Ultrasound-guided Pec infiltration with liposomal bupivacaine for breast surgery: A prospective randomized study.

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Study location
University of Minnesota

Ultrasound-guided Pectoralis 1 and 2 block with liposomal bupivacaine for breast surgery: A prospective randomized study.

Design: Level I randomized prospective outcomes study comparing two groups of patients. One group will receive liposomal bupivacaine for a pectoralis ("Pec") block infiltration and the other will receive incisional bupivacaine infiltration by the surgeon.

Sample Size: 112 patients
Study Duration: Approximately 18 months
Population: Patients presenting to the University of Minnesota Medical Center, M health Ambulatory Surgery or Fairview Maple Grove Clinics Ambulatory Surgery Center, for elective lumpectomy and partial mastectomy procedures +/- axillary node dissection.

Primary Objective:
1. To determine if liposomal bupivacaine Pec infiltration provides decreased peri-operative opioid usage when compared to incisional bupivacaine infiltration.

Secondary Objectives:
1. To determine if a pectoralis 1 and 2 block with liposomal bupivacaine provides decreased maximal pain scores when compared to incisional bupivacaine infiltration

2. To determine if a pectoralis 1 and 2 block with liposomal bupivacaine provides decreased rate of conversion to general anesthetic when compared to incisional bupivacaine infiltration

3. To determine if a pectoralis 1 and 2 block with liposomal bupivacaine improves quality of recovery score post-operatively when compared to incisional bupivacaine infiltration.

4. To observe the effect on chronic postoperative pain in patients who have breast surgery.

2. Synopsis and Medical Application:

Specific Aims:

> **Primary Hypothesis:**
> A pectoralis 1 and 2 block with liposomal bupivacaine will result in decreased total opioid usage relative to bupivacaine infiltration after an elective partial mastectomy
> **Secondary Hypotheses:** A pectoralis 1 and 2 block with liposomal bupivacaine will result in improved quality of recovery score, decreased maximal pain scores, and decreased rate of conversion to general anesthetic.

Background and Significance:

Liposomal bupivacaine is a multivesicular formulation of bupivacaine that has been shown to provide up to 72 hours of analgesia compared to bupivacaine, which provides up to 24 hours of analgesia post injection.[1] These two medications have been compared in incisional infiltration but have yet to be compared in the setting of a pectoralis ("Pec") infiltration vs incisional infiltration. A Pec 1 infiltration is an injection of local anesthetic is in between the pectoralis major and pectoralis minor muscle layers. A Pec 2 infiltration is an injection of local anesthetic between the pectoralis minor and serratus anterior muscle layers or deep to the serratus anterior. These layers are found using an ultrasound, which is a beam of high frequency sound that allows one to visualize images in the body. With the ultrasound it is possible to visualize the needle as it pierces the fascial covering of the pec minor or serratus anterior layer and watch as the local anesthetic is injected into this plane. This is done on both sides of the chest wall to provide analgesia to the skin, muscle, and facial layers of the chest wall if the procedure is bilateral or just on one side if unilateral. Data has shown the Pec infiltration to provide useful pain control after breast surgery, however it is of limited duration provided by bupivacaine.[2,3,4]

Incisional infiltration. The surgeon will infiltrate local anesthetic (bupivacaine) into the surgical site at the start of the procedure, within the subcutaneous and dermal regions immediately surrounding the incision. Additional incisional bupivacaine infiltration will be performed as needed throughout the procedure. Accidental intravascular injection is minimized by continuous needle movement and frequent aspiration.

This will be the first study of its kind looking prospectively at Pectoralis 1 and 2 blocks with liposomal bupivacaine compared to surgeon infiltration for postoperative pain in breast partial mastectomy procedures.

Subjects:

Demographics: All patients undergoing elective breast lumpectomy and partial mastectomy at the University of Minnesota Medical Center, M health Ambulatory Surgery Center or Fairview Maple Grove Clinics Ambulatory Surgery Center, with all Pec infiltration to be placed by the Primary Investigator and other staff anesthesiologists on the perioperative and interventional pain service and surgeon infiltration to be done by the co-investigators.

Entry Criteria:
Subjects will be evaluated and confirmation of the following will be documented:

<u>Inclusion criteria assessed during surgery:</u>

- All patients undergoing partial mastectomy procedures.
- Ages 18-75

Exclusion criteria:

- Patient on chronic anticoagulation
- Pregnant women
- Non-english speaking patients
- Any individuals who are unable to give informed consent
- Any individual with diminished capacity to give informed consent
- Allergy to local anesthetics
- Patients who remain intubated overnight after surgery or who are unable to provide information regarding their pain immediately postoperatively
- Daily use of opioid for more than three weeks
- Significant liver disease, defined as liver enzymes greater than 3x the upper limit of normal
- Lack of patient cooperation including those patients who refuse a MAC anesthetic
- Patient with pectoral muscle involvement of tumor
- Contraindication to regional anesthesia
    - Infection at injection site
    - Inability to guarantee sterile equipment or sterile conditions for the block
    - Patient refusal
    - Severe Coagulopathy or bleeding disorder

Randomization procedure:
Patients will be identified by members of the treatment team in either the surgeon's clinic, pre-assessment clinic, or preoperative area. Patients who have opted out of research will not be asked to participate in the study. Patients will be approached to consent for the study by a surgeon, anesthesiologist, or member of the research team. Patients who agree to participate in the study will sign both a study consent and HIPAA authorization allowing the use of specified information contained in medical records for research purposes.

