. The described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated Federal regulations, and all applicable institutional research requirements.

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

Use of study medications within this study is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in the labeling for the drug. Additionally, use of study medications within this study is not intended to support a significant change in the advertising for the product.

1.1 Background

Background and Significance

Uncontrolled postoperative pain can be associated with significant deleterious consequences, including elevated stress response, decrease quality of life, increase in morbidity and mortality, and the potential for persistent post-surgical pain.¹ Total shoulder arthroplasty (TSA) is considered to be a major surgical procedure resulting in severe postoperative pain, especially in the first 48 hours after surgery.² Establishing a clinical pathway for total joint arthroplasty, utilizing a multi-modal analgesic approach including regional anesthetic techniques, appears to improve perioperative outcomes.³ The use of interscalene brachial plexus nerve block remains the cornerstone for analgesia following shoulder surgery in comparison to suprascapular nerve block, intra-articular injection, and intravenous opioids.^{4,5} Single injection interscalene blockade (SISB) provides adequate pain relief; however, no optimal dose has been identified and the duration of action is variable.⁶ Continuous interscalene nerve block (CISB) provides extended analgesia compared to SISB, suggesting its use may be more appropriate for moderate-to-severe painful shoulder procedures.^{7,8} Although analgesia following intra-articular and subacromial local anesthetic injections compared to interscalene brachial plexus block has shown to be less efficacious, variability includes operator experience, injection technique, medication solution with various adjuvants, and surgical procedure.^{9,10}

CISB has the potential to improve analgesia when compared to SISB; however, potential problems encountered include technical difficulty of catheter placement, increased procedure time, catheter dislodgement, leakage at the site of insertion, and developing an infrastructure to support the catheter.

With the advent of local infiltration analgesia (LIA)¹¹, there has been increasing interest in its use for total joint arthroplasty.¹²⁻¹⁴ Theoretical advantages would include comparable pain scores to regional anesthesia techniques, while minimizing motor and/or sensory blockade as well as complications seen with interscalene brachial plexus blocks. Another advantage would be to

avoid utilizing catheter based regional anesthesia techniques and its potential problems as listed above. LIA is regularly performed for hip and knee surgery, and has been extended to shoulder surgery as well.^{15,16} Currently, there is limited evidence that demonstrates the superiority of either technique specifically for TSA.

Since the benefits of local infiltration analgesia within a comprehensive multimodal analgesia clinical pathway have yet to be established for total shoulder arthroplasty, differences in the analgesia outcomes between these three intervention groups would provide for an evidence-based clinical pathway that will emerge as a result of this study.

The primary aim is to investigate the hypothesis that within our current total joint regional anesthesia pathway, utilizing multimodal analgesia and regional anesthesia techniques, continuous interscalene nerve block provides superior analgesic benefit via the Overall Benefit of Analgesic Score (OBAS)¹⁷ compared to single injection interscalene blockade and local infiltration analgesia on POD 1 for primary total shoulder arthroplasty.

1.2 Investigational Technique and Agents

Local infiltration analgesia, developed by Kerr and Kohan, has only recently become a popular technique for postoperative analgesic control.¹¹ The proposed technique was developed for knee and hip joint replacement; therefore, most of the current literature utilizing local infiltration analgesia is for total hip and total knee replacements.^{12,14,18} There is limited literature utilizing local infiltration analgesia for total shoulder arthroplasty, hence the basis for this study. It is known that local infiltration analgesia involves injection of local anesthetic into the peri-articular tissues and intra-articular capsule in a systematic approach. Injection into the peri-articular tissue is thoughtfully considered, as injection of medication should be directed at tissues with high density of pain receptors.¹⁹ The two orthopedic surgeons have discussed with each other the peri-articular tissue areas of significance (a priori), which would provide the greatest postoperative analgesic control.

The local infiltration analgesia (LIA) group will receive a one-time injection of the “cocktail” solution (ropivacaine weight base dose mixed with epinephrine, ketorolac, and normal saline 0.9%), injected into the periarticular structures by the surgeons. This will occur after implantation of the final prostheses, but prior to closure of the fascia. All surgeons will complete the infiltration following a similar protocol, equally distributing the study medication around the glenoid and humerus, subscapularis, deltoid, posterior capsule and subcutaneous tissue.

Bupivacaine and Ropivacaine are amide local anesthetics which inactivates voltage gated sodium channels. In nerves, this results in loss of action potential and signal conduction along the nerve fiber leading to sensory and/or motor blockade. Bupivacaine and Ropivacaine are considered to be a long acting local anesthetic, and is indicated for multiple uses including local infiltration and peripheral nerve block.^{20,21}

1.3 Dose Rationale and Risk/Benefits

Local infiltration analgesia (LIA) involves injecting local anesthetic into the tissues around and within areas of the surgical wound, with the intent of providing satisfactory pain control, immediate mobilization of the surgical joint, and earlier discharge from the hospital.¹¹ Additional benefits for utilizing local infiltration analgesia techniques for the management of postoperative pain include its simplicity, decreased cost, reduced quadriceps weakness (in total knee arthroplasty patients), and reduction in risk of nerve injury following common peripheral nerve blocks.¹²

The use of interscalene brachial plexus nerve block remains the cornerstone for analgesia following shoulder surgery in comparison to suprascapular nerve block, intra-articular injection, and intravenous opioids.^{9,10} Local infiltration analgesia for shoulder surgery, despite showing to be less efficacious in terms of pain control, has not shown to be associated with adverse events.^{15,16} Theoretical advantages would include comparable pain scores to regional anesthesia techniques, while minimizing motor and/or sensory blockade as well as complications seen with interscalene brachial plexus blocks. Another advantage would be to avoid utilizing catheter based regional anesthesia techniques and its potential problems which include difficulty of catheter placement, catheter dislodgement, and leakage at insertion site. The theoretical advantages of local infiltration analgesia and the limited studies evaluating its use, particularly for total shoulder arthroplasty, are the basis for this study.

A complication associated with LIA would include local anesthetic systemic toxicity (LAST). Local anesthetic systemic toxicity is suspected if a patient has acute onset of central nervous system changes (tinnitus, metallic taste in mouth, perioral numbness) or cardiovascular changes (bradycardia, hypotension, EKG changes). This complication can occur with an intravascular injection, high systemic absorption depending on the vascularity of the site, and doses exceeding manufacturer's recommendation. LAST can also be seen with peripheral nerve blocks; therefore, the risk exists for all three intervention arms.

There are cases of chondrolysis after shoulder surgery following intra-articular infusions of local anesthetic.²² This would have no impact on our study population for two reasons: the first involves patients undergoing total joint replacement (total shoulder arthroplasty) where the cartilage and supporting structures will be replaced with an artificial joint, and the second reason involves the use of a single shot peri-articular injection (i.e. no catheters will be placed into the surgical site).

