Comparison of Preoperative Ultrasound Guided Nerve Blocks to Intraoperative Nerve Block Catheters for Breast Reconstruction: A Prospective Randomized Trial

NCT03201809

6/21/2018

1) Protocol Title

Title: Comparison of Preoperative Ultrasound Guided Nerve Blocks to Intraoperative Nerve Block Catheters for Breast Reconstruction: A Prospective Randomized Trial

Protocol Version Date: *6/21/18*

2) Objectives

Aim 1: Report the efficacy and safety of pectoralis nerve blocks for breast reconstruction surgery in a prospective fashion

- Hypothesis: we anticipate >90% efficacy of all pectoralis nerve blocks and no complications

Aim 2: Comparison of intraoperative versus preoperative placement of pectoralis nerve blocks

2A: Comparison of block efficacy and safety

- Hypothesis: We anticipate a significantly better block efficacy with intra-operatively placed block catheters as opposed to pre-operatively placed blocks, as intra-operatively placed blocks are done under direct visualization and can be left in place. We anticipate no difference in safety profile.

2B: comparison of secondary outcomes, such as cost, block placement time, post-op nausea/vomiting, patient satisfaction, and operative times.

- Hypothesis: We anticipate a faster overall time (From admission to clearance for PACU discharge) with intra-operatively placed blocks. We anticipate use of less inhalational anesthesia with pre-operatively placed blocks. We anticipate no difference in secondary outcomes, such as post-operative nausea and vomiting, narcotic use and patient satisfaction between the two block groups.

3) Background

Level 1 data shows improved post-operative analgesia with decreased anesthetic and opiate use, decreased hospital length of stay, and improved patient satisfaction scores with the use of regional nerve blockade.[1-5] Using nerve blocks to limit general anesthesia (GA) and improve post-operative analgesia is additionally important due to the mounting evidence that volatile anesthetics and opioid analgesics impair immune function[6,7], and increase the risk of ileus, thromboembolism and myocardial infarction[8]. Despite these advantages, the use of regional nerve blockade is still limited to selected cases.

Pectoral nerve (Pecs) blocks are ultrasound guided inter-fascial plane blocks that target the tissue planes between the pectoralis major and minor (Pecs I), and pectoralis minor and serratus anterior muscles (Pecs II)[9,10]. Targeting these planes with local anesthetic blocks the medial and lateral pectoral nerves, anterior divisions of the thoracic

intercostal nerves from T2-T6, long thoracic nerve, and thoracodorsal nerves providing analgesia to the anterior and lateral thoracic walls with an extension into axilla. Pecs blocks have shown excellent efficacy in post-operative analgesia after breast surgery[11].
The main disadvantages of the traditional Pecs blocks are the need for ultrasound trained personnel, increased anesthesia wait times as well as the need for a secondary procedure. Placement of the blocks under direct visualization addresses these limitations of and may allow more accurate plane targeting.

This research will be significant to the fields of anesthesia/pain management, breast surgery and plastic surgery. With this study, we hope to provide objective, prospective data on pectoralis nerve block efficacy and safety. We furthermore hope to examine the differences between blocks placed by anesthesia and catheter based blocks placed intra-operatively by the surgical team, as listed above under Aims.

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5. Wolf O, Clemens MW, Purugganan RV, et al. A Prospective, Randomized, Controlled Trial of Paravertebral Block versus General Anesthesia Alone for Prosthetic Breast Reconstruction. Plast Reconstr Surg 2016: 137: 660e-6e.
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7. Gong L, Dong C, Ouyang W, Qin Q. Regulatory T cells: a possible promising approach to cancer recurrence induced by morphine. Med Hypotheses 2013: 80: 308-10.
8. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin North America 2005: 23: 21-36.
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10. Blanco R, Fajardo M, Parras Maldonado T. Ultrasound description of Pecs II (modified Pecs I): a novel approach to breast surgery. Rev Esp Anestesiol Reanim 2012: 59: 470-5.
11. Bashandy GM, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med 2015: 40: 68-74.

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4) Inclusion and Exclusion Criteria

Individuals will be screened for study eligibility by reviewing the operative schedule in advance. Criteria for inclusion will be consenting female patients over 18 years of age presenting for immediate breast reconstruction with sub-muscular tissue expander placement with or without acellular dermal matrix sling. Patients with a history of chronic opioid use, brachial plexus injuries, or planned alternate regional anesthesia will be excluded from the study. Individuals under 18 years of age, pregnant women, prisoners and patients unable to provide consent will additionally be excluded.

5) Study Timelines

Subjects will be approached up to three days prior to their surgery to make them aware of the study. They will sign consent on the day of surgery. Pectoral nerve blocks will be placed in the operating room, either pre-operatively by the anesthesiologist or intra-operatively by the surgeon. Post-operative care will be routine. Pain surveys will be emailed out via redcaps at 6h, 12h, and 24h post-operatively, as well as on days 2-7. A satisfaction survey will be emailed to the patient one week after surgery. After the satisfaction survey, patient participation will be complete.

We anticipate completing our enrollment in 5 years, and completing data analysis by six months after the final patient has been enrolled.

