

Official Study Title: Use of liposomal bupivacaine for postoperative pain management after arthroscopic rotator cuff repair

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Scientific Background:

Arthroscopic rotator cuff repair is among the most painful of orthopedic surgeries. Hundreds of thousands of these procedures are carried out in the U.S. each year. Many involve the use of a brachial plexus nerve block, which serves to control pain for 12 to 14 hours. However, when the block wears off, many patients are left with severe pain. This severe pain is must then be managed at home with oral opioids, which have numerous undesirable side effects, and may lead to chronic opioid dependence. Thus, any therapy which might reduce the pain burden on these patients and therefore reduce opioid use and side effects, would be advantageous.

Recently, a long-acting form of bupivacaine, prepared in liposomes, has been approved for use by injection in the surgical field, though not for peripheral nerve blockade. The drug has been used to improve postoperative pain after total knee arthroplasty and total hip arthroplasty when injected in the peri-articular tissues by the orthopedist, as well as in other surgeries, both orthopedic and non-orthopedic. Liposomal bupivacaine is FDA approved for administration into the surgical site to produce postsurgical analgesia and mitigate pain, but it hasn't been yet used for rotator cuff surgery.

Study Objectives:

The purpose of this research study is to determine if liposomal bupivacaine, injected into the surgical field during rotator cuff repair surgery provides superior analgesia post operatively (after the standard nerve block resolves) compared with standard therapy.

The primary outcome measure is pain score at 24 hours, which will be obtained by phone follow up. Secondary outcomes include maximal pain score on postoperative day 1, 2 and 3, total oral opioid morphine equivalent after 3 days, and occurrence of typical opioid side effects (nausea, vomiting, and/or drowsiness). In addition to follow up phone call on POD 1, patients will keep a pain diary, documenting pain scores and opioid use for the first 72 hours, which will be collected by the surgeon in his office at the first postoperative visit. Any adverse occurrences related to nerve blockade or prolonged bupivacaine effect will also be recorded. In addition, the development of chronic pain at the surgical site will be assessed and compared between the two groups, with appropriate referral to the chronic pain service for any patient who experiences this outcome.

Study Design and Methods:

This randomized, double blind, placebo-controlled study was approved by the University of Pittsburgh Institutional Review Board (PRO17020089), and registered with ClinicalTrials.gov (NCT03149887).

Patients will provide written consent for participation on the day of surgery. A computer-generated randomization number will be assigned by the Investigational Drug pharmacy at our institution, and patients will be accordingly designated to receive either liposomal bupivacaine or normal saline injection. The pharmacy will then prepare the study drug (either liposomal bupivacaine or saline), packaged in a fashion that cannot be recognized by the investigators, and then sent to the operating room for injection by the surgeon.

The patients and the research team will be blinded to which group the patients are in. It is not possible to prepare an effective placebo solution for the liposomal bupivacaine, so the surgeon will remain un-blinded. Other members of the research team will determine the primary and secondary outcomes, and the

surgeon will not take part in the data collection for primary or secondary analyses. By the time of the first surgical follow up examination, the outcomes will have been determined and recorded by investigators.

All patients will undergo standard interscalene nerve blocks with plain bupivacaine 0.5% or ropivacaine 0.5%, with volumes varying between 15 and 20 ml based upon visual analysis of injectate spread by the anesthesiology team. Once an effective nerve block is demonstrated (inability to raise the arm, biceps weakness, loss of sensation over the C4 and C5 dermatome regions), patients are to be taken to the operating room. Anesthesia for the procedure will consist of the interscalene nerve block, along with infusion of propofol for sedation, accompanied by small doses of ketamine (20 to 40 mg), and dexmedetomidine (12-20 mcg).

