Prolonging the Interscalene brachial plexus block by adding liposomal bupivacaine or preservative free dexamethasone to bupivacaine: a non-inferiority trial

FUNDER: Department of Anesthesiology

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PROTOCOL SYNOPSIS

Protocol Title:	Prolonging the Interscalene brachial plexus block by adding liposomal bupivacaine or preservative free dexamethasone to bupivacaine: a non-inferiority trial
Protocol Number:	2019_0424
Protocol Date:	5/28/2021
Sponsor:	Department of Anesthesiology
Principal Investigator:	David Kim, MD
Objective:	The intervention being studied is the usage of liposomal bupivacaine in conjunction of standard bupivacaine in an interscalene block (ISB). It is being compared to standard bupivacaine. Does the mixture of liposomal bupivacaine and bupivacaine provide extended analgesia in comparison to bupivacaine with preservative free dexamethasone?
Study Design:	Randomized Controlled Clinical Trial
Enrollment:	112
Subject Criteria:	1. Patients scheduled for elective outpatient arthroscopic shoulder surgery 2. ASA I-III 3. Ages 18 years or older
Data Collection:	Sources: EPIC, Medical Records, and Patient Reported. Variables: Demographics, Surgery type, Incidence of adverse effects (Horner's, hoarseness, dyspnea, hiccups), sensory exam (alcohol swab), motor exam (handgrip strength: present/weak/absent), NRS Pain scores at rest and at movement, Patient satisfaction, Opioid Consumption, Neuropraxia, Nerve Block Success, Length of PACU stay, Time to meet discharge criteria, Post Anesthetic discharge scoring system (assessed every 15 min after one hour in PACU, Brief Pain Inventory short form, LAST (local anesthetic systemic toxicity), Admission for pain.
Statistical Analysis:	• Alpha level: 0.05 • Beta or power level: 0.8

	• Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable): Mean difference of 1.3 +/- 1.0 • Interim analysis at 50% enrollment mark • Proposed analysis: T-Test • Effect size or change expected between groups: Noninferior margin of 1.3 • Total sample size required: 102 + 10% (for attrition/withdrawal) = 112

1.0 INTRODUCTION

Liposomal bupivacaine has chemical properties that indicate that it could provide longer block duration that standard bupivacaine. In this study, patients receiving a shoulder scope will be enrolled and randomized to receive either liposomal bupivacaine and standard bupivacaine or only bupivacaine. Preservative free dexamethasone is a well-studied additive that has shown prolongation of the interscalene block (up to 22 hours) and has been well adopted as a very common clinical practice. Liposomal Bupivacaine has recently been approved by the FDA for interscalene nerve blocks. The study that was used to grant its approval compared the liposomal bupivacaine to placebo. There has yet to be a study comparing the newly approved additive to a comparable additive. Unlike other studies that compared it to placebo or a plain local anesthetic, the goal of this study is to compare liposomal bupivacaine to a long acting interscalene block with preservative free dexamethasone. Liposomal bupivacaine is being advertised as a single-shot alternative to catheters. There have been comparative studies with liposomal bupivacaine infiltration with catheters but no comparison to additives such as dexamethasone.

Rebound pain is a known phenomenon that led clinicians to seek out blocks that would last longer. Williams et al[1] demonstrated that by prolonging the block for over 48 hours for knee surgery, it mitigates the intense rebound pain we witness with shorter acting blocks. Abdullah et al[2] demonstrated in their meta-analysis that the interscalene block provides little benefit for shoulder surgery if the duration is less than 24 hours. There are several prospective studies, and reviews supporting preservative-free dexamethasone perineural application to prolong the block[3,4,5]

Liposomal bupivacaine (Exparel) has been FDA approved for infiltration use. Just recently, it has been approved for the interscalene nerve block. There is only one prospective study comparing liposomal bupivacaine mixture to plain bupivacaine with results showing modest benefit with regards to worst pain and patient satisfaction after following patients over a week[6]. It is unclear if the effect would be the same if the liposomal bupivacaine mixture did not contain any standard bupivacaine. However, the reason the authors added standard bupivacaine was the delayed onset of liposomal bupivacaine precludes its use as a surgical anesthetic for the study. As the goal of the study was to observe the analgesic effect of adding liposomal bupivacaine to the interscalene block, it would be a fairer comparison group to measure it against a proven adjuvant like dexamethasone. This study will help elucidate liposomal bupivacaine's analgesic benefit in prolonging nerve blocks by comparing it to an effective alternative. The study led to liposomal bupivacaine's FDA approval compared its analgesic properties to placebo[7].