6) Study Endpoints

The primary study endpoint will be after completion of study (after surgery and survey completion) of 252 patients (126 in each treatment arm). Secondary endpoints include time to PACU clearance and time to hospital discharge. Because the intervention is a single-shot injection, there are no specific safety endpoints. Please see below for a discussion of potential adverse from the pectoralis nerve blocks.

7) Procedures Involved

Subjects presenting for immediate breast reconstruction and meeting inclusion criteria will be approached pre-operatively to make them aware of the study. On the day of surgery, patients will be asked to sign consent for the study. Patients who sign consent will then undergo randomization to a study arm (pre-op placement of intra-op catheter placement). Randomization will be done by study personnel using the i-phone application "Randomizer." Randomization will follow a blocked scheme; that is, if one patient is randomized to the anesthesia block group, the next will automatically get the catheter treatment. This will ensure equal numbers in both study arms. After consent and randomization is complete, patients will be told of their study arm. Patients will then be asked to fill out a pre-operative pain survey discussing their baseline level of breast pain.

For those randomized to the pre-op placement arm, anesthesia will perform this block prior to surgery but after their pre-operative survey is complete. The anesthesia

department is already performs pectoralis nerve blocks on selected patients, and have the work flow set up for this. The dose will be 10 mL of 0.25% Ropivicaine for the pecs 1 injection, and 20 mL of 0.25% Ropivacaine for the pecs 2 injection. Ropivacaine is a standard sodium channel blocking anesthetic already FDA approved for peripheral nerve blocks. For those randomized to the intra-operative arm, catheter placement will be performed after the pectoralis muscle flap has been raised, for more accurate targeting of the tissue planes and nerves. Blocks will be performed by the operating surgeon . Instead of single shot blocks, a commercially available On-Q nerve block catheter (Halyard Health, Alpharetta, Georgia) will be placed. Through these catheters, 0.2% Ropivacaine will be instilled at 4 mL/hr for a total of 400 mL (amount in standard On-Q reservoirs). Vitals are continuously monitored in the operative suite and in the Post Anesthesia Care Unit (PACU), with a high level of supervision by the anesthesiology team. In the very rare event of an adverse reaction to the injection, appropriate action will be taken immediately and in accordance with standard work-flow for local anesthetic toxicity (epinephrine for severe allergy or circulatory support, intravascular lipid emulsion and sodium bicarbonate for overdose, although our doses should not be high enough to precipitate this, even with inadvertent intravascular injection). If hypoxia not due to opioids and not responsive to supplemental oxygen is present, a chest radiograph will be ordered to rule out pneumothorax from inadvertent visceral pleural puncture.

Post-operatively, the patients will be monitored in the PACU. They will have standard anesthesia pain and nausea management orders written for (these are ordered en bloc as part of an already existing order set). PACU nursing staff will dose medications according to the written orders. PACU clearance time (which is currently time-stamped in the chart by the PACU resident) will be noted. Often patients will remain in PACU due to ward over-crowding, so actual time of PACU discharge will not be noted. Post-PACU hospital course will proceed as is standard of care, with PRN pain and nausea medication ordered. Standard hospital discharge criteria will be used for all groups.

Information will be collected from all subject's hospital stays, including time in pre-op holding area, time under general anesthesia, duration inhalational anesthetic, amount of narcotic used in morphine equivalents (divided into OR amount, and amounts in first 6, 12, 18 and 24 hours after surgery) after surgery, incidence of nausea/vomiting, number and amount of antiemetic used (same time intervals as above), pain scores overall and by breast on the 0-10 analog scale (average over the same time intervals), time of PACU clearance, and time of hospital discharge. In addition, a RedCaps survey with questions about the patient's pain level will be emailed pre-op and at post-op hours 6,12,24 and days 2-7.

For patients with pain catheters, these catheters will be removed at the patient's regularly scheduled post-operative appointment (generally POD 4 or 5). On-Q balls will not be refilled such that all catheter patients will have infusion for the same amount of time.

One week after hospital discharge, subjects will be emailed a short survey through the RedCap survey system (see supplemental forms for survey questions). Hospital billing

will be examined with the assistance of the billing department using CPT codes and using publically available cost data.

8) Data and/or Specimen Management and Confidentiality

During the review, the investigator (or research staff) will record data collected in a manner that includes indirect identifiers. Additionally, a single location will include indirect and direct identifiers (to match the two).

To elaborate: Subjects will be identified by a unique study ID (A = pre-op placement, B = intra-op placement; so 1A would be the first patient enrolled in the pre-op placement group). An enrollment log, including a "crib sheet" identifying patients by their study ID and their consent paperwork, will be kept in a binder. That binder will be stored in a locked cabinet in the plastic surgery Lab in Research Building 2. After the IRB has been closed, study consents will be maintained for 3 years, and HIPAA consents for six years, in compliance with IRB rules and regulations. Any data compiled off of the Electronic Medical Record (EMR) will be identified by subject ID only and collected onto a spreadsheet on the PI's password protected computer.

With respect to the surveys, Redcap is a mature, secure web application that has been used successfully by many other investigators at our institution to collect secure survey data.