A random number generator will be used to determine if the patient will have pectoralis liposomal bupivacaine infiltration or bupivacaine infiltration directly into the incision space. The primary or co-investigator will access the number generator in the pre-op area. The website www.random.org will be used as the random number generator.

Treatment technique:
For the Pec infiltration, the patient will be in the supine position. The pectoralis major and pectoralis minor muscle layers will be identified via ultrasound. Using sterile technique, a nerve block needle will be inserted and advanced under ultrasound guidance until it is below the fascial covering of the pec minor muscle layer. Gentle aspiration for air or blood will be performed in 5cc incremental doses. Then injection of 10 mL of bupivacaine 0.25% with epinephrine 1:200,000 and 10mL of a mixture of liposomal bupivacaine and saline (5 mL liposomal bupivacaine and 5 mL saline) for a total injection for pec 1 block of 20 mL. For each 5cc of local anesthetic injected, aspiration will be performed. Upon completion of the injection the needle will be removed. We will then use the ultrasound probe to identify the second rib on anterolateral chest wall and

move the probe to the 4th rib. Here we will identify the pec minor and serratus anterior muscles. We will advance our needle under ultrasound-guidance beneath pec minor and above serratus anterior or if unable to visualize the serratus/pec minor border will inject under the serratus anterior. Here we will inject 10 mL 0.25% bupivacaine with epinephrine 1:200,000 followed by 20 mL mixture of 15 mL liposomal bupivacaine and 5 mL saline for a total volume of 30ml for Pec 2 Block. Upon completion of the injection, the needle will then be removed and the patient will be monitored in the preoperative area until he/she is brought into the operating room for their procedure.

If deemed necessary for coverage the surgeon will be allowed to inject additional local anesthetic up to a maximum of 40 mL of 0.25% bupivacaine. This will be noted in the chart.

For the surgeon infiltration, the patient will be brought directly to the operating room where intraoperative anesthetic with an opioid-sparing MAC technique will be provided as described below. Just prior to the skin incision, 0.25% bupivacaine will be used to infiltrate the dermis and subcutaneous space in the proposed incision. Throughout the procedure, additional incisional bupivacaine infiltration into the surrounding tissues will be performed as needed for local anesthesia. A total of up to 30 mL of 0.25% bupivacaine will be divided equally for the two sides of the incision. An additional 5 mL of 0.25% bupivacaine will be infiltrated into the pectoralis major muscle at the deep margin of resection. Accidental intravascular injection is minimized by continuous needle movement and frequent aspiration.

The following vital signs will be monitored throughout the procedure: Heart rate, blood pressure, oxygen saturation, and respirations, and patient's state of consciousness. We will monitor the patient until they are brought to the operating room for surgery.

All patients will receive multimodal analgesia in the preoperative area. They will receive 975 mg of oral acetaminophen and 300 mg of gabapentin orally prior to surgery.
The intraoperative anesthetic will be an opioid-sparing MAC anesthetic. If patients are unable to tolerate procedure under MAC they would be converted to a general anesthetic with an laryngeal mask airway (LMA). For those patients receiving a lumpectomy with axillary dissection, they will receive a general anesthetic with LMA. Patients will receive IV midazolam 0-2 mg followed by 40-100mg of IV lidocaine, and followed by a propofol infusion and a 0.25 mg/kg bolus of ketamine followed by 0.25 mg/kg /hour infusion of ketamine. Opioids will be avoided unless HR or BP increases by 20 % above baseline. Then only short acting opioids (fentanyl) will be given.

In the recovery room if the patient experiences pain greater than 5/10 they will receive either IV or oral pain medications. If pain score is less than 5 patients will get non opioid medications unless the patient desires an opioid medication.

When the operation is complete the patient will either be brought to the PACU or Phase II. Each day a member of the research team will contact and evaluate the patient for signs of complications and ask the patient their minimum and maximum pain score

(scores will be evaluated at 1 hr, 2 hr, 6hrs, 24hrs, 48hrs, 72hrs). They will record daily opioid use, any modality related complications, how many phone calls were made regarding pain control and modality related complications. At time period 72 hours a Quality of recovery survey (see appendix) and OBAS (see appendix) survey will be presented to patient. Patients will be offered phone calls for contact, but patients may opt to be contacted via text message if they do not wish to have phones calls. We will provide patients with an additional consent for text messaging if they wish to use this method.

