Prospective, randomized clinical trial comparing analgesic efficacy of liposomal bupivacaine single-injection interscalene blockade to continuous interscalene blockade for patients undergoing primary total shoulder arthroplasty

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Study Product:	Liposomal Bupivacaine (Exparel®)
Protocol Number: (IRBe)	21-000908
ClinicialTrials.gov	*NCT05005260*

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ASA	American Society of Anesthesiologists
ASES	American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form
C-ISB	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
IRB	Institutional Review Board
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
LAST	Local Anesthetic Systemic Toxicity
LB-SISB	Liposomal Bupivacaine Single injection interscalene blockade
NRS	Numeric Rating Scale
OBAS	Overall Benefit of Analgesic Score
OME	Oral Morphine Equivalents
PACU	Post-anesthesia Care Unit
PHI	Protected Health Information
PI	Principal Investigator
POD	Postoperative Day
QoR-15	Quality of Recovery 15-item short form patient survey
RASS	Richmond Agitation-Sedation Scale
SAE	Serious Adverse Event/Serious Adverse Experience
TDABC	Time-Driven Activity-Based Costing
TSA	Total Shoulder Arthroplasty

Title	Prospective, randomized clinical trial comparing analgesic efficacy of liposomal bupivacaine single-injection interscalene blockade to continuous interscalene blockade for patients undergoing primary total shoulder arthroplasty
Running Title	LB-SISB vs CISB
Protocol Number	21-000908
Phase	Phase IV
Methodology	Single center, unblinded, randomized control trial with two intervention arms
Overall Study Duration	14 Months (time when data collected for last patient)
Subject Participation Duration	Up to 7 days post-operatively
Single or Multi-Site	Single-Site
Objectives	Primary objective is to assess analgesia efficacy between liposomal bupivacaine single injection interscalene blockade vs. continuous interscalene nerve block 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 for up to 7 days after surgery depending on follow-up availability.
Number of Subjects	88 patients will be randomized to one of two interventions: liposomal bupivacaine single injection interscalene blockade or continuous interscalene nerve block.
Diagnosis and Main Inclusion Criteria	Patients presenting for unilateral primary total shoulder arthroplasty (includes anatomic and reverse total shoulder arthroplasty), who can provide consent, older than 18 years of age, and have American Society of Anesthesiologists (ASA) physiological status I-III.
Study Product, Dose, Route, Regimen	Liposomal bupivacaine (Exparel®). Patients will receive a one-time interscalene nerve block injection of 5 mL of bupivacaine 0.5% (25 mg) admixed with 10 mL of liposomal bupivacaine (133 mg).
Duration of Administration	One-time injection
Reference therapy	Continuous interscalene nerve block through an indwelling nerve catheter utilizing standard bupivacaine hydrochloride
Statistical Methodology	Randomization of each patient to a study arm will occur in a 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

1 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 U.S. Food & Drug Administration (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

Uncontrolled postoperative pain can be associated with significant deleterious consequences, including elevated stress response, decrease quality of life, increase in morbidity and mortality, and 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] In our recently published randomized clinical trial[3] (IRB 15-009646; Mayo Clinic, Rochester, MN, USA), we reported that within a multimodal analgesic protocol, the continuous interscalene blockade (ISB) through an indwelling nerve catheter provides superior analgesia compared to single-injection interscalene blockade and local infiltration analgesia in the immediate postoperative period after primary TSA.[3] Despite this, a few drawbacks to the continuous ISB 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.

Since our publication, liposomal bupivacaine, an extended-release bupivacaine formulation (currently marketed as Exparel®; Pacira Pharmaceuticals, Inc., Parsippany, New Jersey) had been approved by the FDA for use in single-injection ISB.[4] Limited data has shown liposomal bupivacaine single-injection ISB to provide enhanced and prolonged analgesia compared to placebo and standard bupivacaine HCl single-injection ISB with a similar safety profile.[5,6] There is a paucity of data comparing continuous-ISB (C-ISB) to liposomal bupivacaine single-injection ISB (LB-ISB) in a head-to-head clinical trial. Furthermore, the cost-effectiveness of either technique remains unknown in the context of the overall episode of care.

The primary aim of this study is to evaluate the analgesia efficacy between liposomal bupivacaine single injection interscalene blockade (LB-ISB) vs. continuous interscalene nerve block (C-ISB) for patients undergoing primary total shoulder arthroplasty.

1.2 Investigational Agent

Liposomal bupivacaine was approved by FDA in 2011 for surgical site infiltration and in 2018 for use in interscalene brachial plexus nerve blocks for postoperative pain control.[4] Liposomal bupivacaine consists of vesicles of bupivacaine loaded in the aqueous chambers using DepoFoam® technology (Pacira Pharmaceuticals Inc, San Diego, CA).[4] These vesicular liposomes will dissolve slowly and release bupivacaine over time, providing a longer analgesic effect than standard bupivacaine HCl. Chahar et al. provides a detailed review regarding liposomal bupivacaine's pharmacokinetics and molecular structure.[7] Given the slow release of bupivacaine utilizing this unique DepoFoam® technology, analgesic effects can last up to 72 hours after a single injection into the surgical site.[4,8]

Liposomal bupivacaine (Exparel®) is supplied in one vial, containing either 133 mg or 266 mg (1.3%; 13.3 mg/mL) of bupivacaine suspended in multivesicular liposomes in normal saline.

