

A Double-Blind Randomized Comparison Trial of Postoperative Pain in Patients Undergoing
Total Shoulder Arthroplasty Who Receive Interscalene Blocks With or Without Liposomal
Bupivacaine (PoPTSAWoW Trial)

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Sponsor: NorthShore University HealthSystem

Type of Research: Prospective randomized double-blinded controlled trial

Intervention: Preoperative Interscalene Blocks will be performed on each patient with:
Experimental group: 10 mL (133 mg) Liposomal bupivacaine and 20 mL (50 mg) 0.25% bupivacaine and 6 mL of saline (183 mg) vs. Control group: 36 mL (180 mg) 0.5% bupivacaine

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I. Introduction: Background and Rationale

Patients undergoing shoulder surgery can suffer from significant postoperative pain which can lead to an increase in recovery time, opioid use and potential dependency, and a decrease in quality of recovery.^{1,2} The interscalene brachial plexus block is a common effective regional anesthesia technique used for a variety of procedures involving the shoulder.² The number of total shoulder arthroplasty surgeries being performed annually in the United States is increasing every year.³ Liposomal bupivacaine was FDA approved for use in patients undergoing interscalene block in 2018 to reduce postoperative pain from shoulder surgery. The information from the manufacturer indicates that the liposomal encapsulation may release the drug for up to approximately 72 hours after it has been administered, providing a prolonged analgesic effect.^{4,5} Evidence to the prolonged analgesic effect of liposomal bupivacaine has varied in the current literature. A recent meta-analysis suggested that liposomal bupivacaine may provide a statistically significant, but clinically insignificant decrease in opioid consumption and pain scores over time.⁶ The authors noted a possible limitation of their study is that the meta-analysis included a variety of surgical procedures and block techniques, and was not specific to shoulder surgery or interscalene block. The authors noted that this variability in anesthetic regimens between study groups could have affected the observed outcomes.⁶ A more recent randomized controlled trial of interscalene blocks in total shoulder arthroplasty reported that plain bupivacaine did not demonstrate non inferiority when compared to a combination of bupivacaine and liposomal bupivacaine in regards to 72 hour opioid consumption, however this difference was clinically insignificant. One of the limitations of this study reported by its authors was that it might have been relatively underpowered for a noninferiority comparison.⁷

Recently, we performed a retrospective quality improvement study to investigate the potential benefit of liposomal bupivacaine used for interscalene blocks among 491 patients undergoing shoulder arthroplasty between 2018 and 2021. We compared the difference in the proportion of patients with clinically tolerable pain scores (defined as VAS $\leq$ 4) in those patients receiving liposomal bupivacaine vs. those receiving another local anesthetic (plain bupivacaine, mepivacaine or ropivacaine) vs. those receiving no block. The results of this study suggested that there was significant difference in the proportion of patients with clinically tolerable pain scores when receiving liposomal bupivacaine during all observations and at 3 days postoperatively versus those patients who did not. The patients who received liposomal bupivacaine also had a significant reduction in morphine milligram equivalents (MMEs). (See Table 1)

Based on our retrospective results, we performed a power analysis which allowed for the development of this prospective randomized double blinded trial comparing liposomal bupivacaine plus plain bupivacaine vs. plain bupivacaine only in near equipotent doses. We believe that this is a very important and unique trial to perform as it could change the way pain management is delivered in this patient population. Our study differs from

previous similar studies because we will compare the proportion of patients with clinically tolerable pain scores (defined as VAS ≤ 4) between the two block groups in near equipotent doses. Similar to comparing pain scores and opioid consumption in previous studies, our study will also compare Quality of Recovery Scores. Longer acting local anesthetic used for interscalene blocks may increase the number of patients who have tolerable pain and require less or no opioids. This could reduce or inevitably eliminate the unwanted effects of opioids (nausea, vomiting, constipation, urinary retention, opioid induced respiratory depression, dependency and addiction) and result in an improvement in the quality of recovery of patients undergoing total shoulder arthroplasties.

II. Hypothesis: Key Questions

A greater proportion of patients undergoing total shoulder arthroplasty receiving liposomal bupivacaine for interscalene blocks will have clinically significant tolerable pain (defined as a VAS score of ≤ 4), 24, 48, and 72 hours postoperatively, and an improved quality of recovery during all observations and at 3-days postoperatively compared to those patients receiving plain bupivacaine only.