The LIA group will utilize weight based dosing of Ropivacaine as part of a "cocktail" solution (Table 1), and will receive a total volume of 120 mL injected in the periarticular structures by the surgeon. This is a one-time injection. This will occur after implantation of the final prostheses, but prior to closure of the fascia. All surgeons will complete the infiltration following a similar protocol, equally distributing the study medication around the glenoid and humerus, subscapularis, deltoid, posterior capsule and subcutaneous tissue. Medications and dosage of the LIA group is as follows:

Table 1: LIA Group

Drug	50-74.9kg	75-99.9 kg	100-125kg
Ropivacaine	200 mg	300 mg	400 mg
Epinephrine	100 mcg	200 mcg	300 mcg
Ketorolac	30 mg	30 mg	30 mg

*Normal Saline will be added to bring the total volume to 120 mL

This “cocktail” solution has been used in several studies assessing analgesic efficacy of local infiltration analgesia for a variety of orthopedic surgery.^{11,12,23} It is noted that there currently is no standard solution; therefore, the dosages and various adjuvants vary from study to study. The addition of these various adjuvants has shown to possibly provide synergy and improve analgesia^{24,25}, and is currently being used by the surgeons at our institution to perform local infiltration analgesia.

Volume is required and advocated in studies to adequately target areas of interest; therefore, it is not uncommon to see volumes greater than 100 mL for local infiltration analgesia.^{12,18}

All drug products mentioned in this study are FDA approved and commercially available. All products are administered per product prescribing information without further manipulation.

By enrolling in this study there will be no additional risk in the operation or postoperative care as these are already established modalities of care, and all acceptable alternatives. Known risks for peripheral nerve blockade include the following: bleeding, infection, and nerve damage.

Since the benefits of local infiltration analgesia within a comprehensive multimodal analgesia clinical pathway have yet to be established for total shoulder arthroplasty, differences in the analgesia outcomes between these three intervention groups would provide for an evidence-based clinical pathway that will emerge as a result of this study.

2 Study Objectives

Primary Objective

We aim to test the hypothesis that patients undergoing total shoulder arthroplasty within a clinical pathway utilizing preemptive low-dose opioid and non-opioid medications for multimodal analgesia randomized to the continuous interscalene nerve block group will report a lower OBAS score on POD 1 (from 9 am to 12 pm) when compared to randomization to the single injection interscalene blockade and local infiltration analgesia groups.

Overall benefit of Analgesic Score (OBAS) is a recently validated tool measuring patient’s experience with their postoperative pain regimen.¹⁷ This simple 7 question (Q1 to Q7) scoring system entails a combination of pain intensity, adverse opioid events, and patient satisfaction. Per Lehmann et al, the total OBAS score is calculated via ‘sum items Q1 through Q6 and add [4 – score from Q7].’¹⁷ This score consists of a 29-point scale ranging from 0 (best) to 28 (worst); therefore, lower OBAS scores indicate more analgesic benefit. This will be administered to patients on POD 1 by the study team.

Secondary Objective

Secondary outcomes consist of pain scores via NRS every four hours (if available) since PACU admission (pain score recorded to the closest time interval will be acceptable), the use of additional opioid medications (measured in morphine equivalents), length of hospital stay (number of postoperative days), reason for hospital length of stay > 1 night (i.e., social work/disposition, inadequate pain control, nausea/vomiting, other), complications during regional anesthesia block placement (inadvertent intravascular injection, inadvertent epidural or subarachnoid injection, local anesthetic systemic toxicity and pneumothorax) or during local infiltration analgesia injection (local anesthetic systemic toxicity), catheter-related complications (presence of site infection, hematoma, local anesthetic systemic toxicity), inadvertent catheter dislodgement, and a postoperative follow up at 12-16 weeks via telephone call or office visit evaluating multiple factors including a chronic pain assessment, health-related quality of life, and functional outcome specific to shoulder surgery.

Patients reporting a pain score via NRS > 3 at the 12-16 week postoperative period will be asked to complete the validated Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) during the visit.^{26,27} The primary purpose of the LANSS scale is to assess nerve damage resulting in neuropathic pain.

Health-related quality of life will be assessed with the Medical Outcomes Study 12-Item Short Form (SF-12) questionnaire preoperatively and at the 12-16 week postoperative visit or telephone call. The SF-12 is a widely used, standardized and validated instrument.²⁸ Briefly, the SF-12 is a shorter version of the Medical Outcomes Study 36-Item Short Form (SF-36)²⁹, and scores 8 scales (physical functioning, role functioning-physical, bodily pain, general health, energy, social functioning, role functioning-emotional, and mental health), with higher scores indicating better health. SF-12 is commonly used as a general health-related quality of life measure in shoulder surgery.³⁰⁻³³

American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form (ASES) is a scoring system developed by the Society of the American Shoulder and Elbow Surgeons to standardize outcome measures in shoulder and elbow surgery.³⁴ It is widely used in North America, and considered a valid and reliable tool.^{33,35,36} ASES questionnaire will be collected pre-operatively and 1 to 1.5 years postoperatively via office visit or telephone call. Collected data will be used in a follow-up study.

3 Study Design

3.1 General Design

Single-center, unblinded, randomized control trial with three intervention arms assessing acute pain management. These three arms include: 1) single shot interscalene blockade (SISB group); 2) continuous interscalene nerve block (CISB group); 3) local infiltration analgesia (LIA group) into the periarticular soft tissues at the time of shoulder replacement.

The study will be registered with www.ClinicalTrials.gov

After approval by Mayo Clinic IRB, we will work closely with the department of orthopedics at Mayo Clinic Hospital, Methodist Campus to enroll patients into the study. Potential subjects will consist of patients who present for elective primary TSA meeting the inclusion and exclusion criteria (sections 4.1 and 4.2). Subjects will be approached by study staff for recruitment in person and informed consent will be obtained. Subjects unable to give consent themselves will not be approached for participation. No remuneration will be provided. All efforts will be made to enroll participants regardless of ethnic heritage. No passive recruitment methods (newspapers, advertisements, or flyers) will be used.

One hundred and twenty-nine patients are required for this clinical trial. After baseline values are established, data will prospectively be collected during the peri-operative period up to 16 weeks post-operatively (patient will have follow-up via office visit or telephone call) for the purpose of this study. Data will continue to be collected up to 1.5 years post-operatively, particularly the ASES score, and resulting data will plan to be used in a follow-up study. Data will be collected utilizing the institution's electronic medical record system, and be transferred to an electronic research database (REDCap).

3.2 Primary Study Endpoints

To investigate the hypothesis that within our current total joint regional anesthesia pathway, utilizing multimodal analgesia and regional anesthesia techniques, continuous interscalene nerve block provides superior analgesic benefit via the Overall Benefit of Analgesic Score (OBAS) compared to single injection interscalene blockade and local infiltration analgesia on POD 1 (defined as 9 am to 12 pm) for primary total shoulder arthroplasty.