Bupivacaine HCl is an amide local anesthetic 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 is a long-acting local anesthetic indicated for multiple routes of administration including local infiltration and peripheral nerve blocks.[9]

1.3 Clinical Data to Date

Clinical Efficacy

Most studies evaluating liposomal bupivacaine are limited to administration via surgical site infiltration; these clinical trials demonstrate prolong analgesia and decrease opioid consumption when compared to placebo in patients undergoing various surgical procedures.[6,10,11] In contrast, analgesic outcomes were inconsistent when liposomal bupivacaine was compared to bupivacaine HCl for surgical site infiltration in total knee and hip surgery.[12-14] Similarly, clinical trials evaluating interscalene nerve block with bupivacaine HCl compared to liposomal bupivacaine surgical site infiltration have shown variable analgesic outcomes.[15-17]

Current data pertaining to the administration of liposomal bupivacaine via interscalene nerve blocks are sparse. Patel et al. reported significantly improved pain scores and reduced opioid consumption up to 72 hours postoperatively after comparing LB-ISB (utilized 133 mg of liposomal bupivacaine) to placebo ISB (using normal saline).[6] Vandepitte et al. compared LB-ISB to ISB with standard bupivacaine HCl in patients undergoing major shoulder surgery.[5] In the LB-ISB group, the authors admixed 5 mL of 0.25% bupivacaine HCl with 133 mg of

liposomal bupivacaine, while the control group received 15 mL of 0.25% standard bupivacaine HCl. The LB-ISB group had a moderate reduction in worst pain score in the first postoperative week compared to the control group (generalized estimating equation [GEE] estimated marginal mean values, 3.6 ± 0.3 vs 5.3 ± 0.4 points on the Numeric Rating Scale, difference, 1.6 ± 0.5; 95% CI, 0.8–2.5).

Recently, a retrospective investigation evaluating LB-ISB vs C-ISB reported improved pain scores for LB-ISB on postoperative day (POD) 0 and 1, with similar opioid consumption and better cost efficiency compared to C-ISB.[18] In the LB-ISB group, the authors prepared an injectate mixture composed of 10 mL of 0.5% bupivacaine HCl with 133 mg of liposomal bupivacaine. There were no complications noted in either group.

Safety

In a meta-analysis, the safety profile of liposomal bupivacaine was similar to bupivacaine HCl. The most common side effects in the liposomal bupivacaine group (800 patients) were nausea (3.3%) and constipation (2.0%). Cardiac complications were tachycardia (4%), and bradycardia (2%), which did not require treatment and were similar to bupivacaine HCl group. One death was reported in the 800 patients that received liposomal bupivacaine, and one in the bupivacaine HCl group; both drugs were not deemed to be causative agents.[19]

Ilfeld et al. evaluated the safety of liposomal bupivacaine in peripheral nerve blocks (ankle, femoral nerve, and intercostal nerve block patients), and reported the most common adverse events to be mild in severity.[20] These symptoms included nausea, pyrexia, constipation, vomiting, and pruritus. The incidence of central nervous system and cardiac adverse events were similar between liposomal bupivacaine, bupivacaine HCl, and placebo groups. The authors concluded that liposomal bupivacaine shares a similar safety profile to bupivacaine HCl and normal saline.

Patel et al. compared the interscalene neve block with liposomal bupivacaine to normal saline and reported a similar incidence of adverse events between both groups.[6] Most of the adverse events were considered mild in severity (nausea was the most reported adverse event). The authors performed pharmacokinetic assessments in patients receiving 166 mg and 266 mg of liposomal bupivacaine via interscalene block and reported peak concentrations occurring at 48 hours, with the mean peak concentrations (209 and 461 ng/mL, respectively) remaining below the thresholds for local anesthetic associated cardio- and neuro toxicity (2,000–4,000 ng/mL).

Similarly, in a clinical trial comparing LB-ISB to ISB with standard bupivacaine HCl, there were no increased risk of complications in the LB-ISB group (RR, 1.6; 95% CI, 0.9–2.7).[5] Budge et al. reported no complications in their retrospective investigation comparing LB-ISB to C-ISB.[18]

User Experience

At our institution, liposomal bupivacaine has been used by our surgical colleagues for a variety of procedures (breast, hip, shoulder, knee, abdominal) without any reported side effects attributed to the medication. Furthermore, we have used liposomal bupivacaine for interscalene nerve block on numerous patients after FDA approval without any adverse events.