Objectives: Primary and Secondary Outcomes

Primary Outcome

- 1) The difference in the proportion of patients with clinically significant tolerable pain scores (defined as VAS ≤ 4) post-op Day One in those patients receiving an interscalene block with liposomal bupivacaine with plain bupivacaine vs. plain bupivacaine.

Secondary Outcomes

- 1) The difference in the proportion of clinical tolerable pain scores in each group.
 - a. Post-op Day Two
 - b. Post-op Day Three
 - c. Post-op Day Four
 - d. Post-op Day Five
- 2) The difference in VAS pain scores (0 – 10) in each group
 - a. Upon PACU admission and discharge
 - b. Post-op Day One
 - c. Post-op Day Two
 - d. Post-op Day Three

- e. Post-op Day Four
 - f. Post-op Day Five
- 3) The difference in quality of recovery survey-15 responses (see attachments)
 - a. Post-op Day One
 - b. Post-op Day Two
 - c. Post-op Day Three
 - d. Post-op Day Four
 - e. Post-op Day Five
- 4) Opioid use in morphine milligram equivalents (MME)
 - a. Day of Surgery
 - b. Post-op Day One
 - c. Post-op Day Two
 - d. Post-op Day Three
 - e. Post-op Day Four
 - f. Post-op Day Five
- 5) Non-opioid analgesics (NSAIDs, acetaminophen, gabapentanoids, skeletal muscle relaxants)
 - a. Day of Surgery
 - b. Post-op Day One
 - c. Post-op Day Two
 - d. Post-op Day Three
 - e. Post-op Day Four
 - f. Post-op Day Five
- 6) Adverse Block Event
 - a. Post-op Day 1
 - b. Post-op Day 2
 - c. Post-op Day 3
 - d. Post-op Day 4
 - e. Post-op Day 5
 - f. Post-op Day 30

Subject Population

All subjects included in this study are derived from NorthShore University HealthSystem Orthopaedic and Spine Institute undergoing a primary total shoulder arthroplasty or reverse total shoulder arthroplasty (patients may be included twice if they are having both shoulders operated on for the first time).

Inclusion:

- 1) Subject ages 18-90 years old
- 2) Male or Female subjects

- 3) Primary TSA or reverse TSA
- 4) Weight ≥ 60 kg.
- 5) Must be able to consent in English

Exclusion:

- 1) Ages: <18 and >90
- 2) Weight < 60 kg
- 3) Revision surgeries
- 4) Multiple surgeries during one hospital stay
- 5) Emergency surgery
- 6) Allergy or any contraindication to local anesthetics used in trial.
- 7) Pregnancy
- 8) Severe liver/kidney disease
 - a. Defined as a diagnosis of end-stage renal disease (ESRD) defined as being on dialysis
- 9) Subject who received another local anesthetic block prior to the interscalene block.
- 10) Unable to consent in English

III. Study Design: Prospective Randomized Double-blinded Control Trial

We plan to enroll 130 study subjects undergoing total shoulder arthroplasty or reverse total shoulder arthroplasty. Subjects will be presented with the option to be a part of the study during their pre-operative appointment or pre-operative phone call with the orthopaedic surgeon and/or clinic team. At that time, if they are interested, they will be provided a patient recruitment letter with more detail and a copy of the informed consent in their surgery information packet or via NorthShoreConnect message. The patients will then be contacted by trained research coordinators to further explain the study and go through the informed consent process. This will be done in person using a paper consent or remotely using an electronic consent with a dedicated REDCap database that will also be used for the patient data collection. Subjects will be asked to complete a baseline QoR15 survey 3-5 days prior to surgery. A randomization allocation table will be generated by the study biostatistician and used to create a randomization module in REDCap for assigning the participants to the treatment groups.

QoR15 (see attachments) is an accepted measurement tool for quality of recovery that includes a 15-item questionnaire which has a scale of 0-10 pertaining to a patient's comfort, support system, pain, well-being, and ability to carry out daily activities. Number "0" indicates none of the time and number "10" indicates all of the time.⁸ Additionally, pain levels will be measured using the VAS scale with patients entering their average pain over the last 24 hours. Subjects will rate their pain level on a scale of 0-10. Number "0" indicates no pain and number "10" indicates worst pain ever experienced by subject. The REDCap survey instrument will also ask the patient to select

the pain medications and number of doses they have taken in the last 24 hours. A VAS pain and medication data collection sheet is attached. Patients will receive an electronic version viewable on mobile device or computers.

On the day of surgery, those subjects enrolled in the study will receive either 36 mL of 0.5% bupivacaine (180mg) (PB group) or 10 mL of liposomal bupivacaine and 20 mL of 0.25 % bupivacaine and 6 mL of saline (183mg) (LB group).

Subjects and surgeons will both be blinded to the type of anesthesia administered. Subjects will receive an interscalene block prior to surgery under ultrasound guidance and sedation with midazolam and up to 100 mcg fentanyl at the anesthesia provider's discretion. Since a standard of care for regional anesthesia is to aspirate prior to any injection to ensure that the needle is not intra-vascular, the anesthesiologist must be able to visualize the tubing therefore, it has to be transparent. Because liposomal bupivacaine appears white while plain bupivacaine is clear, it is impossible to blind the anesthesiologist in the study. All possible measures will be taken to restrict the blinding to all personnel except the anesthesiologist by limiting personnel in the room for the block procedure.

General Anesthesia Parameters

All subjects enrolled in the study will receive the standard general anesthetic with inhaled sevoflurane to keep the bispectral index (BIS®) between 40-60, which is an estimate of anesthetic depth during general anesthesia. Fentanyl will be used for analgesia at the discretion of the anesthesia provider on when to administer, but will be based on a 20% increase in heart rate and/or blood pressure from baseline. Induction drugs for general anesthesia will be at the discretion of the anesthesia providers. Patients will receive approximately 2 – 3 mg/kg of propofol, 0.6mg/kg of rocuronium or 1mg/kg of succinylcholine, and 100mcg fentanyl. Subjects will be given rocuronium exclusively for maintenance of intraoperative neuromuscular blockade. Providers will titrate neuromuscular blockade to a twitch count of 2-4/4 throughout the intraoperative case. All subjects will be administered sugammadex (minimum of 2mg/kg assuming a twitch count of 2-4/4) or neostigmine and glycopyrrolate in anticipation of extubation after neuromuscular blockade reversal. All patients will receive 4 mg of dexamethasone and 4 mg of ondansetron for postoperative nausea and vomiting.

Following a total shoulder replacement, patients are brought to the PACU. In the PACU, nurses will assess the subjects' pain by using VAS (0-10). Subjects will receive hydromorphone 0.2-0.4 mg Q5MINPRN for pain scores ≥ 4 , the standard anesthesia PACU orderset.

After they are ready for discharge from the PACU, they are either discharged home the same day from the Ambulatory Care Unit or admitted into the hospital with a planned stay overnight and most frequently discharged the next day. For patients admitted to the hospital, a postoperative pain control regimen is ordered at the surgical team's discretion. Pain medications received will be recorded. Nurses on the floor regularly evaluate

patients with a standard VAS scale for pain as well as any opioid side effects. Patients subsequently receive pain medication based on their pain. Any issues with pain control are escalated to the physician assistants, (PA), the surgeon or an anesthesia pain consult. VAS pain levels recorded by nursing staff and medications given are recorded in the electronic health record (Epic). At the time of discharge, the patient's medications are also recorded. Depending on the pain and medications needed during the hospitalization, the standard outpatient pain medications are hydrocodone/acetaminophen and tramadol. The pain levels and opioids utilized during the hospitalization will be extracted from the EDW and entered into the REDCap database with the opioids converted to morphine milligram equivalents (MME). Opioids administered in the operating room and PACU will be tracked separately from those after admission to the hospital.

For patients that have surgery as outpatients where they go home the same day, instructions concerning pain control and prescriptions for pain medications are given to all patients. Patients will be provided with a pain medication diary for postoperative days 1-5 to help track their pain score and medications throughout the day before entering responses in the REDCap VAS and medication surveys.

The study investigators, research coordinator, and research assistant will collect data using REDCap and Epic to send various surveys beginning the day after discharge as well as collect patient information. For patients having same-day surgery, this will be the first postoperative day. Patients will receive an e-mail daily covering the first five days and POD 30 after surgery generated automatically in REDCap that contains a link to the survey. If subjects do not fill out the survey, they will be contacted by the research coordinator or research assistant reminding them to fill out the survey with the option to answer the questions over the phone.

The electronic medical record will be utilized to record demographic and surgical information on patients. The demographics data will include: age, sex, race, BMI, medical history, surgical history, prior and current medications, alcohol and tobacco use, and ASA status. Surgical information will include: the type of surgery, length of surgery, hospital admission/outpatient surgery, return to operating room, hospital length of stay, surgical complications, and block complications.

IV. 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).

The following steps will be used to keep all PHI confidential:

- The investigators will use an encrypted and password protected anesthesiology research collaboration portal and NorthShore University HealthSystem REDCap data warehouse for the data collection forms only accessible to the PI, co-investigators,

- and research coordinators. The MRN's and subject numbers will be decoupled from the data collection forms and be stored on the collaboration portal at NorthShore University HealthSystem.
- The data will be stored for three years after the study is published. It will be stored on the same password protected and encrypted NorthShore University HealthSystem anesthesiology research collaboration portal for the specific decoupled MRNs and subject #s.

V. Statistical Considerations

Data analysis will be performed by utilizing the resources of the NorthShore Research Institute Biostatistics Department. Comparison data will be analyzed between groups using Student t-test for continuous variables, Chi-square test for categorical variables, non-parametric tests will be used when necessary. Regression models will be used for multivariate analysis. Mixed effects regression models will be used for longitudinal data analysis. We anticipate that patient demographic and clinical characteristics will be similar between the two experimental groups due to random assignment. However, we will control these variables in multivariable analysis when appropriate.

Power/Sample Size

To achieve a power of 80%, $\alpha = 0.05$ in a two-tailed test of 2 independent proportions of 194/282 (69%) and 79 / 178 (44%), we would need 2 groups of 61 (122 total). At NorthShore University HealthSystem, in 2022, there were 246 total shoulder replacement surgeries. We plan to enroll 130 patients over about one year to complete this study.

VI. Foreseeable Risks and Benefits

Risks: The interscalene brachial plexus block used in this study might have undesired effects. Undesired side effects may be mild, moderate, or very serious. Sometimes they can be life-threatening. The effects can be serious, long lasting or may never go away. The interscalene block carries a minimal level of risk and is the standard of care at NorthShore University HealthSystem. This study poses only risk of the nerve block and general risk of surgery and anesthesia. All drugs used for the interscalene blocks are FDA approved and are in use in our clinical practice.

Benefits: There are no absolute benefits outside of being part of the study to investigate the potential benefits of liposomal bupivacaine in terms of reducing postoperative pain and improving the quality of recovery for patients when compared to plain bupivacaine.

VII. Equitable Selections of Subjects

Patients will not be categorically excluded from this research. The study population will be limited to those who are eligible based on the inclusion criteria for this study. We anticipate an equal number of males and females to be enrolled in this randomized trial. No patients will be excluded based on sex, religion, or culture beliefs.

VIII. Recruitment and Consent Procedures

Physicians' clinical practices will be the basis of recruitment for this study. The subject's orthopaedic surgeon and/or clinic team will introduce the study to the subject via the

standard of care communication methods used in clinic that may include in-person at their pre-operative clinic appointment and/or pre-operative phone call. If the subject is interested in participating, they will receive a patient recruitment letter and consent form explaining the study in their surgery information packet, or via NorthShoreConnect message. They will be given as much time as they need to review. The clinic staff will inform study staff that there is a potential subject. A member of the study team will then call the subject to explain the study in more detail and answer any questions. Informed consent can be obtained in person using a paper consent or via an e-consent link directly from REDCap. E-consent will be the preferred method due to limited space for meeting with subjects.

For subjects that will be consented via a REDCap e-consent, their secure e-mail addresses will be confirmed prior to sending the REDCap e-consent link. Once the consent has been signed by the subject and confirmed to be valid by the research team, the required questionnaires will then be sent also through the REDCap system by study staff. Research coordinators will be available by phone to assist subjects with accessing and completing any of the forms if needed.

Any questions, concerns, or ambiguities will be clarified by Dr. Johnny Lee, and/or a research coordinator or co-investigators prior to the subject signing consent. Subjects will sign informed consent and only then will begin participation in the study.

IX. Data and Safety Monitoring

The research team will conduct weekly research meetings with study staff to review study progress, including recruitment strategies, enrollment numbers, protocol issues, and safety issues. Patients will be asked to contact an investigator or study staff member at any time during or after their participation in the study should they have any questions or concerns. An adverse event survey will be sent on POD 1-5 and POD 30. This survey will monitor patients for any adverse reaction to the interscalene block itself. Should a subject experience any symptoms of nerve injury or extended block at POD 5 or 30, they will be instructed by the study team to contact their provider. The provider will then follow up with the subject.

X. Monitoring and Quality Assurance

During the study, monitoring will be conducted by the PI, Dr. Johnny Lee. Dr. Lee will be responsible for monitoring the data collected as well as ensuring that the study is being executed in accordance with the protocol. There are no plans for internal or external audit visits for this study.

XI. Financial Considerations

There are no financial incentives to patients as a part of this study.

XII. Conflict of Interest

There is no conflict of interest about the conduct of this study.

XIII. Attachments

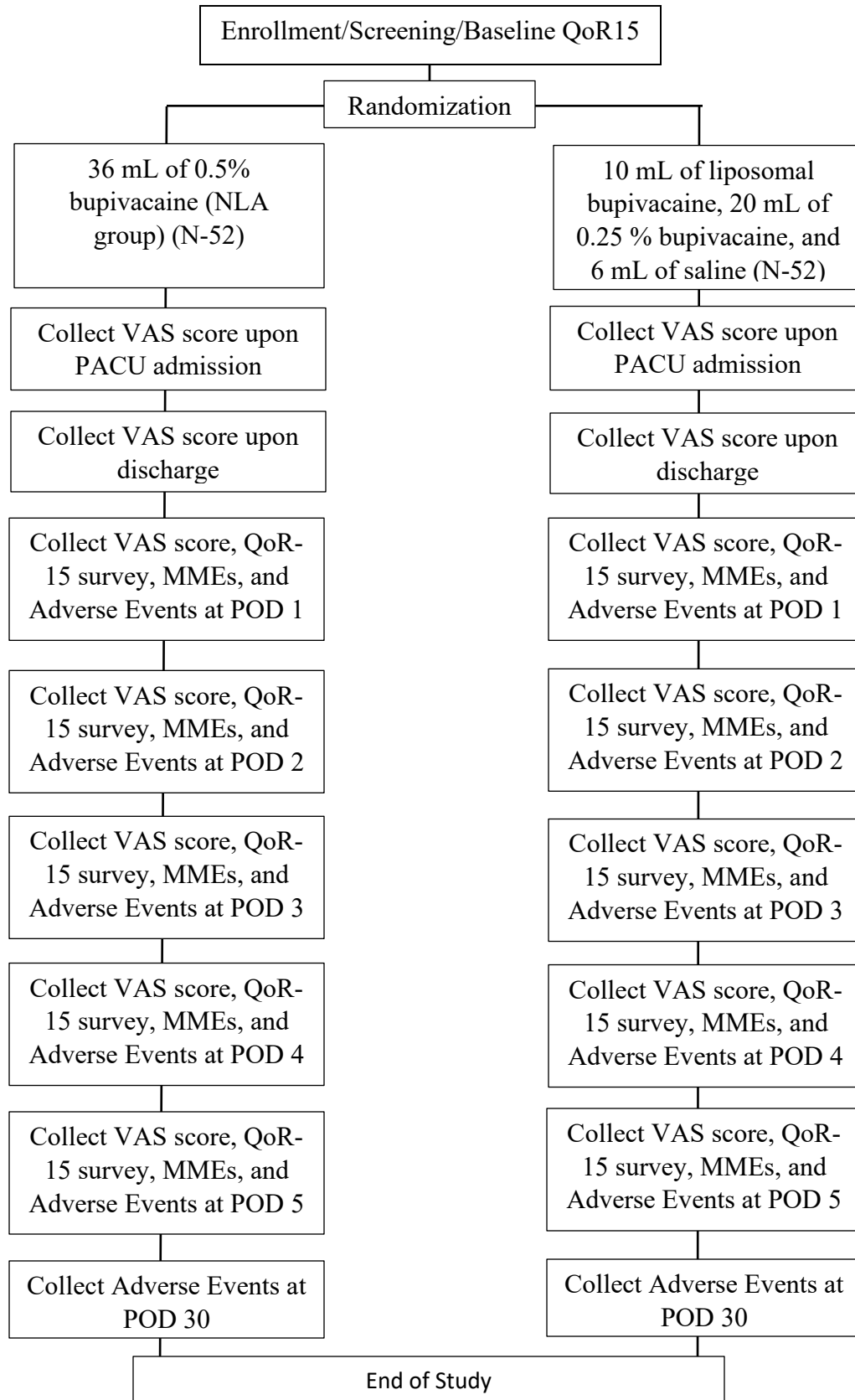
Table 1

Variable	Liposomal Bupivacaine, N = 285 ¹	Other Block, N = 178 ¹	No Block, N = 28 ¹	p-value ²
Mean VAS during 24 hr	3.39 (1.54)	4.23 (1.48)	5.20 (1.76)	<0.001
Unknown	3	0	0	
Mean VAS≤4 during 24hr	194 / 282 (69%)	79 / 178 (44%)	5 / 28 (18%)	<0.001
Unknown	3	0	0	

¹Mean (SD); n / N (%)

²Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Study Flowchart



QoR-15 Patient Survey

Date: __/__/__

Study #: _____

Preoperative ☐

Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

- | | | | | | | | | | | | | | |
|---|------------------|---|---|---|---|---|---|---|---|---|---|----|-----------------|
| 1. Able to breathe easily | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 2. Been able to enjoy food | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 3. Feeling rested | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 4. Have had a good sleep | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 5. Able to look after personal toilet and hygiene unaided | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 6. Able to communicate with family or friends | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 7. Getting support from hospital doctors and nurses | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 8. Able to return to work or usual home activities | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 9. Feeling comfortable and in control | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 10. Having a feeling of general well-being | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

- | | | | | | | | | | | | | | |
|--------------------------------|------------------|----|---|---|---|---|---|---|---|---|---|---|-----------------|
| 11. Moderate pain | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |
| 12. Severe pain | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |
| 13. Nausea or vomiting | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |
| 14. Feeling worried or anxious | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |
| 15. Feeling sad or depressed | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |

Medications Survey

A Double-Blind Randomized Comparison Trial of Postoperative Pain in Patients Undergoing Total Shoulder Arthroplasty who Receive Interscalene Blocks with or without Liposomal Bupivacaine (PoPTSAWoW Trial)

Please complete the survey below.

Thank you!

Please select the number of pills of each type that you have taken in the past 24 hours.

Advil 600 mg (Ibuprofen 600 mg)	v
Tylenol 325 mg (Acetaminophen 325 mg)	v
Tylenol 500 mg (Acetaminophen 500 mg)	v
Norco 5/325 (Hydrocodone 5 mg/acetaminophen 325 mg)	v
OxyContin 5 mg (Oxycodone 5 mg)	v
Ultram 50 mg (Tramadol 50 mg)	v
Other:	v

Submit

XIV: Budget:

Overhead	
IRB Fees:	
Initial Review	\$2,750
Annual Renewals	\$1,100
Revisions, Amendments, etc.	\$1,100
Coverage Analysis	\$1,200
Study Personnel Time:	
Research coordinator	100 patients with 2 hour per patient for consent) x \$50/hr.= \$10,000
Research assistant	(data collection, entry) 100 patients x 1 hours per patient x \$25/hr= \$2,500
Statistician	(50hours x \$100/hr.= \$5,000)
PI invested time	1 day per month x 10months x \$2000/day= \$20,000
Total	\$43,650

The costs for this study will be shared between the Departments of Anesthesiology and Orthopedic Surgery

XV References

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