Data analysis will be done using http://vassarstats.net. Statistical comparisons will be performed across the study groups using T-test for two-group comparisons.

All research personnel will be up to date with their HIPAA training.

For our power analysis, we set our alpha = 0.05 and beta (power) = 0.8. Using the Bashandy et al. paper[1], the mean morphine requirement in the PACU was 2.9 ± 1.861 mg for the Pecs block group, and 6.9 ± 1.861 mg for the control group ($p < 0.001$). Based on our preliminary experience with pre-operatively placed pecs blocks, we estimate that they work well about 70% of the time. If we hope to see a 20% improvement with more accurate plane targeting, then our average morphine requirement in the intra-operative placement group would be 2.3 mg. Therefore, we would have to enroll 126 patients in each arm to have an 80% chance of seeing a difference, if there truly is one.

1. Bashandy GM, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med 2015: 40: 68-74.

9) Provisions to Monitor the Data to Ensure the Safety of Subjects

The EMR of every subject who completes the injection portion of this study will be assessed within 24 hours of pectoralis nerve block placement. Any untoward events, such as intravascular injection, allergic reaction, pneumothorax or other unanticipated event will be assessed for its causative relationship to the pectoral nerve block . We anticipate these to all be very unlikely, as the current literature on the pectoralis nerve blocks report a 0% complication rate (see citations, above). If a serious adverse event occurs, these will be reported immediately to the IRB and will be a trigger for an immediate suspension in enrollment and a review of the injection protocol with the Chiefs of both the Departments of Anesthesiology and Surgery. If any performer error can be identified and corrected, then with approval from the departments enrollment will continue. If not, the study will be terminated.

We will cumulatively review the data after 20 subjects in each study arm have been enrolled, and then again at 50 patients, 75 patients, 100 patients, and 126 patients.

10) Withdrawal of Subjects

There are limited circumstances in which a patient would be withdrawn from research, particularly without their consent. The only circumstance would be in the case of aborted tissue expander placement. If the plastic surgeon does not feel that the mastectomy flaps can support the added stress of an expander, then the plastic surgery portion of the procedure is aborted (standard protocol). In this circumstance, the pre-op block arm will already have gotten a block. No intra-operative catheters will be placed. After awakening from anesthesia, the patient will be alerted to their expulsion from the study, and no other data would be collected regarding their hospital stay, and no survey information collected.

Of note, a single patient was enrolled into the control arm of the study prior to this arm being abolished. This patient's survey data has already been collected but will not be used for data analysis. Their hospital data will not be collected.

11) Risks to Subjects

The main foreseeable risk to study subjects is that the nerve block would not work well. In this event, subjects would be appropriately treated with adjunctive pain medications.

Two very rare risks – never reported in the literature, so currently theoretical rather than described – are intravascular injection and pneumothorax, as outlined above. These could have potentially serious consequences, such as bupivacaine toxicity (at worst, leading to hypotension or seizure) or hypoxemia requiring chest tube placement and potentially other procedures. However, pectoralis nerve blocks have been in use for over 5 years, and more risky blocks, including the paravertebral block and intercostal block (both of which have higher rates

reported of the above complications) for over 30 years. Therefore, these risks are generally considered to be outweighed by the benefits of peripheral blocks.

With respect to the nerve catheters, potential risks to patients with placement are less than with the ultrasound guided block, as these catheters are placed through the skin and into the mastectomy pocket under direct visualization. Additional risks would include the small risk of a post-operative infection related to the catheter. This risk will be minimized by sterile placement, a sterile dressing, and expeditious removal of the catheter within the first post-operative week. As these catheters are standard of care at UC Davis currently, this risk is generally felt to be acceptable.

12) Potential Benefits to Subjects

Study subjects potentially will have decreased anesthetic requirements and improved post-operative pain control. Decreased general anesthesia could mean less postoperative nausea/vomiting. Improved pain control will lead to less narcotic use and therefore may decrease the chance of ileus, nausea, itching and other common narcotic side effects.

13) Sharing of Results with Subjects

No additional information will be shared with subjects.

14) Provisions to Protect the Privacy Interests of Subjects

Patients will be approached about enrolling in this study in the preoperative area. Patient beds in this area are one bed per room; therefore, the conversation will be in private, between the physician and patient. Family members may be present, but this is standard for all preoperative consents (anesthesia consents, block consents, sometimes surgical consents if they are not on file). The consent process will specifically site that refusal to enroll will not result in any penalty, including any withholding of pain medication in the future. Post-operatively, no specific research contact will be made until an online questionnaire is sent out by email.

15) Compensation for Research-Related Injury

There is no specific compensation for study participation. Because breast reconstruction is a planned procedure, all patients undergoing surgery will have insurance. Nerve blocks are a billable procedure, recognized by insurance companies. Any complications related to the procedure will likewise be covered by insurance.

16) Economic Burden to Subjects

As outlined above, the cost of the nerve blocks will be covered by insurance, and no additional out of pocket funds requested. There is no downtime or leave time required for these nerve blocks – in fact, if there is a decrease in narcotic use, then the nerve blocks may even hasten subject's ability to return to work.