Per our institutional review board, it is essential that the joint capsule be closed before injection of liposomal bupivacaine, since liposomal bupivacaine is not approved for intra-articular use. If the capsule cannot be closed for surgical reasons at the end of the procedure, an enrolled patient will be removed from the study at that point, and will not receive the injection of the study drug. The rotator cuff repairs are to be performed in the beach chair position by a single surgeon with either three or four routine portals, including anterior, posterior, and one or two lateral portals. The total dose of liposomal bupivacaine will be 266 mg, diluted with an additional 40 ml of saline to a total of 60 ml. In control patients, 60 ml of normal saline are to be injected in like fashion. In each group, the sixty milliliters of solution was divided into two thirty milliliter syringes. After completion of the arthroscopic rotator cuff repair, which includes a subacromial decompression, an eighteen gauge spinal needle will be placed under direct vision into the subacromial space and secured with tape. The arthroscopic instrumentation will be removed and each of the three or four portals then infiltrated at the superficial skin and the deep tissue, including the deltoid muscle surrounding the portal tract, with equally divided amounts from one of the thirty milliliter syringes using a one and one-half inch twenty-two gauge needle. The portals will then be closed with absorbable suture and the remaining thirty milliliters of solution in the second syringe injected into the subacromial space via the previously placed eighteen gauge spinal needle. Finally, the needle is to be removed, and the dressings as well as a sling are applied.

At the conclusion of surgery, patients will be taken to PACU, where they report their NRS pain score, and intravenous dilaudid will be provided for analgesia for scores greater than 3/10. Patients are to be called the day after surgery (approximately 24 hrs after leaving the hospital), and asked about their pain experience. Specifically, for the primary outcome, they will be asked to relate NRS pain score, at the time that the interscalene block had, in their perception, completely resolved (restoration of hand sensation, movement at elbow, and onset of pain at the shoulder). For the secondary analyses of pain and opioid use, patients will record their NRS scores in a 72 hour postoperative diary, for pain at rest and (for patients instructed to do so) when participating in range-of-motion exercises ("pendulum swings"). In addition, the participants are to record oral opioid doses, use of other analgesics (such as acetaminophen), and any side effects that they encounter. Patients also will rate their satisfaction regarding pain management at the end of the 72 hour period. The pain diary will then be brought to the one-week follow up appointment, collected by the research team, and the data transcribed. Finally, the surgeon will note any patient who develops chronic pain requiring referral to a pain management specialist.

Eligibility Criteria:

Those eligible for inclusion are adults ages 18-65, in American Society of Anesthesiologist physical status class 1 through 3, who are undergoing arthroscopic rotator cuff repair, either primary or revision. Exclusion criteria include pre-existing nerve damage, pre-existing chronic pain in the shoulder joint, opioid use for greater than 30 days preoperatively, coagulopathy, renal or liver disease, pregnancy, allergy

to local anesthetics, patient refusal, infection at the site of injection, age over 65 years, or incompetent rotator cuff/joint capsule.

Statistical Considerations:

Sample size is calculated based on the a priori assumption that liposomal bupivacaine would result in a reduction of pain scores at the time of block resolution by two or more units in the NRS rating (0 to 10 scale). The minimum clinically important difference for acute pain, acute postoperative pain, and shoulder-related pain range between 1 and 2 (out of 10), We chose a change in the score of 2 units to represent a clinically important improvement in pain control. To detect a decrement of 2 units or more with a two-tailed significance level of 0.05 and a power of 0.8, a sample size of 50 is required, 25 in each group.

The analysis of data will be carried out using SAS software, Version 9.4, of the SAS System for Windows (Copyright 2016 SAS Institute Inc., Cary, NC, USA). Continuous measures, such as pain scores, oral morphine equivalents, and some demographic information, are presented as mean \pm standard deviation, and compared using t-tests. Frequency distributions of categorical variables, such as opioid related side effects, and other demographic information, are compared using the Fisher's exact test. Opioid use will be converted to oral morphine equivalents. A two-tailed p value of <0.05 is considered to reflect statistical significance, while a difference in the primary outcome of 2 or more on the NRS scale is our threshold for clinically meaningful change