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Title: A Prospective Randomized Controlled Trial Examining the Effectiveness of a Single Shot of Liposomal Bupivicaine for Reducing Post-operative Pain and Narcotic Use in Outpatient Rotator Cuff Surgery

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Introduction

This document is a protocol for a human research study. This study is to be conducted according to United States standards of Good Clinical Practice in accordance with applicable Federal regulations and institutional research policies and procedures.

Liposomal bupivacaine (LB) has been shown to decrease post-operative pain and narcotic use when administered perioperatively as a local injection during arthroplasty procedures. Studies have also demonstrated that LB used in conjunction with dexamethasone may increase the duration of effectiveness of LB. This study seeks to evaluate if there is a difference in post-operative pain and narcotic use when LB is administered in an interscalene block during outpatient rotator cuff repair surgery. Furthermore, this study aims to determine if the addition of dexamethasone with LB results in a prolonged decrease in post-operative pain and a reduction in narcotic use.

Background Information and Scientific Rationale

Outpatient surgery has become the gold standard for arthroscopic rotator cuff repair. Innovations in pain management with regional anesthesia and multimodal techniques have greatly contributed to this transition over the past several decades. Despite overall improvements, uncontrolled postoperative pain leads to prolonged ambulatory stays, increased patient dissatisfaction, unexpected admissions to the hospital or visits to the Emergency Room after surgery, and a greater incidence of complications.[11,16,20,26,27,30,36,39-42,49,] Furthermore, in the wake of the "opiod epidemic", concerns with narcotic consumption and addiction have become heightened with regulations and laws recently enacted making prescribing and managing postoperative pain ever more difficult.[58]

Interscalene nerve blockade for shoulder procedures has become an increasingly common technique to provide perioperative pain control with good efficacy, low complication rates and reduced narcotic consumption.[12,15,28,34,35,54] While the utilization of ultrasound to help administer the block has aided in the accuracy providing a more consistent analgesic effect, its overall short duration (12-24 hours) remains one of the major limitations of this technique.[18,28,35] Modalities to prolong its effect have included use of indwelling catheters and the addition of perineural dexamethasone.[2,10,12,15,25,29,32,51]

Recently, liposomal bupivacaine (LB) (Exparel) was approved for single shot interscalene administration by the FDA. This medication has been purported to provide up to 72 hours of extended release of bupivacaine via its multivesicular and honeycomb-like structure that predictably breaks down resulting in a slow and sustained release of the medication.[9] Although numerous studies have been conducted and several meta-analyses performed looking at the overall efficacy of local injections of LB for operative procedures in an inpatient setting, no study to date has independently assessed its efficacy in the new perineural indication for outpatient shoulder surgery.[6,8,22,44,52] Furthermore, no study to date has compared the use of LB to the use of LB with dexamethasone in a perineural indication to see if the duration of efficacy is further prolonged with the addition of dexamethasone. All existing literature is in regard to use of liposomal bupivacaine injected locally within the surgical site. This will be the first study

to examine the perineural use of LB for outpatient shoulder surgery, and to determine if there is a prolonged decrease in pain and a decrease in narcotic consumption with the use of LB with dexamethasone when delivered as an interscalene block in an ambulatory setting.

Study Objectives

Utilizing a prospective randomized controlled trial, this study seeks to evaluate if there is a difference in post-operative pain and narcotic use when LB is administered in an interscalene block during outpatient rotator cuff repair surgery. Furthermore, this study aims to determine if the addition of dexamethasone with LB results in a prolonged decrease in post-operative pain and an overall reduction in narcotic use.

Primary Aims & Objective

Aim 1a: To determine if the use of LB in an interscalene block decreases patient-reported post-operative VAS pain in patients undergoing outpatient rotator cuff surgery

Hypothesis: There will be a decrease in VAS pain for up to 120 hours post-operatively among participants who receive LB or LB plus dexamethasone, as compared to the control group (bupivacaine plus dexamethasone).

Objective: Utilizing a prospective randomized controlled trial, post-operative patient-reported VAS pain (on a scale of 1-10) will be collected 3 times per day (every 8 hours) for 5 post-operative days (PODs), corresponding to a total of 120 hours after surgery. For each 24-hour period (corresponding to each POD), the pain scores will be averaged and compared between the three treatment groups (control, LB, and LB plus dexamethasone) for each of the 5 PODs.