At 3 months, 6 months, and 12 months patients will be called to answer a survey with regards to chronic pain.

Patients will be instructed to take acetaminophen 1000 mg every 8 hours while at home for 3 days. They will be given a prescription of opioid pain medications either oxycodone or hydromorphone and will be instructed to take as needed for pain.

Enrollment procedures:

Patients will be recruited from the group of adult surgical patients at the University of Minnesota undergoing partial mastectomy procedures. Patients will be approached in either the surgeon's clinic or pre-assessment clinic by a research staff member to determine their interest in participation. Subjects interested in the study will be presented with consent and Health and Insurance Portability and Accountability Act (HIPAA) forms, with the REDCap e-consent process being preferentially used. The patient will review the forms with the surgeon, anesthesiologist or other study staff. Subjects will be reminded that participation is completely voluntary, and that they may stop participation at any time without question or penalty. The surgeon or anesthesiologist will answer any questions that the subjects may have about the study. If the patient decides to participate, they will be asked to sign the consent and HIPAA forms. One copy will be saved for study records, and the subject will be provided with a copy of the forms for their own records. If they need additional time to consider enrollment, they will be asked if we can reach out to them by phone the night before surgery or if we should revisit the study with them on the day of surgery. If the patient is unable to be consented prior to day of surgery, the research staff will approach them in the preoperative surgical area. These patients will have significant time to review the study with research staff as well as the physicians performing the procedure due to the fact they arrive several hours prior to their scheduled surgery. All subjects will have enough time to ask questions about the study and the potential risks involved regardless of which venue they are consented. Any patient that refuses to participate in the study at any time point will be placed on a secured list to avoid duplicate attempts to recruit them. All forms will be locked and stored in a file cabinet in the research department. Enrolling consecutive patients will help reduce selection bias. Any patient who does not complete all necessary paperwork and answer questions at the appropriate time intervals will be eliminated from the study. Patients lost to follow-up, or patients who decide not to participate in the study after initial enrollment, or patients who are eliminated from the study for any reason will have their study records shredded and will not be included in the final data-analysis.

Assessments:

Post-operatively patients will be evaluated 1 and 2 hr post-operatively by the PACU nurse and 6 hrs post-operatively by a medical student or research coordinator. This person will not be aware of the patient's mode of analgesia. The medical student or research coordinator will evaluate at, 24, 48, and 72 hours post injection +/- 5 hours. If sent home they will be contacted via preferred contact method at, 24, 48, and 72 hours post-operatively. Patients will be asked to rate their pain on scale of 0-10. The amount of opioids used by the patient will be recorded as will any other adjuvant pain medication used. Any modality related complications will be recorded. The patients will be asked at 72 hours post-injection to fill out a quality of recovery and OBAS survey. All complications will be recorded from time of consent to last follow up date. Patients will be called at 3, 6, and 12 months post operatively to fill out a chronic pain survey.

All data will be recorded in a locked encrypted database. Data collection will continue until Postoperative day (POD) #3. Should patients be re-admitted to the hospital in the next two weeks (Up to POD #19) for pain a notation will be made in study records. Additional contacts by the research assistant or medical student will continue up until the 3, 6, and 12 month postoperative times.

An analysis of the total cost of analgesics (including patient costs for opioid prescriptions) will be tabulated at the conclusion of the study to determine the most cost effective treatment option as this will be added into the cost of hospitalization including the number of days each patient spent in the hospital.

Blinding Procedure:

The research coordinator in this study will be blinded to the method of analgesia for the patient. The research coordinator will assess pain one time per day. This person will not be responsible for any clinical testing and will record all data in the protected database daily. Any questions from the patient will be referred to the on-call resident or staff on call.

Subject Identification:

Subject names will be collected as part of the informed consent process, and are thus considered private data. At the time of consent, subjects will be assigned an independent study identification (ID) number that will be used subsequently throughout the study. All data sheets will be identified only by an ID number. Data will be stored in a locked file cabinet in the research office at UMMC. Consent forms will also be stored in a separate locked file cabinet. Web based data will be accessible only by the primary investigator and research staff. It will be password protected and any information that is printed will be stored in a locked file cabinet in the research office at UMMC.

Risks:
Risks to subjects of this study include

- Failure of the block
- Wound infections
- Complications related to placement of the Pec block including
    - lung perforation, nerve injury or intravascular injection.
- Local anesthetic toxicity

These complications all fall within the standard risks of surgery. Any intervention being provided as a part of this study falls within the standard of care of Pec infiltration and surgeon infiltration and are within the standard treatments for post-operative pain and are currently used as analgesic options at UMMC. There may also be certain unforeseen risks that will be treated as necessary by the operating physician. All complications will be noted by the operating physician and reported to the IRB and research staff. