Liposomal Bupivacaine vs. Interscalene Nerve Block for Pain Control After Total Shoulder Arthroplasty: A Randomized Clinical Trial

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

The incidence of shoulder replacements is quickly rising with the growing elderly population and new technologies, such as the reverse shoulder replacement.[1-2] At this time, there are 53,000 shoulder replacements performed annually according to the Agency for Healthcare Research and Quality. The interscalene (IS) brachial plexus nerve block is considered the gold standard for shoulder anesthesia. While complications for IS nerve blocks are rare, they include chronic neurologic complications and substantial respiratory, cardiovascular, and central nervous system events.[3] Femoral nerve blocks used in total knee arthroplasty are associated with complications such as insomnia, antalgic ambulation, and difficulty with rehabilitation, and increased incidence of falls.[7,9]

A new approach to postoperative analgesia is the periarticular injection method, by which the surgeon administers local infiltration analgesia without the help of an anesthesiologist. Recent literature has shown that the liposomal bupivacaine (Exparel ®) injection provides better pain control, shortens hospital stays, and decreases costs for total knee and hip arthroplasties compared to the gold standard nerve block methods. [4-12] Broome et. al found that total knee arthroplasty patients who had a liposomal bupivacaine injection saved an average of $600 compared to those who received a femoral nerve block.[4] This translated to a savings of approximately one million dollars per year at their hospital alone. Eliminating the costs associated with interscalene nerve block administration in shoulder replacements could allow for significant cost-savings to our healthcare system.

Currently, no published literature exists directly comparing liposomal bupivacaine and interscalene (IS) nerve blocks in shoulder replacements. This study would provide a direct comparison of available postoperative analgesia techniques for shoulder arthroplasty. The results of this work will demonstrate whether the liposomal bupivacaine injection technique results in the same postoperative pain compared to the typical interscalene nerve block method.

2. Objectives (include all primary and secondary objectives)

<u>Aim #1</u>: Determine clinical outcomes as they relate to pain control of the interscalene nerve block vs. liposomal bupivacaine injection in patients undergoing total shoulder arthroplasty.

This will be evaluated using the Visual Analog Scale (VAS) pain score and pain medication data and side effects from opioids (nausea/vomiting, GI distress, itching, etc) from inpatient medical records and through daily follow-up questionnaires after patients are discharged until 96 hours after surgery. Data will be collected at routine clinical follow up appointments after surgery.

Aim #2: Determine the length of stay of liposomal bupivacaine compared to interscalene nerve block in patients undergoing total shoulder arthroplasty and calculate costs associated with any differentials.

3. **Background** (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

We conducted a retrospective cohort analysis of 58 shoulder arthroplasties performed by a single surgeon. Patients who underwent total, reverse, and hemiarthroplasties were included. The control group included patients who received interscalene nerve blocks for postoperative pain control. The experimental group included patients who received periarticular liposomal bupivacaine injections. Baseline demographic data included age, sex, body mass index (BMI), and American Society of Anesthesiologists' (ASA) classification of physical health. We measured length of stay (LOS), pain medication administration, numeric rating scale (NRS) pain scores at four time intervals postoperatively (0.5 hours, 8-14 hours, 18-24 hours, 27-36 hours). Statistical analysis was performed.

There were 21 patients in the IS nerve block group and 37 patients in the liposomal bupivacaine group who met all inclusion criteria. Baseline demographic data for age ($p=0.53$), sex ($p=0.71$), BMI ($p=0.09$), and ASA ($p=0.33$) did not differ between groups. The primary outcome measure, NRS pain score, showed no significant differences between groups at 0–1 hours after surgery ($P = .99$) or 8–14 hours after surgery ($P = .208$). At 18–24 hours after surgery, the liposomal bupivacaine group had a lower mean NRS score than the ISNB group ($P = .001$). This was statistically significant when taking repeated measures of variance into account (Fig. 1). Mean NRS score was also lower for the liposomal bupivacaine group at 27–36 hours after surgery ($P = .029$). This was not statistically significant when repeated measures of variance were considered (Table II).

There was no difference in the amount of intravenous acetaminophen given during the hospital stay between groups. There was no statistically significant difference in opioid consumption on postoperative day 1 in the hospital ($P = .59$). However, there were significant differences between groups on postoperative days 2 and 3 (Fig. 2). On postoperative day 2, the ISNB group required significantly more opioids (112 mg) than the liposomal bupivacaine group (37 mg) ($P = .001$). The ISNB group also required significantly more opioids (25 mg) on postoperative day 3 than the liposomal bupivacaine group (5 mg) ($P = .002$).

Sixteen of 37 patients in the liposomal bupivacaine group and 2 of 21 in the ISNB group (Table III) were discharged on the day after surgery. The mean LOS was 46±20 hours for the liposomal bupivacaine group and 57 hours±14 hours for the ISNB group ($P = .012$).

There were no major cardiac or respiratory events in either group. No long-term paresthesias or neuropathies were noted. There were no readmissions for either group.

Liposomal bupivacaine injections may provide better pain control 18-24 hours after surgery and shorten hospital stays after shoulder arthroplasty compared to interscalene nerve blocks as a means of postoperative pain control. Based on these results, larger analytic studies including randomized trials should be performed to explore the potential benefits of liposomal bupivacaine injections for pain control after shoulder arthroplasty.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Study Design: After the decision to proceed with shoulder replacement surgery, patients will be asked to participate in this prospective randomized clinical trial.

Study Groups:

- Group 1 will receive interscalene nerve block.
- Group 2 will receive liposomal bupivacaine with local bupivacaine for postoperative analgesia.

Study Procedures:

1. Before Surgery: The Informed Consent process will be completed prior to any data collection. Consent will be completed after explanation of each treatment group and the data to be collected. The following baseline data will be collection prior to surgery:

- Demographics (including age, sex, BMI, work status, living environment)
- Medical and Surgical History
- ASA Physical Status Classification
- Charlson Comorbidity Index Score
- Pain History and Medications
- VAS pain score

2. Randomization: Subjects will be randomized prior to surgery into one of the two perioperative analgesia groups. Randomization will be stratified by gender.

3. Surgery/Inpatient Stay:

- Group 1: Patients in the interscalene nerve block group will be given a single shot block in the preoperative area by a fellowship-trained anesthesiologist. The shot will contain a local anesthetic like 5% Ropivacaine (5 mg/1 mL) with a 44 millimeter 22 gauge needle with the patient in the supine position.
- Group 2: The surgeon at each site will be trained prior to enrollment on the correct way to perform Exparel injections intraoperatively. The surgeon will give patients in the liposomal bupivacaine group the periarticular injection

containing 266 mg of the drug in 40 mL injectable saline in the operating room; local 0.5% bupivacaine-epinephrine will also be used not to exceed dose limits.

- Surgical/Inpatient Data Collection:
    - Pre-op procedure time
    - Surgical time
    - PACU time
    - Admission/Discharge time and date
    - Estimated blood loss
    - Procedures performed
    - Inpatient pain medications administered
    - Patient VAS scores every 6 hours after surgery

4. After Discharge:
    - Patients will record the following information after discharge up until 96 hours from their surgery:
        - VAS scores every 6 hours
        - Pain medication consumption (dosages, times)
        - Opioid-related side effects
        - Level of satisfaction with pain management
    - Study staff may conduct reminder phone calls to ensure patients complete outpatient data collection. The outcome assessor will be blinded to the treatment group.
    - Patients will record their VAS pain scores again at their 1st postop appointment, which typically occurs 10-18 days after surgery.

Sample Size: There will be 60 patients in each group, for a total study population of n = 120.

Study Locations: This will be a multi-center study. The sample size will enroll 120 (to account for 15% drop out rate) patients total, with approximately 30 patients enrolled at each site. The other participating sites are as follows:

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Sports Medicine and Shoulder Service
University of Texas, Southwestern Medical Center
1801 Inwood Rd, 1st Floor
Dallas, TX 75390

Dr. Peter Johnston
MedStar St. Mary's Hospital
25500 Point Lookout Rd
Leonardtown, MD 20650

Dr. Kelly Kilcoyne
William Beaumont Army Medical Center
5005 N. Piedras St
El Paso, TX 79920

Aim #2: Determine the length of stay of liposomal bupivacaine compared to interscalene nerve block in patients undergoing total shoulder arthroplasty and calculate costs associated with any differentials.

b. Study duration and number of study visits required of research participants.

Patients will be enrolled in this study for 2 weeks after their surgical date. This time frame will include their hospital stay and include their time at home after discharge up until 96 hours after their surgery, and their 2-week postop appointment data. If patients are not scheduled for their postop appointment within 10-18 days after surgery (which is standard clinical practice), the study team will call the patient to obtain their pain score and medication data. Patient names will be stored in a password-protected database for 30 days after discharge to calculate 30-day readmission rates.

Routine patient follow up is typically at 3, 6, and 12 months for the first year. Pain data and patient reported outcomes are collected at these visits as routine clinical care. Patients routinely complete the ASES and EQ-5D questionnaires at their 12 month follow up appointment.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Patients will be masked by performing the ISNB under sedation. They will not be completely blinded to their treatment group due to the fact that the Exparel group will not get a needle puncture at the site of the typical ISNB location in the neck since Exparel is injected intraoperatively in the surgical field while the patient is completely under general anesthesia. While the patient and surgeon cannot be blinded for this study, the outcome assessor will be masked to prevent bias in the data collection process.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

e. Justification for inclusion of a placebo or non-treatment group.