1.4 Dose Rationale and Risk/Benefits

C-ISB group

Patients will receive a loading dose of 15-20 mL bupivacaine HCl 0.5% followed by a continuous catheter infusion of bupivacaine 0.2% at 8 mL per hour for 72 hours. We have used this dose for many years in our practice, and we have successfully employed this in our previous randomized clinical trial.[3] Further, this dose is commonly employed in studies involving interscalene blocks.[21] These doses conform to the manufacturer recommended single and daily dose maximum administration and reliably provides postoperative analgesia.[9]

LB-ISB

Patients will receive 5 mL of Bupivacaine HCl 0.5% (25 mg) mixed with 10 mL of liposomal bupivacaine (133 mg). This mixture is in accordance with manufacturer prescribing guidelines: max recommended dose of liposomal bupivacaine for interscalene nerve blocks is 133 mg and mixing dose ratio of standard bupivacaine HCl to liposomal bupivacaine of 1:2 or less (25 mg / 133 mg).[4] Liposomal bupivacaine exhibits a bimodal plasma concentration profile, where an initial peak occurs at 1 hour and a second peak occurs between 12 to 36 hours.[8] Therefore, adding standard bupivacaine HCl to liposomal bupivacaine will bridge the analgesic gap in the first few hours after the nerve block is performed. A similar administration mixture for interscalene blocks was used by Vandepitte et al.[5]

2 Study Objectives

2.1 *Primary Objective*

To evaluate the analgesia efficacy in the first 24 hours postoperative period between liposomal bupivacaine single injection interscalene blockade and continuous interscalene nerve block via numeric rating pain score and opioid consumption for patients undergoing primary total shoulder arthroplasty.

2.2 *Secondary Objective*

To evaluate the following: the analgesia efficacy between both groups up to 7 days postoperatively using numeric rating pain score assessment and opioid consumption, adverse events, duration of hospital stay, surgical recovery via quality of recovery questionnaire, and cost-benefit analysis via time-driven activity-based costing model.

Please refer to Section 3.2 and 3.3 for detailed outcome measures.

3 Study Design

3.1 *General Design*

Single center, unblinded, randomized control trial with two intervention arms assessing acute pain management. These two arms include: 1) liposomal bupivacaine single-shot interscalene blockade (LB-ISB group) and 2) continuous interscalene nerve block (C-ISB group)

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 (Section 4.1 and 4.2). Subjects will be approached by study staff for recruitment in person and informed consent will be obtained during the preoperative clinic visit. Prior to surgery, subjects will be randomized to either one of the two study groups using dynamic allocation in a computer application developed by personnel in the Division of Biomedical Statistics and Informatics (Section 7.3). 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.

Eighty-eight patients are required for this clinical trial. After baseline values are established, data will prospectively be collected during the peri-operative period up to 7 days post-operatively (patient will have follow-up via office visit or telephone call) for the purpose of this study. Data will be collected utilizing the institution's electronic medical record system and be transferred to an electronic research database (e.g. Excel, REDCap). Figure 1 and Table 1 summarizes the data that will be collected during this study.

	Pre-operative	Peri- & Post-operative	
Study Activity	**Pre-op**	**POD 0 (day of surgery)**	**POD 1 - 4**
Informed Consent	x		
Inclusion/Exclusion Criteria	x		
Pain Scores (numeric rating scale)	x	x	x
Patient and Surgical Data Collections	x	x	
OBAS			X
QoR-15 Patient Survey	x		x
Opioid Consumption		x	x
Length of Hospital Stay			x
Adverse Events Monitoring		x	x
Peripheral Nerve Block - catheter related complications		x	x
Follow up via telephone call or office visit		x	X*

Table 1. Summary of data collection

*Patients may be contacted up to postoperative day 7 to collect data depending on availability of patient and study staff during follow-up encounters.