3.3 Secondary Study Endpoints

1. Pain intensity (NRS) assessments prior to post-anesthesia care unit (PACU) discharge, every 4 hours beginning on arrival to patient room (to the closet time interval), and prior to hospital discharge or 12 pm on POD 1 (whichever comes first).
2. Opioid consumption in daily oral morphine equivalents (OME) – preoperative, intraoperative, PACU stay, and total beginning on arrival to patient room until patient discharge or up to POD 3 (whichever comes first).
3. Moderate to severe complications during regional anesthesia block placement (inadvertent intravascular injection⁺, inadvertent epidural or subarachnoid injection, local anesthetic systemic toxicity*, and pneumothorax) or during local infiltration analgesia injection (local anesthetic systemic toxicity).
 - a) ⁺*Inadvertent intravascular injection is suspected if a patient experiences sudden loss of consciousness, apnea, convulsions, hypotension, respiratory depression, nausea or dizziness, or stroke symptomology.*
 - b) ^{*}*Local anesthetic systemic toxicity is suspected if a patient has acute onset of central nervous system changes (tinnitus, metallic taste in mouth, perioral numbness) or cardiovascular changes (bradycardia, hypotension, EKG changes).*

4. Peripheral nerve block catheter-related complications including presence of site infection (tenderness to palpation, erythema, swelling, drainage of pus), hematoma, inadvertent catheter dislodgement, and local anesthetic systemic toxicity.
5. Duration of hospital stay (number of days), in addition to reason for hospital length of stay > 1 night (i.e., social work/disposition, inadequate pain control, nausea/vomiting, other)
6. Postoperative follow-up
 - a. Telephone encounter or office visit follow up 12 to 16 weeks postoperatively- NRS pain scores at rest and with movement of surgical extremity, postoperative neurologic changes (persistent numbness, paresthesia, or weakness of surgical extremity), and complications or adverse events will be noted.
7. Questionnaire Forms
 - a) SF-12
 - i. Collected preoperatively and at the 12-16 week postoperative visit or telephone call.
 - b) ASES
 - i. Collected preoperatively and 1-1.5 year postoperative visit or telephone call (data to be used in a follow-up study).
 - c) LANSS
 - i. Collected at 12-16 week follow-up visit to assess neuropathic pain in patients complaining of pain.

3.4 Primary Safety Endpoints

These methods are already established procedures in the practice of perioperative pain control for a total shoulder arthroplasty. There is minimal risk of placing a peripheral nerve block. Those risks include infection, bleeding, and/or nerve damage. Patients will be monitored during the perioperative period for any adverse events (as defined below and in section 8). During regional anesthesia block placement, trained sedation nurses or anesthesia personnel (staff physicians, residents, or nurse anesthetists) will be monitoring patients. Patients will be monitored throughout the procedure utilizing the American Society of Anesthesiologists (ASA) standard monitors*, aspirating for blood or cerebral spinal fluid (CSF) prior to administration of local anesthetic solution in divided doses, frequent assessment of the patient's well-being via verbal communication, and having emergency medications and airway equipment readily available at all times. Performing this regional block is considered standard in our practice in order to provide optimal postoperative analgesia.

** blood pressure (non-invasive blood pressure cuff cycling every 3 to 5 minutes or continuous arterial blood pressure monitoring placed due to clinical judgment of covering anesthesiologist), 5 lead EKG, continuous pulse-oximetry, and continuous monitoring from operating room anesthesia personnel (if the procedure is performed in the operating room) or frequent assessments by nurses who are trained to care for patients receiving regional anesthesia blocks (if procedure is performed in block room)*

Patients undergoing local infiltration analgesia will have their block placed in the operating room by the surgeon under general anesthesia. Per ASA standards, trained anesthesia personnel will be directly monitoring the patient at all times during the surgical case, in addition to frequent

assessment of vital signs via standard monitors of care, which includes frequent blood pressure reading (blood pressure cuff or arterial line), rhythm analysis (5 lead EKG), heart rate (EKG), oxygen saturation (pulse-oximetry), temperature, and ventilation via end tidal carbon dioxide detection. Similar to regional block placement, blood pressure monitoring involves the following: non-invasive blood pressure cuff cycling every 3 to 5 minutes or continuous arterial blood pressure monitoring (placed due to clinical judgment of covering anesthesiologist).

Patients admitted to the regular nursing floors will have a continuous pulse-oximeter if a continuous peripheral nerve block is present. In addition, vital signs (heart rate, oxygen saturation, and blood pressure) will be captured every 4 hours or more frequently if the clinical situation dictates in all postoperative orthopedic patients.

Daily follow-up will occur by the inpatient pain service and surgical team. Adverse events and/or complications will be monitored, which includes but not limited to, local anesthetic systemic toxicity, neurologic complications, hematoma, bleeding, infection, and wound problems. Nerve damage and assessment is part of the follow-up regarding this study and will be followed closely. In the event an infection was to occur, the PI would be notified, protocol would be followed, and investigators of the study would review the incident.

The principal investigator or a designated co-investigator of the study will be notified if a patient in the study requires an unanticipated ICU admission.

Please refer to section 8 for detailed explanation for management of adverse events or complications.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Adult patients with an American Society of Anesthesiologists (ASA) physiological status I-III
2. Patients presenting for unilateral primary total shoulder arthroplasty (includes anatomic and reverse total shoulder arthroplasty).
3. Patients 18 years of age and older
4. Able to provide informed consent for him or herself

4.2 Exclusion Criteria

- 1) Chronic pain syndromes such as fibromyalgia or complex regional pain syndrome
- 2) Chronic opioid use (>1 mos) with OME >5 mg/day OR acute opioid use (< 1 mos) with OME > 30 mg/day.
- 3) Body mass index (BMI) > 45 kg/m²
- 4) Severe drug allergy* to medications used in this study, including non-steroidal anti-inflammatory drugs (i.e. celecoxib and ketorolac), and local anesthetics.

- **defined as an immune reaction resulting in shortness of breath, hives, anaphylaxis, wheezing, and fever*
- 5) History of Malignant Hyperthermia.
 - 6) Major systemic medical problems such as:
 - Pre-existing severe renal disorder defined as glomerular filtration rate (GFR) <50 units/m² (if labs are available), currently on dialysis, or highly suspected based on history.
 - Severe hepatic disorder defined as current or past diagnosis of acute/subacute necrosis of liver, acute hepatic failure, chronic liver disease, cirrhosis (primary biliary cirrhosis), chronic hepatitis/toxic hepatitis, liver abscess, hepatic coma, hepatorenal syndrome, other disorders of liver
 - Pre-existing medical history of moderate to severe pulmonary disease (obstructive and/or restrictive), use of home oxygen, preoperative baseline oxygen saturation < 94% on room air, FEV 1 < 60% of predicted value (obstructive disease), VC or TLC < 70% predicted value (restrictive disease).³⁷
 - History of contralateral hemidiaphragm dysfunction (e.g., paralysis) or phrenic nerve injury.
 - 7) Contraindication to a regional anesthesia technique (e.g., preexisting neuropathy⁺ in the operative extremity, coagulopathy, sepsis, infection at site of injection, uncooperative, refusal, anticoagulation medications not held within appropriate time frame^{*}).
 - ⁺ *pre-existing neuropathy includes sensory and/or motor deficits due to nerve insult of surgical extremity, radicular symptoms of surgical extremity, history of unresolved brachial plexus injury/brachial plexopathy, and tumors of the brachial plexus. Patients with nerve compression distal to site of surgery, such as history of carpal tunnel syndrome or cubital tunnel syndrome, are NOT considered contraindications to regional anesthesia.*
 - ^{*} *Per ASRA guidelines, Clopidogrel (Plavix) held for at least 7 days, Dabigatran (Pradaxa) held for at least 5 days, Rivaroxaban (Xarelto) held for at least 3 days, Warfarin (Coumadin) held for at least 5 days or recent INR of less than 1.4, Enoxaparin (Lovenox) with doses > 1 mg/kg held for close to 24 hours.*³⁸
 - 8) Previous contralateral total shoulder replacement managed with regional anesthetic nerve block or periarticular injection/intraarticular injection within the previous 12 months.
 - 9) Known to be currently pregnant or actively breastfeeding⁺⁺
 - ⁺⁺ *Patients that have a previous history of menopause, hysterectomy, or tubal ligation will not be required to perform a pregnancy test. Female patients that do not meet this criterion will be asked to submit a urine sample, and will require a negative urine sample in order to proceed with study protocol. Urine sample be collected pre-procedurally.*
 - 10) Impaired cognition

4.3 Subject Recruitment, Enrollment and Screening

After approval by Mayo Clinic IRB, we will work closely with the department of orthopedics at Mayo Clinic Hospital, Methodist Campus to enroll patients into the study. Potential subjects will consist of patients who present for elective primary TSA meeting the above inclusion and exclusion criteria (section 4.1 and 4.2). Subjects will be approached by study staff for

recruitment in person and informed consent will be obtained. Subjects unable to give consent themselves will not be approached for participation. No remuneration will be provided. All efforts will be made to enroll participants regardless of ethnic heritage. No passive recruitment methods (newspapers, advertisements, or flyers) will be used.

Research study coordinators will meet eligible participants at either their preoperative orthopedic appointment or the morning of surgery provided they are not the first surgical case of the day. A sufficient amount of time will be given to the patient to answer any questions he or she may have and to allow the patient to make a well informed decision.

Of note, study staff/clinical research unit, which includes the research study coordinators, is composed of RN's and RRT's. Given that this is an institutional initiated study, the study staff is able to enroll patients meeting all inclusion/exclusion criteria into the study. In the event that there are any questions or concerns, the study coordinators will contact the PI/Co-PI's.

Discussion of study participation will be conducted in a private room in the presence of the patient's family if he/she so desires. Information will be provided to the patient without any time pressure. Interruptions to this discussion will be minimized by holding this discussion after most of the necessary (not study related) preoperative patient care processes are completed. The study recruiter will be different from the care team. Patients will be reassured that participation in the study does not change in any way their care beyond the random allocation to one of the three intervention arms and subsequent data collection.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

If the patient is unable to comply with the study protocol or they wish to withdraw from the study their participation in the study will be terminated. If the interscalene nerve block catheter becomes occluded or is pulled out prematurely, patients will remain in the study as our primary analysis will be performed based on the intention to treat.

In order to account for 10% dropout, which includes patients terminated from the study, a total sample-size of N=129 (43 per group) is proposed. Follow-up will not be performed for patients terminated from the study due to voluntary purposes.

If the patient chooses not to participate he or she will be provided the current perioperative care plan in place by the surgeon and will include pain management regardless of participation.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Patients who voluntarily withdraw from the study will have their data collected in the perioperative and follow-up periods up to the point of termination.

Study team will determine if an adverse event occurred (section 8.1 of IND protocol) and will assess the relationship to study protocol (including study medications). If causality is certain, probable/likely, or possible as per WHO-UMC causality assessment system³⁹, study team will make every attempt to follow up with patient until adverse event is resolved.

Our primary analysis will be performed based on the intention to treat. A subgroup analysis will also be performed on patients who received the allocated treatment as per the planned protocol and.

The primary outcome for this study involves assessing its analgesic efficacy compared to other standard methods of regional anesthesia acute pain management techniques for patients undergoing total shoulder arthroplasty. Survival data will not be assessed in this study; thus, we will plan to exclude data after a patient's termination/withdrawal date.

If the patient chooses not to participate he or she will be provided the current perioperative care plan in place by the surgeon and will include pain management regardless of participation.

5 Study Drugs

5.1 Description

Pre-mixed bupivacaine 0.5% with epinephrine 1:200,000 is packaged within a clear glass vial, containing 150 mg (30 mL) of bupivacaine. Solution is sterile, and clear and colorless. Bupivacaine is readily available and commonly stocked at our institution. Similarly, ropivacaine is a sterile, and clear and colorless solution that is readily available and commonly stocked at our institution.

All drug products mentioned in this study are FDA approved and commercially available. All products are administered per product prescribing information without further manipulation.

5.2 Treatment Regimen

As mentioned above in section 1.3, the LIA group will utilize weight based dosing of Ropivacaine as part of a "cocktail" solution (Table 1), and will receive a total volume of 120 mL injected in the periarticular structures by the surgeon. This is a one-time injection. This will occur after implantation of the final prostheses, but prior to closure of the fascia. All surgeons will complete the infiltration following a similar protocol, equally distributing the study medication around the glenoid and humerus, subscapularis, deltoid, posterior capsule and subcutaneous tissue. Medications and dosage of the LIA group is as follows:

Table 1: LIA Group

Drug	50-74.9kg	75-99.9 kg	100-125kg
Ropivacaine	200 mg	300 mg	400 mg
Epinephrine	100 mcg	200 mcg	300 mcg
Ketorolac	30 mg	30 mg	30 mg

*Normal Saline will be added to bring the total volume to 120 mL

SISB and CISB groups will utilize pre-mixed bupivacaine 0.5% with epinephrine 1:200,000 vial for the initial loading bolus. CISB group will have a continuous catheter attached to a pain pump infusing bupivacaine 0.2% when the patient arrives to the PACU.

Table 2 demonstrates the study medication for SISB and CISB groups.

Table 2: CISB and SISB Group – Bolus Injection

<i>Nerve Blocked</i>	<i>Local Anesthetic</i>	<i>Concentration</i>	<i>Volume milliliters (mL)</i>	<i>- Adjuvants Added</i>
Interscalene Brachial Plexus – CISB and SISB	Bupivacaine	0.5%	15 to 20 mL	1:200,000 Epinephrine

Please refer to section 6.2 for the SISB and CISB groups' technique and administration of local anesthetic.

5.3 Method for Assigning Subjects to Treatment Groups

The treatment allocation will be performed using a randomization schedule which will be created by the Division of Biomedical Statistics and Informatics. This randomization schedule will be generated using a SAS program (SAS version 9.3, SAS Institute Inc, Cary NC) with randomization performed in blocks of size N=6 to ensure that after every sixth patient is enrolled there are an equal number of patients assigned to each of the 3 treatment conditions. Using this randomization schedule, an EXCEL spreadsheet application will be created which will include sequentially assigned subject-ID numbers and corresponding treatment assignments. When a patient is enrolled they will be assigned the next sequential subject-ID number and a member of the anesthesia clinical research unit, who will be different from the care team and are not involved in the medical management of the patient, will use the online system to retrieve the allocated treatment assignment for this subject-ID.

5.4 Preparation and Administration of Study Drugs

Please refer to section 5.2 with regards to treatment regimen and administration of the “cocktail” solution for the LIA group.

Pharmacy prepares the weight based dose Ropivacaine, Epinephrine, Ketorolac 30 mg, in Normal Saline 0.9% (for a total volume of 120 mL) and provides this to the surgical staff. The Department of Pharmacy follows United States Pharmacopeia (USP) <797> preparation standards.⁴⁰ In general, the pharmacy uses environmental engineering controls for air quality of the preparation area, personal protective equipment during compounding, and performs preparation within laminar flow hoods. This “cocktail” solution will be dispensed to OR personnel during the surgical procedure.

The pre-made “cocktail” solution will be placed in a sterile basin located on the operating room table, within the vicinity of the surgeon and operating room technician, who are scrubbed into surgery. Sterility includes a sterile environment such as the operating room, in which a sterile field is created utilizing sterile surgical drapes. Operating room personnel handling the study

solution will be in sterile gloves and surgical gowns, hats and masks, and standing close to the surgical field.

In the SISB and CISB groups, one vial of pre-mixed bupivacaine 0.5% with epinephrine 1:200,000 will be obtained from the anesthesia stock room. Solution is sterile and will be poured in a sterile fashion into the sterile nerve block tray.

5.5 Subject Compliance Monitoring

Patients receiving treatment will be enrolled in a prospective database. No other treatment is necessary, except the treatment assignment during their scheduled procedure.

5.6 Prior and Concomitant Therapy

Patients may receive therapy for any conceivable condition, while enrolled in this trial, as long as they meet the inclusion criteria (section 4.1). Since this clinical trial is assessing analgesia efficacy between three different intervention arms, rescue analgesics will be available to all patients for uncontrolled pain as this is a standard practice at our institution.

5.7 Masking/Blinding of Study

This prospective randomized control trial will be unblinded. We acknowledge that this unblinded study design may be a limitation. We understand that there may be no way for us to prevent participants from being treated differently if the study is unblinded. They may have a different experience dependent upon the intervention biasing their observed outcome. However, we hope to discover the best overall clinical pathway for management of TSA for our patient population.

It would be very difficult to blind patients to the three intervention arms because each intervention arm involves a different nerve block technique (interscalene brachial plexus block⁴¹ vs local infiltration analgesia¹¹). The SISB and CISB groups involve placing a regional anesthesia peripheral nerve block, which is typically done in an awake patient prior to the surgical procedure. The LIA group will have their block performed by the surgeon, while the patient is under general anesthesia, towards the end of the surgical case just as the surgeon is about to close the fascia.

6 Study Procedures

6.1 Pre-Operative Plan

Following informed consent and randomization, study staff will record baseline patient demographics (including baseline NRS values for pain at rest, age, weight, gender, ASA physical status) from the electronic medical record and/or during the patient interview.

NRS pain scores at rest will be measured at the following time points: arrival to post-anesthesia care unit (PACU), prior to PACU discharge, every 4 hours beginning on arrival to patient room. Pain scores will be measured until hospital discharge from the time of the initial assessment in

the recovery room (PACU). All NRS pain scores will be recorded by registered nurses per standard protocol.

Regional Block – Both CISB and SISB:

Based on our current total joint regional anesthesia pathway (MC1156-462rev0115 and MC1156-1321rev1015), all patients will be provided (unless contraindicated and at the discretion of the attending anesthesiologist) a combination of oral analgesic medications preoperatively:

- 1) Tylenol 1 gram – at least 6 hours since last dose
- 2) Celecoxib 400 mg – for patients 18-64 years old and CrCl > 50 mL/min (if lab is available)
- 3)
 - a. Oxycodone (immediate release)
 - i. 5-10 mg once for patients 18-64 years old
- 4) Scopolamine Transdermal patch: 1.5mg - Apply to skin behind ear for 24 hours for high-risk patients (history of motion sickness or postoperative nausea vomiting). This is at the discretion of the anesthesiologist.

Local Infiltration Analgesia (LIA):

- 1) Tylenol 1 gram – at least 6 hours since last dose
- 2) Celecoxib 400 mg – for patients 18-64 years old and CrCl > 50 mL/min (if lab is available)
- 3)
 - a. Oxycodone (immediate release)
 - i. 5-10 mg once for patients 18-64 years old
- 4) Scopolamine Transdermal patch: 1.5mg - Apply to skin behind ear for 24 hours for high-risk patients (Hx: motion sickness or postoperative nausea vomiting). This is at the discretion of the anesthesiologist.

6.2 Intra-Operative Plan

General anesthesia (induction with propofol and maintenance with isoflurane inhaled anesthesia with or without use of nitrous oxide (N₂O) and oxygen combination) with use of endotracheal tube, intraoperative monitoring (standard ASA monitoring), and supplemental analgesia. The covering anesthesiologist may also consider sevoflurane or desflurane as the inhalational anesthetic. Additional intraoperative monitoring such as continuous blood pressure via arterial line will be at the discretion of the attending anesthesiologist. Each patient will receive dexamethasone 8 mg IV⁴² and granisetron 0.1 mg or ondansetron 4 mg unless contraindicated (e.g. brittle diabetes defined as unpredictable and instable blood glucose levels with frequent episodes of hypoglycemia and/or ketoacidosis, or severe drug allergy defined as an immune reaction resulting in shortness of breath, hives, rash, blisters, anaphylaxis, wheezing, and fever). Other medications for nausea prophylaxis will be given at the discretion of the individual

anesthesiologist providing intraoperative care (which may include Droperidol 0.625 mg IV or Propofol infusion).

Intraoperative opioids will be administered at the discretion of the in-room anesthesia provider based on hemodynamic signs of pain such as increased blood pressure or heart rate. This may include but not limited to IV morphine, dilaudid, fentanyl, and ketamine.

All surgeries will be performed by two orthopedic surgeons at Mayo Clinic Hospital, Methodist Campus. All patients will receive a unilateral primary total shoulder arthroplasty, either anatomic or reverse TSA.