N/A

f. Definition of treatment failure or participant removal criteria.

Treatment is a one-time intervention for the nerve block. The assessment of their VAS pain score is routine clinical practice.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

In these cases, routine clinical care will continue based on the patient's needs.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:
Adults age 20-100 years old with degenerative changes of the shoulder joint (documented by radiographs) in patients planning total joint replacement with Dr. Uma Srikumaran (PI of this study) at Johns Hopkins Shoulder Service (Columbia, Odenton Clinic sites; HCGH/Bayview/JHH operative sites), with Dr. Michael Khazzam at the University of Texas Sports Medicine and Shoulder Service, with Dr. Peter Johnston at MedStar St. Mary's Hospital Shoulder Service, and with Dr. Kelly Kilcoyne at William Beaumont Army Medical Center will be included. Patients who require revision surgeries, hemiarthroplasties, or who have chronic pain issues will be included.

Exclusion Criteria:
Patients with an allergy to liposomal bupivacaine will be excluded. Patients with contraindications to the interscalene nerve block (preexisting neurologic defects, local anesthetic allergy, coagulopathy, contralateral phrenic nerve dysfunction, severe chronic obstructive pulmonary disease) will be excluded as these patients could not be randomized.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Drug and dosing used are the same as in the prior retrospective study.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variable.

- VAS pain score at 24 hours postop.

b. Secondary outcome variables.

- VAS scores at all other data points,

- Pain medication consumption (narcotics, NSAIDs, Tylenol)
- Opioid-induced side effects (nausea, vomiting, constipation)
- Length of hospital stay
- 30 day readmission rate.

c. Statistical plan including sample size justification and interim data analysis.

A power analysis was performed to determine the sample size needed determine noninferiority between groups with respect to VAS pain score. The minimal clinically important difference of VAS is 1.4 cm[13]. The number was found to be 42 patients in each group, for a total n = 84. To ensure we reach this number, each of the 4 sites will aim to enroll 30 patients, to account for drop out.

The age of the two treatment groups will be compared using t-test. Sex distribution and the ASA scores of the groups will be compared using a chi-squared test and a Fisher exact test, respectively.

The median and interquartile range of the VAS scores at each of the time points measured will be tabulated by treatment group, and at each time point the difference between groups will be tested using non-parametric rank sum tests.

We will test the longitudinal trajectory of VAS scores over time, taking into account repeated measurements in the same patients using linear mixed model analysis. Treatment group, time period as a categorical variable, and the interaction between treatment and time period will be included as fixed effects, and patient ID will be included as the random effect. An initial omnibus test will be performed for all treatment and treatment by time interaction effects. If significant, the treatment by time interaction will be tested subsequently for each of the measurement periods.

The association of day of discharge (as a categorical variable) with treatment will be tested using the Fisher exact test.

d. Early stopping rules.

We will monitor operative and post-operative complications including implant failures, nerve injuries, hematomas, and infections. We do not anticipate issues with these complications, as both techniques are in routine use in our current clinical practice. We did not find any differences in the complication rates in our retrospective cohort analysis.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
b. Steps taken to minimize the risks.
c. Plan for reporting unanticipated problems or study deviations.
d. Legal risks such as the risks that would be associated with breach of confidentiality.
e. Financial risks to the participants.

No additional risk associated with study for the participant, as study procedures are standard clinical care. There is a remote risk to the study subjects if there is a breach in confidentiality. All data will be collected and entered into a REDCap database. Data will be extracted from REDCap at the time of analysis.

To manage this, we will incorporate the following standard procedures:

1) Patient identifiers key to database will be kept on each site in password protected excel document.
2) We will maintain the data in accordance with University and IRB standards. Data will be kept on password protected university servers, and any printed material will be kept in a locked file cabinet.
3) Only investigators associated with the study will have access to the data

The reporting of unanticipated problems or study deviations will be reported to the JHM IRB pursuant to Hopkins IRB policies.

9. Benefits

a. Description of the probable benefits for the participant and for society.

There is no direct benefit to the participant in the study. This study could help determine if one pain control technique is superior to the other. This could result in higher quality care for patients who undergo total shoulder arthroplasty in the future. It could result in savings for the healthcare system if one technique is found to be cost-effective.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Patients will not be compensated for their participation in this study.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The costs of study procedures will be covered by the participant's health insurance because these procedures are both used for routine care.

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