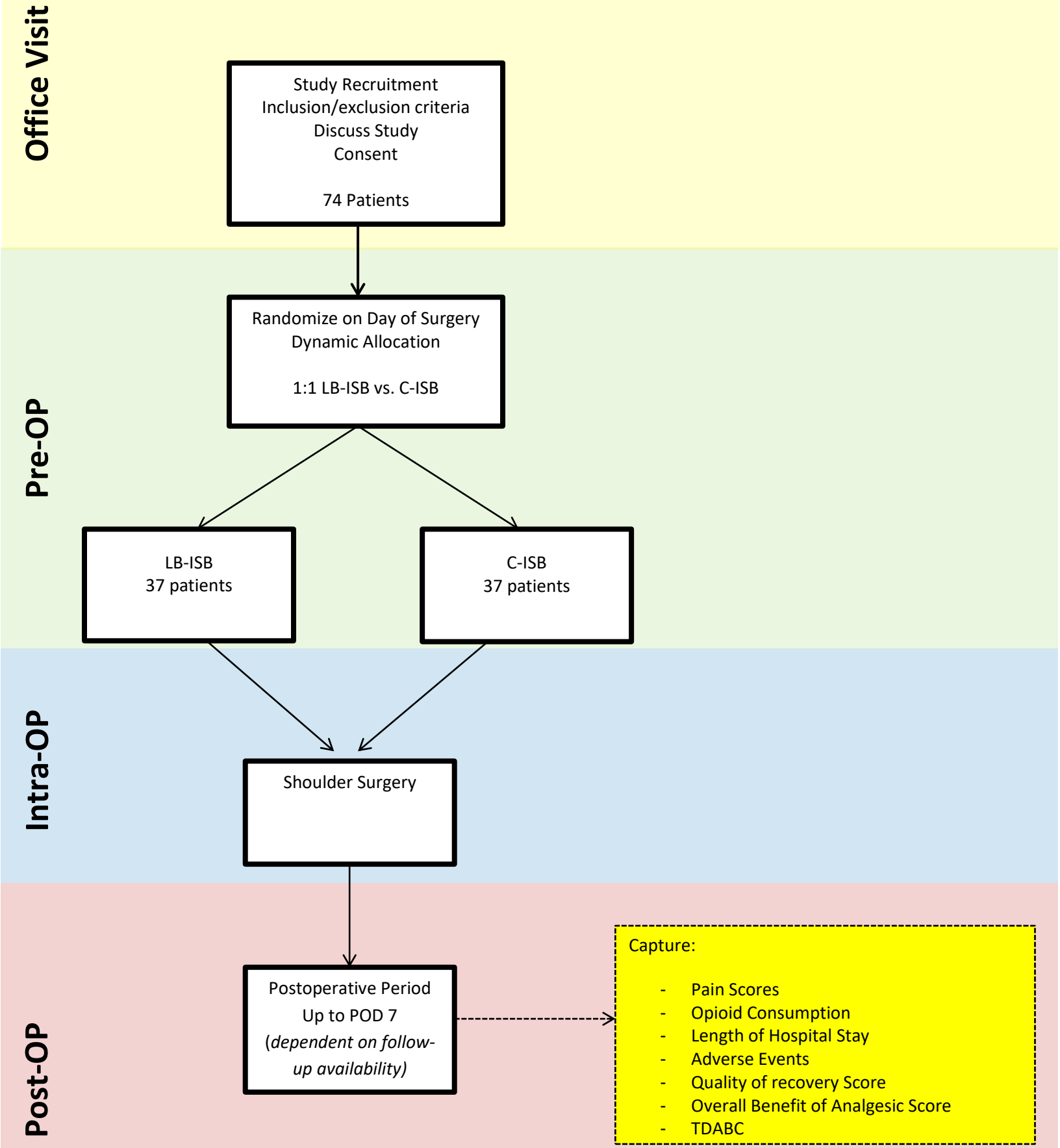

Figure 1. Diagram of patient flow from recruitment to outpatient follow-up

3.2 *Primary Outcome*

To investigate the hypothesis that within our current multimodal analgesia total joint protocol, C-ISB provides superior analgesia via NRS pain intensity scores (difference ≥ 1.5) and opioid consumption (difference ≥ 20 mg oral morphine equivalents) on POD 1 compared to LB-ISB following primary total shoulder arthroplasty.

3.3 *Secondary Outcomes*

1. Pain intensity (NRS) assessments prior to surgery, post-anesthesia care unit (PACU), every 4 to 6 hours beginning on arrival to patient room (to the closet time interval), and hospital discharge up to POD 7.
2. Opioid consumption in daily oral morphine equivalents (OME) – preoperative, intraoperative, PACU stay, beginning on arrival to patient room up to POD 7.
    a) Patients will be asked to record their daily intake of opioids and pain scores at pre-defined intervals. A research team member will follow-up with study patients to document the patient's pain score and opioid consumption values for the previous day as well as administer the quality of recovery 15-item questionnaire.
3. Moderate to severe complications during regional anesthesia block placement (inadvertent epidural or subarachnoid injection, local anesthetic systemic toxicity*, and pneumothorax).
    ** 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, and local anesthetic systemic toxicity.
5. Inadvertent catheter dislodgement
6. 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)
7. Postoperative follow-up
    a. Telephone encounter or office visit to collect NRS pain scores at rest, opioid consumption, questionnaire, and adverse events. Data will be collected for postoperative days 0 to 4; however, patients may be contacted up to postoperative day 7 to collect this information if patients or study staff are unavailable.
8. Questionnaire Forms
    a) QoR-15
        i. Quality of Recovery (QoR) 15-item short form patient survey is a validated, reliable, and feasible scoring system evaluating 5 dimensions of health: psychological support, comfort, emotions, physical independence, and pain.[22,23]
        ii. Collected preoperatively and POD 1 to 4 via office visit or telephone call.
    b) Overall benefit of Analgesic Score (OBAS)
        i. Validated tool measuring patient's experience with their postoperative pain regimen.[24] This simple 7 question (Q1 to Q7) scoring system entails a combination of pain intensity, adverse opioid events, and patient satisfaction. The total OBAS score is calculated via 'sum items Q1 through Q6 and add [4 – score from Q7].' 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 prior to hospital discharge.

9. Cost-benefit analysis
    a) Examining the cost of each analgesic modality within the overall episode of orthopedic surgical care using the time-driven activity-based costing (TDABC) model, which provides a more accurate representation of true costs by estimating the quantity of time and the cost per unit of time of each resource from preoperative visits to hospital discharge[25,26]
10. Additional outcome measures for future investigation
    a) American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form
        i. ASES questionnaire will be collected pre-operatively, 3-month, and at 1 year postoperatively via office visit or telephone call. Collected data will be used in a follow-up study.[27]
    b) Patient-Reported Outcomes Measurement Information System (PROMIS®)
        i. Already an established and standard questionnaire being collected for all orthopedic surgical patients.

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
2. Chronic opioid use (>1 month) with OME >5 mg/day OR acute opioid use (< 1 month) 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 local anesthetics.
    - **defined as an immune reaction resulting in shortness of breath, hives, anaphylaxis, wheezing, and fever*
5. Personal or family history of malignant hyperthermia.
6. Major systemic medical problems such as:
    - Pre-existing severe renal disorder defined as glomerular filtration rate (GFR) <50 units/m^2 (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 requiring medical therapy (obstructive and/or restrictive), use of home oxygen, preoperative baseline oxygen saturation < 93% on room air.
- 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, and refusal).
    - [+] *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.*
8. Known to be currently pregnant or actively breastfeeding[++]
    - [++] *All surgical patients are currently screened using a standardized Pregnancy Assessment tool (http://mayoweb.mayo.edu/sp-forms/mc8800-mc8899/mc8801-161.pdf)*
9. Impaired cognition (e.g. Alzheimer's disease, moderate to severe dementia, encephalopathy)
10. Non-English speaking

4.3 *Early Withdrawal of Subjects*

4.3.1 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. Furthermore, if the placement of the peripheral nerve blocks cannot be performed, if an unanticipated reoperation is performed (during the same hospital stay), if an unanticipated complication unrelated to the study (e.g. pulmonary embolism, myocardial ischemia) where patients are unable to participate in study protocol, or if the patient remains intubated and sedated postoperatively for greater than one day, the patient will be terminated from the study. 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 = 88 (44 per group) is proposed. Follow-up will not be performed for patients terminated from the study.

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

4.3.2 Data Collection and Follow-up for Withdrawn Subjects

Patients who voluntarily withdraw from the study, are terminated due to unforeseen circumstances such as reoperation, or if intubated and sedated postoperatively for greater than one day, will have their data collected in the peri-operative and follow-up periods up to the point of termination. 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.

The safety profile for liposomal bupivacaine has been assessed in previous studies as mentioned in Section 1.3, 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 for liposomal bupivacaine 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 various pain management options regardless of participation.

5 Study Procedures

5.1 *Pre-op Plan*

All patients will undergo a standardized multimodal analgesia total joint pathway (See attached document). 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. Additional sedatives at the discretion of the anesthesia team. 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.[28] 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 to navigate needle placement into the correct position. The proceduralist should attempt to use less than 10 mL of normal saline 0.9% to identify correct placement of peripheral nerve block.

For patients randomized to C-ISB group, a continuous catheter device (Perifix ® Catheter, B.Braun, Bethlehem, PA, USA) 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.

5.2 *Dosing*

The local anesthetic solutions used for each block are displayed in Figure 2. The initial loading dose for the continuous ISB group will be administered through the nerve catheter. The ambulatory nerve catheter system (On-Q CB004, Avanos Medical, INC., Alpharetta, GA) will be connected to the nerve catheter and the infusion rate will be initiated at 8 mL/hr. Infusion rate changes will be at the discretion of the operating room anesthesiologist and, subsequently, the acute pain service. Patients discharged with the ambulatory nerve catheter system will be managed using our institutional protocol which includes patient/family instructions, daily follow-up, and a dedicated team to cover concerns or questions 24 hours, 7 days a week (http://intranet.mayo.edu/charlie/anesthesiology-perioperative-medicine-rst/anesthesia-home/divisions/ce-anesthesia/continuous-nerve-catheters-pilot/#tabs-16274-0-0).

Treatment Arm	Local Anesthetic	Total Volume of Preoperative Bolus	Infusion
Liposomal Bupivacaine Interscalene Nerve Block (LB - SISB)	5 mL of Bupivacaine 0.5% mixed with 10 mL of liposomal bupivacaine (133 mg)*	15 mL	N/A
Continuous Interscalene Nerve Block (CISB)	Bupivacaine 0.5% with 1:200,000 Epinephrine (premixed solution)	15-20 mL	On-Q Select-A-Flow CB004 pump with continuous infusion of bupivacaine 0.2% at 8 mL per hour for 72 hours

Figure 2. Treatment Arms.

** In accordance with manufacturer prescribing guidelines: max dose of liposomal bupivacaine of 133 mg and mixing ratio of standard bupivacaine HCl to liposomal bupivacaine of less than 1:2 (25 mg / 133 mg)*

5.3 *Assessment*

Patients in both groups will undergo sensory testing to evaluate block success. Sensory testing is as follows, sensation to cold over the deltoid muscle (0= absent or diminished, 1 = at baseline). Motor block will be assessed by deltoid contraction (0= absent or diminished, 1 = at baseline). Block will be assessed at least 25 minutes after the placement of the block, if pre-surgical time permits, or 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.

5.4 *Intra-op Plan*

Intraoperative anesthetic management entails general endotracheal anesthesia with standard American Society of Anesthesiologists monitoring. All patients will receive 8 mg of intravenous (IV) dexamethasone. Intraoperative opioids, antiemetic prophylaxis, and additional intraoperative monitoring (e.g., arterial line) are at the discretion of the attending anesthesiologist.

5.5 *Postoperative Management*

Postoperatively, all study patients will follow a standardized multimodal analgesia total joint pathway (see attached document). Medical care will be co-managed by both the orthopedic surgery team and anesthesia acute pain service, which is comprised of a regional anesthesiologist, anesthesia resident, and trained nursing staff. This service provides 24-hour in-hospital coverage with daily patient rounding to act on potential concerns associated with continuous local anesthetic infusion.


multimodal protocol TSA 12272(


TSA Study Post-op standardized meds.

6 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. 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 prior to administration of local anesthetic solution in divided doses, frequent assessment of the patient's well-being via verbal communication, and always having emergency medications and airway equipment readily available. Performing this regional block (ISB) is considered standard in our practice 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 that are not discharged the same day after surgery will be admitted to the regular nursing floors. Vital signs (heart rate, oxygen saturation, and blood pressure) will be captured every 4 to 6 hours or more frequently if the clinical situation dictates in all postoperative orthopedic patients.