Typically, the decision to perform either an anatomic or reverse TSA is dependent on the function and stability of the rotator cuff muscles. The standard total shoulder arthroplasty involves a metal ball replacing the head of the humerus and a plastic implant used to replace the socket of the shoulder blade. In reverse total shoulder arthroplasty, the components are reversed. Limited available studies compare outcomes between standard total shoulder arthroplasty and reverse shoulder arthroplasty. In a recent study by Kiet and colleagues, outcomes between both groups were comparable, including pain.⁴³

If patients are randomized to the LIA group, periarticular injection will occur after implantation of the final prostheses, but prior to closure of the fascia. All surgeons will complete the infiltration following a similar protocol, equally distributing the study medication around the glenoid and humerus, subscapularis, deltoid, posterior capsule and subcutaneous tissue.

Regional Block – Both CISB and SISB:

Preoperatively, patients will be sedated, under the discretion of the anesthesiologist, with intravenous midazolam (1-4 mg) and fentanyl (50-200 mcg) for alleviation of anxiety and pain.

Patients randomized to either the CISB or SISB group will follow institutional practice in accordance to the total joint regional anesthesia pathway (MC1156-462rev0115). The interscalene nerve block will be performed under continuous live ultrasound guidance, obtaining visualization of the roots (C5-C6 is ideal) or trunks (Superior Trunk is ideal) of the brachial plexus in between the anterior and middle scalene muscles as described by Chan.⁴¹ An in plane or out of plane approach to needle advancement under live ultrasound guidance will be at the discretion of the anesthesiologist. In cases with poor ultrasound imaging, a combined nerve stimulator and ultrasound guidance technique is acceptable. Appropriate needle placement will be verified by injecting normal saline 0.9% and visualizing spread within the interscalene groove at the level of the roots/trunks of the brachial plexus. Local anesthetic may also be used for hydrodissection in order to navigate needle placement into the correct position. The proceduralist should attempt to use less than 10 mL (if possible) of saline 0.9% to identify correct placement of peripheral nerve block.

Regional Block – SISB

Once needle position is verified, the initial loading dose of local anesthetic solution to be administered is presented in Table 2.

Regional Block – CISB

Once needle position is verified by ultrasound imaging, a continuous catheter device will be placed within the interscalene groove at the level of the roots/trunks of the brachial plexus. After delivery of the catheter, verification of the catheter within the interscalene groove will be assessed by again evaluating spread of normal saline 0.9% or local anesthetic within the interscalene groove.

The initial loading dose of local anesthetic solution to be administered is presented in Table 2. The local anesthetic solution will be bloused through the catheter, and secured into place above the clavicle and away from the surgical field.

Brachial plexus block evaluation is as follows: sensory – sensation to cold over the deltoid muscle (0= absent or diminished, 1 = at baseline). Block will be assessed either preoperatively (at least 25 minutes after the placement of the block, if presurgical time permits), postoperatively in the recovery room, or patients room on POD 0. This assessment will be charted in the electronic anesthesia medical record when it has been completed.

Table 2: CISB and SISB Group – Bolus Injection

<i>Nerve Blocked</i>	<i>Local Anesthetic</i>	<i>Concentration</i>	<i>Volume milliliters (mL)</i>	<i>- Adjuvants Added</i>
Interscalene Brachial Plexus – CISB and SISB	Bupivacaine	0.5%	15 to 20 mL	1:200,000 Epinephrine

Continuous Interscalene Nerve Block (CISB):

The continuous interscalene nerve block catheter will be loaded in the PACU with bupivacaine 0.2% 10 milliliters (mL), and then an infusion will be initiated of bupivacaine 0.2% at 8 to 10 per hour. Infusion rate will be at the discretion of the pain service and attending anesthesiologist. The catheter will be discontinued on POD 1, unless surgeon requests catheter to remain in for a longer period of time.

Failed Block – CISB and SISB Group

In the event that a failed block were to occur, defined as intact or baseline sensation to cold over the deltoid muscle after 25 minutes since completion of block (pre-op) or pain at the surgical site along with intact or baseline sensation to cold over the deltoid muscle (post-op), the patient will be managed accordingly at the discretion of the covering anesthesiologist (which may include either re-blocking, or utilizing pain medications). Patient’s will still be involved in the study per intention-to-treat analysis.

Local Infiltration Analgesia (LIA):

The LIA group will utilize weight based dosing of Ropivacaine as part of a “cocktail” solution (Table 1), and will receive a total volume of 120 mL injected in the periarticular structures by the surgeon. This is a one-time injection. This will occur after implantation of the final prostheses,

but prior to closure of the fascia. All surgeons will complete the infiltration following a similar protocol, equally distributing the study medication around the glenoid and humerus, subscapularis, deltoid, posterior capsule and subcutaneous tissue. Medications and dosage of the LIA group is as follows:

Table 1: LIA Group

Drug	50-74.9kg	75-99.9 kg	100-125kg
Ropivacaine	200 mg	300 mg	400 mg
Epinephrine	100 mcg	200 mcg	300 mcg
Ketorolac	30 mg	30 mg	30 mg

*Normal Saline will be added to bring the total volume to 120 mL

Study Site: All surgeries included in this study will be performed at Mayo Clinic Hospital, Methodist Campus. Postoperative care will take place at the same hospital.

6.3 Post-Operative Plan

PACU

Pain medications for the PACU are at the discretion of the anesthesiologist. The following medications and doses listed are recommendations and include but not limited to the following:

- 1) **Fentanyl** 25 mcg IV every 2 minutes PRN for pain 4 or greater (maximum 200 mcg)
- 2) **Hydromorphone** 0.2 mg IV every 2 minutes PRN for pain 4 or greater (maximum 2 mg)
- 3) **Acetaminophen** 1000mg PO or IV once for pain (review last dose before administering)
 - a. Oral unless RASS < -1 or nausea/ vomiting present
- 4) **Ketamine** 10 mg IV once as needed for pain scores >4
- 5) **Oxycodone (immediate release)**
 - a. 5 mg to 10 mg once prior to discharge for pain 4 or greater

Floor Care

The following will be the post-op pain management protocol for the nursing floors. This is intended to serve as a guide for the primary service or acute pain management team, and can be modified or adjusted per the discretion by either team in order to provide optimal care on a case by case basis. Of note, this has been reviewed and approved by Pharmacy (Nathan J. Brinkman, Pharm.D., R.Ph. & Laura J. Myhre, Pharm.D., R.Ph.).

TSA Floor Care Analgesic Medications:

Scheduled Analgesics:

- **Acetaminophen:** 1000 mg orally every 6 hours

PRN Analgesics:

- **Oxycodone** 5 to 10 mg orally every 4 hours PRN. Use 5 mg for pain rated 3 to 5. Use 10 mg for pain rated 6 to 10. If after 2 hours of administration pain remains greater than 7, please notify primary service to increase frequency to every 3

hours.