1. Williams BA, Bottegal MT, Kentor ML, Irrgang JJ, Williams JP. Rebound pain scores as a function of femoral nerve block duration after anterior cruciate ligament reconstruction: retrospective analysis of a prospective, randomized clinical trial. Reg Anesth Pain Med 2007; 266: 516-524.

2. Abdallah FW1, Halpern SH, Aoyama K, Brull R. Will the Real Benefits of Single-Shot Interscalene Block Please Stand Up? A Systematic Review and Meta-Analysis. Anesth Analg. 2015 May;120(5):1114-29.

3. Kirkham K, Jacob-Guillarmod A, Albrecht E, Kirkham K. Optimal Dose of Perineural Dexamethasone to Prolong Analgesia After Brachial Plexus Blockade: A Systematic Review and Meta-analysis. January 2018. Vol 126. No 1, 270-279

4. Liu J, Richman K, Grodofsky S, Huffman G, Kelly J, Glaser D, Elkassabany N. Is there a dose response of dexamethasone as adjuvant for supraclavicular brachial plexus nerve block? A prospective randomized doubleblinded clinical study. Journal of Clinical Anesthesia. 2015, 27, 237-242

5. Vera P, Pulai I, Tao GC, Manikantan P, Keller B, Connelly NR. Dexamethasone with bupivacaine increases duration of analgesia in ultrasound-guided interscalene brachial plexus blockade. Eur J Anaesthesiol. 2010 Mar;27(3):285-8.

6. Vandepitte C, Kurosawa M, Witvrouw R, Ludwig A, Bellemans J, Cortez K, Vanelderen P, Mesotten D, Leanne I, Heylen M, Van Boxstael S, Golebiewski M, Van del Velde M, Knezevic N, Hadzic A. Addition of liposome bupivacaine to bupivacaine HCL versus bupivacaine HCL alone for interscalene brachial plexus block in patients having major shoulder surgery. RAPM.2017 May/June;42(3): 334-341

7. Patel M, Gadsden J, Bao X, Bendtsen T. Brachial plexus block with liposomal bupivacaine for total shoulder arthroplasty or rotator cuff repair: results from a randomized controlled trial. Poster presented at: The New York School of Regional Anesthesia 16th Annual Fall Symposium; September 23-24, 2017; New York, NY.

This study will aid in validating or invalidating the claim that liposomal bupivacaine can effectively provide analgesia in the immediate postoperative period, up to 72 hours. By comparing the new, FDA approved local anesthetic to a well-studied cost-effective alternative rather than to a placebo, the study will provide new knowledge to the literature. If the study shows that exparel is non-inferior to dexamethasone over 72 hours, it will potential deter its costly use

2.0 OBJECTIVE(S) OF CLINICAL STUDY

If liposomal bupivacaine does not provide analgesia as adequately as the alternative (preservative-free dexamethasone bupivacaine), it will discourage its costly use. Does the mixture of liposomal bupivacaine and bupivacaine provide extended analgesia in comparison to bupivacaine with preservative free dexamethasone?

The primary outcome is average NRS pain score at rest over 72 hours (average of 3 24-hour time point [24, 48, 72 hours]).

Secondary Outcomes:

1. NRS pain scores at rest on PACU, POD1, POD2, POD3, POD4, POD7

2. NRS pain scores with movement in PACU, POD 1, POD2, POD3, POD4, POD7

3. Brief Pain Inventory short-form in PACU, POD1, POD2, POD3, POD4, POD7

4. Opioid consumption in PACU, POD1, POD2, POD3, POD4, POD 7

5. Patient Satisfaction with pain treatment in PACU, POD 1, POD 2, POD 3, POD 4, POD 7

6. Duration of analgesic block via RA phone call 24, 48, 72 hours after block placement (or longer if block continues): Patient's will be asked "Since being discharged, when did you first take an analgesic medication for shoulder pain?" and "When did your pain relief from the block completely wore off?"

7. Sensory resolution in PACU, POD1, POD2, POD3, POD4, POD7 (full resolution of block will be reported by the patient via RA phone call 24, 48, 72 hours after block placement or longer if duration continues, "When did your numbness completely resolve and returned to normal?", will likely be until POD 1, but would continue until block resolution)

8. Motor block resolution in PACU, POD1, POD2, POD3, POD4, POD7 (full resolution of block will be reported by the patient via RA phone call 24, 48, 72 hours after block placement or longer if block continues, "When did your arm or hand weakness resolve and returned to normal?", will likely be until POD 1, but would continue until block resolution)

9. Success of interscalene block: C5 Dermatome distribution will be assessed in the PACU by the anesthesiologist (co-i). Alcohol swab test (2-normal cold sensation, 1-diminished/dull, 0-absence of cold sensation). Motor test: hand grip (normal-2, weak-1, absent-0)

10. Adverse effects: sensory-motor deficits: incidence of paresthesia / neuropraxia: persistent tingling, numbness on POD7, if patient reports persistent neuropraxia after POD7, will follow up on POD14. If neuropraxia persists, will notify attending anesthesiologist and continue to follow until postoperative neurological symptoms (PONS) resolve. On POD 7, patients will be asked "on the side where surgery was performed, do you have any numbness, tingling, or weakness in the hand or fingers?

11. If the response to continued numbness/tingling in fingers on POD7 is yes, adverse effects will be asked on POD 14.

12. Incidence of ISB related side effects: Horner's syndrome, hoarseness, hiccups, dyspnea in PACU, POD1-4,7

13. Time to readiness for PACU discharge (time of PACU admission to time of readiness to discharge, measured by Post Anesthetic Discharge Scoring System) evaluated every 15 minutes

14. Length of PACU stay (time of PACU admission to PACU discharge)

3.0 STUDY HYPOTHESES

The prolongation of analgesia provided by adding liposomal bupivacaine to bupivacaine is non-inferior to Bupivacaine with preservative free dexamethasone.

4.0 STUDY DESIGN

4.1 Endpoints

4.1.1 Primary Endpoint

- The primary outcome is average NRS pain score at rest over 72 hours (average of 3 24-hour time point [24, 48, 72 hours]).

4.1.2 Secondary Endpoints

- 1. NRS pain scores at rest on PACU, POD1, POD2, POD3, POD4, POD7
- 2. NRS pain scores with movement in PACU, POD 1, POD2, POD3, POD4, POD7
- 3. Brief Pain Inventory short-form in PACU, POD1, POD2, POD3, POD4, POD7
- 4. Opioid consumption in PACU, POD1, POD2, POD3, POD4, POD 7
- 5. Patient Satisfaction with pain treatment in PACU, POD 1, POD 2, POD 3, POD 4, POD 7
- 6. Duration of analgesic block via RA phone call 24, 48, 72 hours after block placement (or longer if block continues): Patient's will be asked "Since being discharged, when did you first take an analgesic medication for shoulder pain?" and "When did your pain relief from the block completely wore off?"
- 7. Sensory resolution in PACU, POD1, POD2, POD3, POD4, POD7 (full resolution of block will be reported by the patient via RA phone call 24, 48, 72 hours after block placement or longer if duration continues, "When did your numbness completely resolve and returned to normal?", will likely be until POD 1, but would continue until block resolution)
- 8. Motor block resolution in PACU, POD1, POD2, POD3, POD4, POD7 (full resolution of block will be reported by the patient via RA phone call 24, 48, 72 hours after block placement or longer if block continues, "When did your arm or hand weakness resolve and returned to normal?", will likely be until POD 1, but would continue until block resolution)
- 9. Success of interscalene block: C5 Dermatome distribution will be assessed in the PACU by the anesthesiologist (co-i). Alcohol swab test (2-normal cold sensation, 1-diminished/dull, 0-absence of cold sensation). Motor test: hand grip (normal-2, weak-1, absent-0)
- 10. Adverse effects: sensory-motor deficits: incidence of paresthesia / neuropraxia: persistent tingling, numbness on POD7, if patient reports persistent neuropraxia after POD7, will follow up on POD14. If neuropraxia persists, will notify attending anesthesiologist and continue to

follow until postoperative neurological symptoms (PONS) resolve. On POD 7, patients will be asked “on the side where surgery was performed, do you have any numbness, tingling, or weakness in the hand or fingers?

- 11. If the response to continued numbness/tingling in fingers on POD7 is yes, adverse effects will be asked on POD 14.
- 12. Incidence of ISB related side effects: Horner’s syndrome, hoarseness, hiccups, dyspnea in PACU, POD1-4,7
- 13. Time to readiness for PACU discharge (time of PACU admission to time of readiness to discharge, measured by Post Anesthetic Discharge Scoring System) evaluated every 15 minutes
- 14. Length of PACU stay (time of PACU admission to PACU discharge)

4.2 Study Sites

This study will take place at the main campus of the Hospital for Special Surgery (HSS).

5.0 STUDY POPULATION

5.1 Number of Subjects

112

5.2 Inclusion Criteria

Subjects of either gender will be included if:

1. Scheduled for elective outpatient arthroscopic shoulder surgery
2. ASA I-III
3. Age 18 years or older

5.3 Exclusion Criteria

Subjects will be excluded from the study if:

- History of allergy to local anesthetic, or one of the study medications
- Pre-existing neurological deficits
- Psychiatric or cognitive disorders that prohibit patients from following study protocol
- History of drug or alcohol abuse
- Chronic Opioid use (longer than 3 months)
- Chronic pain syndromes
- Infection at the site of injection
- Patients with severe pulmonary disease
- Herniated cervical disc, cervical myelopathy
- Contraindication for general anesthesia and/or interscalene nerve blocks
- Pregnancy
- Open shoulder arthrotomies
- Non-English speakers

6.0 PROCEDURES

6.1 Intraoperative Protocol

Following sedation, the interscalene block will be done using an ultrasound-guided, in-plane approach. The anesthesiologist will target below the C5 nerve root. A 22 gauge 1.5-2 inch needle is advanced in-plane from lateral medial through the middle scalene muscle until the needle tip is positioned in the interscalene groove between the C5 and C6 nerve roots. Patients will be randomized to two groups:

1. Dexamethasone: 15mL of 0.5% bupivacaine with 4mg of preservative-free dexamethasone will be injected
2. Exparel: 10mL of 133mg liposomal bupivacaine with 5mL of 0.5% bupivacaine (15mL total)

Premedication will consist of 2-5mg of Midazolam. After block induction, general anesthesia will be performed by administration of propofol (induction doses of 2mg/kg) by the anesthesiologist. LMA will be inserted and anesthesia maintained with Propofol infusion and Fentanyl (Fentanyl 25-50mcg titrated up to 200mcg) as needed. To avoid PONV, 4mg Decadron (Dex group) or 8mg Decadron (Exparel group) will be administered, as well as 4mg Zofran for both groups. Before the end of surgery, 15-30mg Ketorolac will be given (30mg for patients under 65 and over 50kg, 15mg for patients under 65 or under 50kg).

6.2 Postoperative Protocol

Postop medication includes IV acetaminophen (1g IV upon PACU arrival, 750mg if <50kg), ketorolac (30mg IV q hours following intraop dose if not yet discharged, 15mg for 65 years or older, <50kg). For pain control, tramadol 50mg q 6 hours PRN (mild pain [1-3]); tramadol 100mg q hours (or 75mg if <50kg) (moderate pain [4-6]; oxycodone 5mg q 3 hours (severe pain [7-10]); dilaudid IV for rescue analgesia. Patients will be discharged with Naproxen 500mg q 12 hours, Percocet 5-325mg 1-2 tabs q 4 hours PRN, and Zofran 8mg q 8 hours.

6.3 Data Collection

The following data will be collected:

Pre-operative/Baseline

- DOB
- Name
- Gender
- Race
- Ethnicity
- Height, weight, BMI
- ASA
- MRN

- Preop NRS
- Preop Sensory tests
- Preop Brief Pain Inventory

Surgical procedure (Intra-operative)

- Surgeon and Anesthesiologist
- Surgery start and end
- Length of Surgery
- Anesthesia start and end
- Induction start and end
- Type of Shoulder surgery
- Laterality
- Intraoperative fentanyl and dilaudid use

Post-Operative Day 0 (PACU)

- Vital Signs (systolic bp, diastolic bp, pulse)
- Ambulation (steady gait/no dizziness, requires assistance, unable to ambulate/dizziness)
- Nausea and Vomiting
- Pain (NRS)
- Surgical bleeding
- Length of PACU stay (OR to PACU transfer time, PACU discharge time)

Post-Operative Day 1 (POD 1)

- NRS
- Brief pain inventory
- Medication Usage
- Block Resolution
- Side Effects
- Satisfaction

Post-Operative Day 2 (POD 2)

- NRS
- Brief pain inventory
- Medication Usage
- Block Resolution
- Side Effects
- Satisfaction

Post-Operative Day 3 (POD 3)

- NRS
- Brief pain inventory
- Medication Usage
- Block Resolution
- Side Effects
- Satisfaction and Blinding

Post-Operative Day 4 (POD 4)

- NRS
- Brief pain inventory
- Medication Usage
- Block Resolution
- Side Effects
- Satisfaction

Post-Operative Day 7 (POD 7)

- NRS
- Brief pain inventory
- Medication Usage
- Side Effects
- Satisfaction

Post-Operative Day 14 (POD 14)

- Side Effects

7.0 STATISTICAL ANALYSIS

- Proposed analysis: T-Test
- Interim analysis planned: Yes, at the 50% mark of 56 patients
- Alpha level: 0.05
- Beta or power level: 0.8
- Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable): Mean difference of 1.3 +/- 1.0
- Number of groups being compared: 2
- Effect size or change expected between groups: Noninferior margin of 1.3
- Resulting number per group: 51
- Total sample size required: 102 + 10% (for attrition/withdrawal) = 112

8.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report.