Patients admitted to the hospital will be followed daily by the acute pain service and surgical team. Patients discharged with a continuous interscalene nerve block will be followed by the acute pain service team. All study patients, regardless of treatment arm and hospital status (inpatient vs outpatient), will be followed by study personnel. 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.

7 Study Drug

7.1 Description

Liposomal bupivacaine (Exparel®) is supplied in one vial, containing either 133 mg or 266 mg (1.3%; 13.3 mg/mL) of bupivacaine suspended in multivesicular liposomes in normal saline. It is regularly stocked in our pharmacy and automated dispensing medication system (Pyxis Medstation) found in the operating rooms and procedure rooms due to its frequent use for postoperative pain control.

7.2 Treatment Regimen

Patients randomized to LB-ISB will receive a preoperative single-injection interscalene block for pain management following primary total shoulder arthroplasty. The solution administered will contain 5 mL of bupivacaine 0.5% (25 mg) along with 10 mL of liposomal bupivacaine (133 mg), which conforms to manufacture recommended guidelines.[4]

7.3 Method for Assigning Subjects to Treatment Groups

Subjects that are consented and enrolled will be randomized into one of the two study groups: liposomal bupivacaine single injection interscalene blockade or continuous interscalene nerve block. In order to ensure balance on the demographic characteristics of the patients in the two study groups, the subjects will be stratified on sex and age group (≥65 vs. <65), Within each stratum, subjects will be assigned to either of the two study groups using dynamic allocation in a computer application developed by personnel in the Division of Biomedical Statistics and Informatics. Using dynamic allocation will ensure that the subject allocation will remain balanced on the stratification factors and the study group assignment throughout the entire subject accrual phase. This computer-based randomization system will be available only within the Mayo firewall on the intranet and will be username and password protected and accessible only to the study personnel.

7.4 Preparation and Administration of Study Drug

At the time of the peripheral nerve block procedure, liposomal bupivacaine will be dispensed from the Pyxis Medstation and the 0.5% bupivacaine HCl solution will be obtained from the anesthesia stock room. Both solutions are sterile; therefore, they will be poured in a sterile fashion into the wells located in a sterile peripheral nerve block tray. The proceduralist will then mix 10 cc of liposomal bupivacaine (133 mg) with 5 cc of 0.5% bupivacaine (25 mg) into the same syringe for administration during the procedure. For specific injection technique, please refer to section 5.1.

7.5 Subject Compliance Monitoring

Patients receiving treatment will be enrolled in a prospective database. No other treatment is necessary, except the peripheral nerve block before their scheduled procedure.

7.6 Prior and Concomitant Therapy

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

7.7 Packaging

Please refer to section 7.1.

7.8 Masking/Blinding of Study

This prospective randomized control trial will be unblinded. We acknowledge that an unblinded study design carries research limitations. 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, blinding would remove the benefit a single-injection peripheral nerve block which entails the lack of catheter management. However, we hope to discover the best overall clinical pathway for management of TSA for our patient population.

7.9 Receiving, Storage, Dispensing and Return

Liposomal Bupivacaine is already being used throughout the enterprise, and its storage, handling, transport, and disposal will not change.

8 Statistical Plan

8.1 Sample Size Determination

Sample size calculations were performed based on the outcomes of pain (NRS) and opioid consumption (OME) measured at 24 hours after surgery. Using data from Panchamia et al[3] , the standard deviations of NRS pain and opioid consumption were estimated to be 2.4 points and 23.6 mg OME for the single injection inter-scalene block group and 2.3 points and 25.1 mg OME for the continuous interscalene block group, respectively. Assuming that similar variability will be observed in the proposed study, a sample of 40 subjects in each arm (n=80 total) will provide 80% power to detect a difference of at least 1.5 points in NRS pain and 20 mg OME measured at 24 hours post-surgery. In order to protect against a potential drop-out rate of 10%, a total of 88 subjects will be enrolled. Calculations were based on a two-sample t-test, with alpha=0.05, two-sided test.

8.2 Statistical Methods

The primary outcomes will be pain, as measured by NRS pain intensity scores, and opioid consumption, as measured by milligrams of OME, recorded at 24 hours after surgery. Secondary outcomes will include OBAS, intraoperative and postoperative complications, NRS pain scores, length of hospital stay, and QoR-15 score. The outcomes of pain, opioid consumption, OBAS, and QoR-15 score will be compared between the LB-ISB group and the C-ISB group using two-sample t-tests; if the data are not sufficiently normally distributed, non-parametric Wilcoxon rank sum tests will be used. Since this is a prospective, randomized trial, subjects in the two groups are expected to be similar with respect to their baseline characteristics; therefore, no formal comparisons of baseline data will be performed. However, if it is determined that adjustments need to be made, this will be done using a general linear models framework. Length of stay is likely to be skewed, and thus will be analyzed using the non-parametric Wilcoxon rank sum test. Intraoperative and in-hospital post-operative complications will be analyzed using chi-square tests and logistic regression. The primary analysis will be based on the intent-to-treat

approach, in which subjects will be analyzed in the groups they were randomized to, regardless of the treatment actually received. If appropriate, additional secondary analyses may be undertaken to perform the comparisons on the subjects who completed the study per-protocol, and on an as-treated basis.