OR

- **Hydromorphone** 1 to 2 mg orally every 4 hours PRN. Use 1 mg for pain rated 3 to 5. Use 2 mg for pain rated 6 to 10. If after 2 hours of administration pain remains greater than 7, please notify primary service to increase dose. **Order if patient has a sensitivity or allergy to oxycodone.**

Breakthrough pain – IV Medications:

- **Fentanyl** 25 mcg IV every 30 minutes PRN for pain scores 7 through 10 for 3 doses. May administer if pain is greater than 6 after scheduled and PRN regimen exhausted. If pain remains greater than 6, notify primary service.

Endpoints

Data collection will be obtained based on our primary and secondary endpoints as listed in Sections 3.2 and 3.3

Study Activity	Pre-operative	Peri-operative			Post-operative Follow Up	
	Pre-op	Day 0 (day of surgery)	Day 1	Days 2-5	Week 12-16	Years 1-1.5*
Informed Consent	x					
Inclusion/Exclusion Criteria	x					
Pain Scores (numeric rating scale)	x	x	x	x	x	
Patient and Surgical Data Collections	x	x				
OBAS Form <i>(primary outcome)</i>			x			
SF-12 Form	x				x	
ASES Form	x					x
LANSS					x	
Opioid Consumption (up to POD 3)		x	x	x		
Length of Hospital Stay			x	x		
Adverse Events Monitoring		x	x	x	x	
Neurologic Complications		x	x	x	x	

Peripheral Nerve Block - catheter related complications		X	X	X		
Follow up via telephone call or office visit					X	X

- * Follow-up study as described in Section 2.0

6.4 Data Collection

Primary and Secondary Outcomes

The primary outcome (OBAS on POD 1) will be collected prospectively if possible by interviewing patients in their hospital room on POD 1. The rest of the outcome measures will be obtained from DataMart and manual Chart+ record review. Collected data will be transferred into REDCap.

Regional blocks performed on day of surgery will be assessed for loss of sensation over the distal deltoid muscle (indicative of appropriate interscalene nerve blockade). This will be charted in Chart+, and results will be retrieved by manual chart review.

Post-operative Follow Up (12-16 Weeks)

The study staff will follow up with study patients 12-16 weeks following their initial shoulder surgery. This will be conducted via office visit or telephone call. During this encounter, the study staff will utilize data collection form. Collected data includes NRS pain scores at rest and with movement of surgical extremity, postoperative neurologic changes (persistent numbness, paresthesia, or weakness of surgical extremity), and complications or adverse events. In addition, SF-12 and LANSS questionnaire will also be administered.

7 Statistical Plan

7.1 Sample Size Determination

The sample-size for this study was determined in order to provide statistical power of >90% to detect a difference of 3 units for the primary endpoint (OBAS on POD1). Based on a previous study, we hypothesize that the standard deviation of OBAS will be approximately 3 units.⁴⁴ Under this assumption, an effective sample-size of N=39 per group will provide statistical power of >90% to detect a difference between groups of 3 units using a two-sided, alpha=0.017 (multiple-comparison adjusted for 3 groups), non-parametric test. In addition, for the key secondary endpoint of pain (NRS), this sample-size will provide statistical power of 80% to detect a difference of 0.75 standard deviations (approximately 2.25 units on the NRS). In order to accommodate attrition of approximately 10% (due to canceled surgery, failed block, etc.) we propose a total sample-size of N=129 (43 patients per group).

7.2 Statistical Methods

Descriptive Statistics

Baseline characteristics will be summarized using mean and standard deviation for continuous variables that have a normal Gaussian distribution, and median and interquartile range for continuous variables with a non-normal distribution. Frequencies and percentages will be used to summarize categorical baseline characteristics. Baseline characteristics will be compared across groups using analysis of variance, or the Kruskal-Wallis test for continuous variables and the chi square test for categorical variables.

The primary aim of this study is to assess whether continuous interscalene nerve block provides superior analgesic benefit via OBAS compared to single injection interscalene blockade and local infiltration analgesia on POD 1 for primary total shoulder arthroplasty. In order to test this hypothesis, the will be compared across groups using ANOVA (or the Kruskal-Wallis test). Supplemental pairwise comparisons will be performed using two-tailed tests with $\alpha=0.017$ (Bonferroni adjusted) used to denote statistical significance. Similar analyses will be performed for secondary endpoints of pain and total additional opioid medications (moeq) until hospital discharge.

NRS pain scores measured at arrival to PACU, PACU discharge, and every 4 hours until time of hospital discharge following surgery will be analyzed using repeated measures ANOVA with pairwise treatment comparisons performed using linear contrasts.

Postoperative complications will be compared across groups using the chi-square test and hospital length of stay (number of postoperative days) will be compared across treatment groups using the Kruskal-Wallis test with supplemental pairwise comparisons performed using the rank sum test. Similar analyses will be performed for additional endpoints collected at the 12-16 week follow-up visit including NRS pain scores and SF-12 scales.

Our primary analysis will be performed based on the intention to treat. All calculated p-values will be two sided. For the overall analyses comparing across all 3 treatment groups simultaneously p-values less than 0.05 will be considered statistically significant. For supplemental pairwise treatment group comparisons p-values less than 0.017 (Bonferroni adjusted) will be considered statistically significant. The statistical analysis will be performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, United States).

Handling of Missing Data

All Subjects enrolled according to the entry criteria will be eligible for evaluation, regardless of the sequence of treatment that ensues.

Management of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Analysis of the distribution of prognostic factors between subjects with data and those without data will be reviewed for significance to assess selection bias. Adjustments for missing data will be performed only if deemed necessary and will be described

completely. An endpoint analysis (last observation carry forward), as described by Friedman⁴⁵ will be used for success rate assessments.

Outlier values will be evaluated for their validity; all data will be included unless judged to be invalid.

7.3 Subject Population(s) for Analysis

Our primary analysis will be performed based on the intention to treat. Therefore, any subject randomized into the study, regardless of whether they received study drug, will be included in the primary analysis. A subgroup analysis will also be performed on patients who received the allocated treatment as per the planned protocol, and patients undergoing reverse vs anatomic primary TSA.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Non-UPIRTSO

A reportable event that does not meet the Mayo Clinic IRB's definition of a UPIRTSO.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

And/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 7 weeks following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition may be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. Throughout the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Adverse Event Causality

We understand the importance pharmacovigilance, and the significance of establishing a relationship between study drug and adverse events. Causality assessment or algorithms are available to assist with evaluating the likelihood or relationship between study drug and adverse event. We will utilize the WHO-UMC causality assessment system to assess adverse event causality.³⁹

Post-study Adverse Event

Unresolved adverse events related to the study medication/procedure will be followed by the PI/Co-PI's until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in

this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

- Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances: Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

The study team will seek information on adverse events by specific questioning and, as appropriate, by examination. This will occur on daily follow up inpatient encounters as well as telephone or office visit encounters around 12-16 weeks post-procedure. Information on all adverse events will be recorded in the electronic medical record and also in the appropriate adverse event worksheet. Related signs, symptoms, and abnormal diagnostic, laboratory or procedure results will be recorded as well. PI/Co-PI's will be notified of the adverse events.

The clinical course of each adverse event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period will be followed, as stated above. Any serious adverse event that occurs after the study period and is considered related to the study treatment or study participation will be recorded and reported.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

Serious adverse events will be evaluated and reported per institutional policy and regulatory requirements.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

Information collected on the adverse event worksheet (*and entered in the research database*):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):

- If the adverse event was expected:
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will review the adverse event worksheet and only directly related SAEs/UPIRTSOs will be reported to the IRB.

For NON-UPIRTSOs, the investigator reports problems or events that do NOT meet the criteria of an UPIRTSO to the Mayo Clinic IRB in summary format at the time of the next continuing review.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

Any applicable IND regulations will be followed related to reporting to the FDA of all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

8.4 Unmasking/Unblinding Procedures

This study is an unblinded study.

8.5 Stopping Rules

Adverse events and serious adverse events, as defined in Section 8.1 of IND protocol, will be monitored by the study team for patient safety. Known serious adverse events associated with interscalene nerve blocks (SISB and CISB groups) include inadvertent intravascular injection⁺, local anesthetic systemic toxicity (LAST)*, inadvertent epidural or subarachnoid injection, and pneumothorax. Additionally, patients will be monitored throughout the procedure utilizing standard ASA monitors, aspirating for heme or cerebral spinal fluid (CSF) prior to administration of local anesthetic solution in divided doses, frequent assessment of the patient's well-being via verbal communication, and having emergency medications and airway equipment readily available at all times. Performing this regional block is considered standard in our practice and these methods are already established procedures in the practice of perioperative pain control for a total shoulder arthroplasty.^{4,5}

Serious adverse event associated with local infiltration analgesia (LIA group) is local anesthetic systemic toxicity (LAST).

⁺ *Inadvertent intravascular injection is suspected if a patient experiences sudden loss of consciousness, apnea, convulsions, hypotension, respiratory depression, or stroke symptomology.*

^{*} *Local anesthetic systemic toxicity is suspected if a patient has acute onset of central nervous system changes (tinnitus, metallic taste in mouth, perioral numbness) or cardiovascular changes (bradycardia, hypotension, EKG changes).*

LAST is a known serious adverse event with any local anesthetic administration. Preventive measures include high degree of suspicion, vital sign monitoring (blood pressure, EKG, oxygen saturation), using an appropriate dose of local anesthetic, injecting local anesthetic in divided dose, aspirating prior to injection of medication looking for heme, consider using epinephrine in solution as a vascular marker, being prepared to treat a LAST event immediately (checklist, external defibrillator, resuscitate medications, emergency airway equipment), and having lipid emulsion therapy readily available (standard of care).⁴⁶ We acknowledge that despite the rarity of these serious adverse events, the potential still exists.

Study stopping criteria includes:

CISB and SISB groups:

- a) The study will stop if 5% of subjects in either group experience inadvertent intravascular injection, inadvertent epidural or subarachnoid injection, and pneumothorax.
- b) The study will stop if 5% of subjects in either group experience LAST.

LIA group

- a) The study will stop if 5% of subjects experience LAST.

We acknowledge that unanticipated adverse events may arise during this study.

CISB, SISB, and LIA groups:

- a) The study will stop if 5% of subjects in any group (4 patients) experience an unanticipated serious adverse event (as defined in section 8.1 of IND protocol).

If the study is stopped for any of the reasons listed above, a root cause analysis will be performed to determine cause of adverse event and relationship to study protocol. The study team will formulate an appropriate plan of action to ensure patient safety. Such a plan may include, but is not limited to, protocol modifications, immediate termination of accrual, and adjustments in management of previously enrolled participants continuing to undergo study interventions.

8.6 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 (see section 10 “Study Monitoring, Auditing, and Inspecting”). 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

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records

include: hospital records, clinical and office charts, laboratory notes case report forms, and recorded data from automated instruments

Data Management

A study case report form (CRF)/data collection form will be established and utilized by the study team to record outcome measures. The data will then be transferred to an electronic research database (REDCap). Data from the electronic research database will be utilized for primary and secondary analysis.

Data Security and Confidentiality

All patient information will be de-identified and kept in secure locations where only authorized study personnel can have access. All computers are password protected and secured behind institution firewall. Case report forms will be maintained, in a secure location within the institution campus.

Data Quality Assurance

All data will be entered by appropriately trained personnel. This is a single site study. Data will be collected manually and electronically abstracted through the use of our EMR and our OR database/ICU database. Data collected will be manually entered into the RedCap system for electronic data storage and analysis.

Every 50 of subject study data will be cross-referenced for accuracy.

Data Clarification Process

Incomplete, or erroneous data will be corrected by analyzing the patient's electronic record.

9.3 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. Records will be maintained according to regulatory and institutional requirements.

In order to constitute evidence with respect to product safety or regulatory or legal compliance, the Investigator agrees to retain study-related documents in a location that is secure and to which access can be gained if required. The following documents must be archived: the Investigator's File containing all required GCP documents, including signed Informed Consent Forms and Subject-related materials, and CRFs.

With respect to coding case report forms and subject identification code list, as described in section 5.3, patients will be randomized using a randomization schedule. Using this randomization schedule, an EXCEL spreadsheet application will be created which will include sequentially assigned subject-ID numbers and corresponding treatment assignments. All case

report forms utilize this subject-ID numbers. Case report forms are maintained in a de-identified manner by including subject ID, subject's initials, and dates of pertinent study involvement.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

A data and safety monitoring plan will be incorporated within the protocol. The goal of the data and safety monitoring plan is to make adequate provision to monitor the data collected to ensure the safety of subjects, and that adequate provisions to protect the privacy of subjects and the confidentiality of the data are maintained (45 CFR 46.111). 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.

Studies being conducted under an IND may be monitored during the conduct of the trial by staff from the Mayo Clinic Office of Research Regulatory Support. Clinical trial monitoring may include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

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.

12 Study Finances

12.1 Funding Source

Funding will be obtained internally through the institution from the Department of Orthopedic Surgery at Mayo Clinic Hospital, Methodist Campus. The funds will be used to support the use of an anesthesia clinical research unit (ACRU) to recruit patients, collect data, and monitor for adverse events. This will also fund a statistician to analyze data.

13 Publication Plan

Subsequent to trial closure, data will be analyzed, and a manuscript will be submitted to the appropriate journal, after consensus among all the investigators. No funding agency is involved with this study.

The study will be registered with www.ClinicalTrials.gov

We plan on conducting a follow up study in accordance to this trial. Data collected for the follow up study includes ASES scores (Section 2.0).

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