Aim 1b: To determine if the use of LB plus dexamethasone in an interscalene block decreases patient-reported post-operative VAS pain for a longer duration than the LB or the control group (bupivacaine plus dexamethasone) in patients undergoing outpatient rotator cuff surgery

Hypothesis: There will be a decrease in VAS pain for greater than 72 hours post-operatively among participants who receive LB plus dexamethasone, as compared to the LB and the control group (bupivacaine plus dexamethasone).

Objective: Utilizing a prospective randomized controlled trial, post-operative patient-reported VAS pain (on a scale of 1-10) will be collected 3 times per day (every 8 hours) for 5 post-operative days (PODs), corresponding to a total of 120 hours after surgery. For each 24-hour period (corresponding to each POD), the pain scores will be averaged and compared between the three treatment groups (control, LB, and LB plus dexamethasone) for each of the 5 PODs.

Secondary Aims & Objectives

Aim 2a: To determine if there is a difference in time at which post-operative narcotics are first used among three groups receiving different interscalene blocks (LB plus dexamethasone, LB, and control) in patients undergoing outpatient rotator cuff surgery.

Hypothesis: Narcotic use will begin at a later time among those receiving LB plus dexamethasone, as compared to the LB and the control group (bupivacaine plus dexamethasone).

Objective: Utilizing a prospective randomized controlled trial, narcotic use will be collected at 8-hour increments for a total of 5 post-operative days (PODs), corresponding to a period of 120 hours post-surgery. The 8-hour time period during which a participant first begins using a narcotic will be recorded and compared between three treatment groups (control, LB, and LB plus dexamethasone).

Aim 2b: To determine if there is a difference in patient-reported post-operative narcotic use (measured in morphine equivalents) among three groups receiving different interscalene blocks (LB plus dexamethasone, LB, and control) in patients undergoing outpatient rotator cuff surgery.

Hypothesis: There will be a decrease in cumulative narcotic use (measured in morphine equivalents) among participants who receive LB plus dexamethasone, as compared to the LB and the control group (bupivacaine plus dexamethasone).

Objective: Utilizing a prospective randomized controlled trial, post-operative patient-reported narcotic use (measured by the number of tablets ingested and converted to morphine equivalents) will be collected 3 times per day at 8-hour increments for a total of 5 post-operative days (PODs), corresponding to a total of 120 hours after surgery. For each 24-hour period (corresponding to each POD), narcotic use will be tabulated and compared between three treatment groups (control, LB, and LB plus dexamethasone). Furthermore, cumulative narcotic use during the 5-day (120 hour) study period will be calculated and compared between three treatment groups (control, LB, and LB plus dexamethasone).

Study Design

The study design is a randomized double-blind randomized controlled trial.

Research Design

Patients will be randomly assigned to one of three treatment groups (see Intervention Description). Patients will randomly select one of 78 sealed envelopes they will give to the anesthesiologist for administration the day of surgery. Patients will be blinded to the medication utilized as well as the treating surgeon (PI). A consecutive series of patients will be enrolled to prevent selection bias. A single surgeon will be performing all procedures to minimize

variability. Unfortunately, it would not be feasible to have the same anesthesiologist for each procedure; however, this study will use a core team of anesthesiologists, each with multiple years of experience performing the ultrasound guided blocks. Furthermore, the medications and dosages for each treatment group are clearly outlined, and the method of administration is the same for all groups. The research team will ensure that each anesthesiologist understands the randomization protocol and will be trained on how to follow the instructions outlined in this study protocol.

Data Collection will occur post-operatively for 5 days. Data will be collected at 16 timepoints, corresponding to 8-hr time intervals for a period of 120 hours (see Study Visits). Data will be collected using CareSense, a smart phone application that uses a text message system to collect information. Patients will be notified by text alert 3 times per day (8am, 2pm and 8pm) asking to rate their pain on a scale of 0-10 (VAS). Patients will also respond to the number of pain pills taken in the slotted time span. All patients will be prescribed the same narcotic regimen (oxydone IR) barring any allergies encountered. Alerts will be sent starting the evening of surgery (8pm) and then continued for 120 hours. Patients who fail to respond to the text alert will be notified by the data collection system and contacted via phone by study personnel. Patients lacking smartphone technology will all be notified via telephone and also asked to keep a personal log to capture the information needed.