8.3 *Descriptive Statistics*

The data will be summarized using standard descriptive statistics, including means and standard deviations for continuous data, and counts and percentages for categorical data. Baseline characteristics will be reported separately for each of the two study groups. Summary data will be reported both in the text and in tabular format.

8.4 *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, and the primary analysis will be conducted as an intent-to-treat analysis. Management of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Analysis of the distribution of subjects with data and those without data in each study group will be reviewed for impact to assess potential bias. Adjustments for missing data will be performed only if deemed necessary and will be described completely. Outlier values will be evaluated for their validity, and all data will be included unless judged to be invalid.

8.5 *Subject Population(s) for Analysis*

Our primary analysis will be performed based on the intention-to-treat. Therefore, any subject randomized into the study and undergoing the planned surgical procedure, regardless of whether they received a liposomal bupivacaine single injection interscalene blockade or a continuous interscalene nerve block, will be included in the primary analysis in the group they were randomized to. If appropriate, additional subgroup analyses may be performed on patients who received the allocated treatment as per the planned protocol, and on an as-treated basis.

9 Safety and Adverse Events

9.1 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, data and safety monitoring board (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 up to 4 days 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.[29]

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.

9.2 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 up to 7 days post-procedure. Information on all adverse events will be recorded in the electronic medical record and 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.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate 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.

A safety committee, consisting of anesthesiologists not involved in the study, will be established prior to subject recruitment. This group will review any serious adverse events and evaluate for causality.

9.3.1 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 report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

9.4 Unmasking/Unblinding Procedures

This study is an unblinded study.

9.5 Stopping Rules

Adverse events and serious adverse events, as defined in Section 9.1 of this protocol, will be monitored by the study team for patient safety. Known serious adverse events associated with interscalene nerve blocks include 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 prior to administration of local anesthetic solution in divided doses, frequent assessment of the patient's well-being via verbal communication, and always having emergency medications and airway equipment readily available. 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.[3,30,31]

> ** 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, 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).[32] Similar to our current clinical practice, this protocol entails numerous methods to monitor and prevent LAST in accordance with the American Society of Regional Anesthesiology and Pain Medicine recommended guidelines for LAST.[33] We acknowledge that despite the rarity of these serious adverse events, the potential still exists.

Study stopping criteria includes:

a) The study will stop if 5% of subjects in either group experience inadvertent epidural or subarachnoid injection, and pneumothorax.
b) The study will stop if 5% of subjects in either group experience LAST.
c) The study will stop if 5% of subjects in any group experience an unanticipated serious adverse event (as defined in section 9.1 of this 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.

9.6 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 11 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10 Data Handling and Record Keeping

10.1 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.

10.2 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 (EXCEL). 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 using our electronic medical record and our OR database/ICU database. Data collected will be manually entered into the RedCap system for electronic data storage and analysis. Every 1 in 50 records will be cross-referenced for accuracy.

Data Clarification Process

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

10.3 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 7.3, 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.

The sponsor-investigator will retain the specified records and reports as outlined in the Mayo Clinic Research Policy Manual – "Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

11 Study Monitoring, Auditing, and Inspecting

11.1 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.

11.2 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.

12 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.

13 Study Finances

13.1 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 a statistician to analyze data.

14 Publication Plan

After 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

References

1. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet.* 2006;367(9522):1618-1625.
2. Ullah H, Samad K, Khan FA. Continuous interscalene brachial plexus block versus parenteral analgesia for postoperative pain relief after major shoulder surgery. *The Cochrane database of systematic reviews.* 2014;2:CD007080.
3. Panchamia JK, Amundson AW, Jacob AK, et al. A 3-arm randomized clinical trial comparing interscalene blockade techniques with local infiltration analgesia for total shoulder arthroplasty. *J Shoulder Elbow Surg.* 2019;28(10):e325-e338.
4. EXPAREL (bupivacaine liposome injectable suspension) [prescribing information]. Parsippany, NJ: Pacira Pharmaceuticals, Inc; 2016. http://www.exparel.com/pdf/EXPAREL_Prescribing_Information.pdf. Accessed May 15, 2017.
5. Vandepitte C, Kuroda M, Witvrouw R, et al. Addition of Liposome Bupivacaine to Bupivacaine HCl Versus Bupivacaine HCl Alone for Interscalene Brachial Plexus Block in Patients Having Major Shoulder Surgery. *Reg Anesth Pain Med.* 2017;42(3):334-341.
6. Patel MA, Gadsden JC, Nedeljkovic SS, et al. Brachial Plexus Block with Liposomal Bupivacaine for Shoulder Surgery Improves Analgesia and Reduces Opioid Consumption: Results from a Multicenter, Randomized, Double-Blind, Controlled Trial. *Pain Med.* 2020;21(2):387-400.
7. Chahar P, Cummings KC, 3rd. Liposomal bupivacaine: a review of a new bupivacaine formulation. *J Pain Res.* 2012;5:257-264.
8. Hu D, Onel E, Singla N, Kramer WG, Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. *Clin Drug Investig.* 2013;33(2):109-115.
9. Marcaine (TM) [package insert]. Lake Forest, IL: Hospira, Inc; Revised January. 2015. http://www.hospira.com/en/images/EN-3556_tcm81-92523.pdf. Accessed.
10. Gorfine SR, Onel E, Patou G, Krivokapic ZV. 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.
11. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam(R) bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. *Adv Ther.* 2011;28(9):776-788.
12. Bagsby DT, Ireland PH, Meneghini RM. Liposomal bupivacaine versus traditional periarticular injection for pain control after total knee arthroplasty. *J Arthroplasty.* 2014;29(8):1687-1690.
13. Bramlett K, Onel E, Viscusi ER, Jones K. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. *Knee.* 2012;19(5):530-536.
14. Perets I, Walsh JP, Mu BH, et al. Intraoperative Infiltration of Liposomal Bupivacaine vs Bupivacaine Hydrochloride for Pain Management in Primary Total Hip Arthroplasty: A Prospective Randomized Trial. *J Arthroplasty.* 2018;33(2):441-446.
15. Okoroha KR, Lynch JR, Keller RA, et al. Liposomal bupivacaine versus interscalene nerve block for pain control after shoulder arthroplasty: a prospective randomized trial. *J Shoulder Elbow Surg.* 2016;25(11):1742-1748.

16. Sabesan VJ, Shahriar R, Petersen-Fitts GR, et al. A prospective randomized controlled trial to identify the optimal postoperative pain management in shoulder arthroplasty: liposomal bupivacaine versus continuous interscalene catheter. *J Shoulder Elbow Surg.* 2017;26(10):1810-1817.
17. Namdari S, Nicholson T, Abboud J, Lazarus M, Steinberg D, Williams G. Randomized Controlled Trial of Interscalene Block Compared with Injectable Liposomal Bupivacaine in Shoulder Arthroplasty. *J Bone Joint Surg Am.* 2017;99(7):550-556.
18. Budge M, Orvets N, Shields E. Single-shot liposomal bupivacaine interscalene nerve block provides equivalent pain relief compared to continuous catheter interscalene nerve block in total shoulder arthroplasty. *Seminars in Arthroplasty: JSES.* 2020;30(4):285-290.
19. Viscusi ER, Sinatra R, Onel E, Ramamoorthy SL. The safety of liposome bupivacaine, a novel local analgesic formulation. *Clin J Pain.* 2014;30(2):102-110.
20. Ilfeld BM, Viscusi ER, Hadzic A, et al. Safety and Side Effect Profile of Liposome Bupivacaine (Exparel) in Peripheral Nerve Blocks. *Reg Anesth Pain Med.* 2015;40(5):572-582.
21. Vorobeichik L, Brull R, Bowry R, Laffey JG, Abdallah FW. Should continuous rather than single-injection interscalene block be routinely offered for major shoulder surgery? A meta-analysis of the analgesic and side-effects profiles. *Br J Anaesth.* 2018;120(4):679-692.
22. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology.* 2013;118(6):1332-1340.
23. Myles PS, Myles DB, Galagher W, Chew C, MacDonald N, Dennis A. Minimal Clinically Important Difference for Three Quality of Recovery Scales. *Anesthesiology.* 2016;125(1):39-45.
24. Lehmann N, Joshi GP, Dirkmann D, et al. Development and longitudinal validation of the overall benefit of analgesia score: a simple multi-dimensional quality assessment instrument. *Br J Anaesth.* 2010;105(4):511-518.
25. Akhavan S, Ward L, Bozic KJ. Time-driven Activity-based Costing More Accurately Reflects Costs in Arthroplasty Surgery. *Clin Orthop Relat Res.* 2016;474(1):8-15.
26. Menendez ME, Lawler SM, Shaker J, Bassoff NW, Warner JJP, Jawa A. Time-Driven Activity-Based Costing to Identify Patients Incurring High Inpatient Cost for Total Shoulder Arthroplasty. *J Bone Joint Surg Am.* 2018;100(23):2050-2056.
27. Richards RR, An KN, Bigliani LU, et al. A standardized method for the assessment of shoulder function. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al].* 1994;3(6):347-352.
28. Chan VW. Applying ultrasound imaging to interscalene brachial plexus block. *Reg Anesth Pain Med.* 2003;28(4):340-343.
29. The use of the WHO-UMC system for standardized case causality assessment. World Health Organization (WHO) — Uppsala Monitoring Centre. [Last accessed on 2015 Sept 28]. Available from: http://www.who-umc.org/Graphics/24734.pdf. In.
30. Bowens C, Jr., Sripada R. Regional blockade of the shoulder: approaches and outcomes. *Anesthesiol Res Pract.* 2012;2012:971963.
31. Sulaiman L, Macfarlane RJ, Waseem M. Current concepts in anaesthesia for shoulder surgery. *Open Orthop J.* 2013;7:323-328.
32. Checklist for Treatment of Local Anesthetic Systemic Toxicity. American Society of Regional Anesthesia and Pain Medicine. [Last accessed on 2015 Sept 28]. Available from: https://www.asra.com/content/documents/asra_last_checklist.2011.pdf. In.
33. Neal JM, Barrington MJ, Fettiplace MR, et al. The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity: Executive Summary 2017. *Reg Anesth Pain Med.* 2018;43(2):113-123.