Data Management

The CareSense database is password protected and HIPPA compliant data collection system currently utilized by the lead physician (Dr. Badman). Patients upon enrollment will be assigned an ID to allow for data tracking within the application. Primary data will be collected via the web-based system and stored electronically and encrypted under password protection. The principal investigator will only have access to the database. At the conclusion of the study, the data will be exported to a password-protected encrypted Excel file on a password-protected computer. Once the data have been checked for accuracy and prior to statistical analysis, patient identifiers will be removed from the data set. The de-identified password-protected Excel spreadsheet will be provided to a statistician who will import the file into SPSS for analysis.

Study Agent, Device, and/or Intervention Description

The medication administered in the interscalene block is the intervention in this study. There are three different types of interscalene blocks that will be administered in order to compare the independent effectiveness of LB with the effectiveness of LB plus dexamethasone. Study participants will be randomized into one of three groups. The treatment groups are listed below:

Group 1 (Control)	Group 2	Group 3
30 ml of 0.5% bupivacaine and 0.4ml (4 mg) of dexamethasone	15ml 0.5% bupivacaine and 10ml (133mg) of LB	15ml 0.5% bupivacaine and 10ml LB (Exparel) and

	(Exparel) and 5.4ml normal saline	0.4ml (4 mg) dexamethasone and 5ml normal saline

The LB (Exparel) has been FDA approved for use as an interscalene brachial plexus nerve block to produce post-surgical regional analgesia following shoulder surgery in adults. Patients in Groups 2 and 3 will receive LB. The 15mg dose of LB chosen for this study is the same dose that was utilized in the protocol of Study 402C-327, which was the study elicited for FDA approval for the use of Exparel in interscalene nerve block. This dose also closely mimics the present standard of care (30ml of 0.5% bupivacaine with 4mg dexamethasone) in volume which is essential, as significant changes in volume can alter the impact of dermatomes blocked by the local anesthetic. The addition of standard bupivacaine was included in Groups 2 and 3 as it provides immediate onset (versus the delay seen with LB), allowing for better anesthetic management during surgery and alleviating pain immediately after surgery. Finally, normal saline was added to groups 2 and 3 to have equal injectable volume in each arm.

Dexamethasone is utilized in Group 3 to prolong the duration of amide local anesthetics. (ref) Study 402-C-327 only examined the independent use of LB, and did not utilize dexamethasone to prolong the duration of the block. Although the use of dexamethasone is standard of care in our institution, the utilization of dexamethasone is not a universally accepted practice. Several studies have demonstrated conflicting evidence regarding its overall utility to enhance peripheral nerve blockade. Furthermore, it can pose issues with glucose levels in insulin resistant and diabetic patients. Accordingly, if there is no proven benefit to including it into the mix in conjunction with the liposomal bupivacaine, it would be advantageous to remove it from treatment recommendations. The intent, therefore is to look at the two groups and determine if there are significant differences in pain and narcotic use between the LB and LB plus dexamethasone groups.

Sample Size

Previous studies have shown large effect sizes of greater than f=0.75 when comparing daily post-operative VAS pain[45] and cumulative narcotic use between LB and a control group.[45,59] However, the effect sizes for differences in VAS pain and narcotic use between LB and LB plus dexamethasone has not been reported, but it is anticipated that they would be smaller than those found between LB and control group comparisons. For an analysis of variance (ANOVA) test, a sample size of 22 participants per group would be required, given an effect size of f=0.40, a power of 80%, and a two-tailed alpha level of 0.05. However, to account for 15% subject attrition, a total of 26 patients per group will be enrolled, yielding a total of 78 participants.

Subject Selection

Patients who meet the following criteria will be included in the study:

Inclusion Criteria

1. Age 18 and older
2. Primary diagnosis of rotator cuff tear
3. Able to provide informed consent
4. Is willing and able to accept text messages

Patients who meet the following conditions will be excluded from participation:

Exclusion Criteria

1. Known allergies to the study medications.
2. Known narcotic or alcohol abuse (< 3 months)
3. Revision rotator cuff surgery
4. Contraindication to regional anesthesia
5. Current narcotic regimen or contract with pain management specialist
6. Diagnosed with any of the following co-morbidities
    a. Pre-existing coagulation disorder
    b. Diabetic patients

Study Outcome Measures (Endpoints)

Primary Endpoint: Patient-reported post-operative VAS pain (on a scale of 1-10), measured post operatively, in 8-hour increments, for a total of 120 hours post-surgery

Patients will be prompted via text message to provide VAS pain every 8 hours. If a response text message is not received, a phone call will be made to obtain the information. Patients who do not have a smart phone will receive a phone call or keep a personal log of VAS pain.

Secondary Endpoint: Patient-reported post-operative opioid use (converted to morphine equivalents), collected post operatively, in 8-hour increments, for a total of 120 hours post-surgery

Patients will be prompted via text message to provide the amount of narcotics (number of pills converted to morphine equivalents) taken over the course of the previous 8 hours. If a response text message is not received, a phone call will be made to obtain the information. Patients who do not have a smart phone will receive a phone call or keep a personal log of narcotic use.

Study Procedures

Subject Recruitment and Screening

Participants will be recruited from the clinical practice of Dr. Brian Badman. Patients who present for an office visit and are diagnosed with a rotator cuff tear requiring outpatient surgical intervention will screened for eligibility for participation in the study. If a patient is eligible for the study, Dr. Badman will discuss the study with the patient and obtain informed consent during the routine office visit.

Randomization

This is a double-blinded study, thus, neither the surgeon nor the patient will know which type of interscalene block is used. A total of 78 envelopes containing will be generated consisting of 26 with Group 1", 26 with "Group 2" and 26 with "Group 3" designation. Envelopes will be sealed and randomly chosen by the anesthesiologist prior to surgery. The anesthesiologist will randomly select one of the envelopes which will determine the treatment group and indicate medications that will be included in the interscalene block. Once the recipe is verified, the name of the patient will be added to the envelope along with the treatment group, and the envelope will be sealed. The treatment group and name of patient will be kept confidential until completion of the study. Envelopes will be opened at end of study for data collection and analysis purposes with patient information deidentified. They will be stored in a locked container at the surgery center only accessible by the chief of staff. It is not possible to blind the anesthesiologist, as the liposomal bupivacaine is a cloudy fluid and will be obvious to the administering physician. It is also prudent that the anesthesiologist is aware of the medication being administered for proper perioperative management of the patient. Patients will be blinded to the medication utilized as well as the treating surgeon. All anesthesiologists (sub-investigators) in the study are skilled and expertly trained in regional anesthesia using ultrasound guidance.

Study Visits/ Study Duration

Participants enrolled in this study will receive a peri-operative injection and be followed for a period of 120 hours, post-operatively. Three times per day (in 8 hour increments), patients will self-report VAS pain and indicate their narcotic use (number of tablets injested). Data concerning pain and narcotic use will be collected via text message (or phone if patients fail to respond to text messages).

Post-operative day (POD)	Data Collection Timepoint	Data to be Collected
POD 1	8 hrs	VAS Pain; narcotics used
	16 hrs	VAS Pain; narcotics used
	24 hrs	VAS Pain; narcotics used
POD 2	32 hrs	VAS Pain; narcotics used
	40 hrs	VAS Pain; narcotics used
	48 hrs	VAS Pain; narcotics used
POD 3	56 hrs	VAS Pain; narcotics used

	64 hrs	VAS Pain; narcotics used
	72 hrs	VAS Pain; narcotics used
POD 4	80 hrs	VAS Pain; narcotics used
	88 hrs	VAS Pain; narcotics used
	96 hrs	VAS Pain; narcotics used
POD 5	104 hrs	VAS Pain; narcotics used
	112 hrs	VAS Pain; narcotics used
	120 hrs	VAS Pain; narcotics used

The enrollment period for study participation is anticipated to last for 12 months only for data analysis.

Specimen Collection, Preparation, Handling and Shipping

N/A

Statistical Analysis Plan

After data checking and validation are completed, the analysis of the data will begin with examination of the distribution of each of the study variables. In this process, outliers will be identified and evaluated for inclusion in the final study database. Appropriate summary statistics will be calculated. Means and standard deviations will be reported for normally distributed continuous variables, a median and range will be tabulated for continuous variable that are not normally distributed, and frequencies and percentages will be provided for categorical variables. The remainder of the analysis will correspond to the specific aims provided above.

Specific Aims 1a-b: To determine if there is a difference in mean VAS pain between the control group, LB group, and LB plus dexamethasone groups, up to 120 hours post-operatively

If data are normally distributed, analysis of variance (ANOVA) with Tukey's HSD pairwise comparisons will be used to compare VAS pain between the three groups at each PODs 1-5. If data are not normally distributed, then Kruskal-Wallis with Dunn's multiple comparisons tests will be used.

Specific Aim 2a: To determine if there is a difference in time at which post-operative narcotics are first used among three groups receiving different interscalene blocks (LB plus dexamethasone, LB, and control)

The data collection timepoint (8-hour interval) during which narcotic use begins will be compared between groups. If data are normally distributed, analysis of variance (ANOVA) with Tukey's HSD pairwise comparisons will be used to compare time of first narcotic use between the three groups. If data are not normally distributed, then Kruskal-Wallis with Dunn's multiple comparisons tests will be used.

Aim 2b: To determine if there is a difference in patient-reported post-operative narcotic use (measured in morphine equivalents) among three groups receiving different interscalene blocks (LB plus dexamethasone, LB, and control)

If data are normally distributed, analysis of variance (ANOVA) with Tukey's HSD pairwise comparisons will be used to compare narcotic use (converted to morphine equivalents) between the three groups at each PODs 1-5. Cumulative narcotic use during all 5 PODs will also be compared between groups. If data are not normally distributed, then Kruskal-Wallis with Dunn's multiple comparisons tests will be used.

Potential Risks and Benefits

Potential Risks

This research is collecting data on a combination of medicines which are routinely used for nerve blocks. They are all FDA approved. The following risks can be related to the procedure, study analysis, and medications given:

1. Risk of nerve block: Interscalene nerve block is a routine component of anesthesia for shoulder surgery. Like any medical procedure, there are risks associated with interscalene block. These risks include both occasional and unlikely risks. Occasional risks include block failure (pain immediately following the procedure), a spread of the numbing agent beyond its intended site causing unintended symptoms (including temporary eyelid droop, pupil dilation, hoarseness, and shortness of breath), and bruising at the injection site. Unlikely risks have been described with interscalene block. These include introduction of infection, damage to the lung requiring placement of a chest tube, injection of numbing agent into the bloodstream which can lead to heart failure and death, result in death and permanent nerve injury. Fortunately, these risks are extremely rare. Ultrasound guidance is utilized by the anesthesiologist to help accurately place the medications around the nerves and lessen these risks.

2. Risk of text alerts: A HIPPA compliant and password protected database called CareSense is the application that will help gather and collect the data. Texting is not a secure form of communication and there is a risk of loss of privacy by entering the data. Measures to lessen these risks include using a password protected database and all personal information will be deidentified with your name removed. In addition, the only information you will provide will be regarding pain level and number of pain pills taken. Your phone number will be kept confidential and not shared with any outside party.

3. Risks of medications: Patients may have unknown allergies to one or more of the medications in the interscalene injection. Common side effects for each medication utilized are listed below.

    a. Bupivicaine: Common side effects can include nausea, vomiting, chills, shivering, headache, dizziness, anxiety, ringing in the ears and blurred vision.

    b. Dexamethasone: Common side effects can include increased appetite, insomnia (difficulty sleeping), heartburn, increased blood sugar levels, irritability, nausea, bloating, headache and dizziness.

c. Exparel: Common side effects can include dizziness, nausea, constipation, vomiting, itching, headache, and constipation.

Potential Benefits

An individual benefit from this study is that patients will be monitored closely via text messages three times per day; thus if any side effects or complications occur related to interscalene block, the PI will be alerted. Additionally, knowledge gained from this study will allow investigators to determine the most effective treatment methods for minimizing post-operative pain and narcotic use in patients who undergo outpatient rotator cuff surgery. These findings will benefit future patients.

Adverse Event Reporting:

Adverse Events

Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately. All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document.

Notification of Adverse Events

All adverse events will be reported according to WIRB guidelines.

Ethical Considerations

N/A

Funding Source

N/A

Subject Stipends or Payments

N/A

Publication Plan

The paper will be submitted for publication in the Journal of Shoulder and Elbow Surgery or the Journal of Bone and Joint Surgery upon completion.

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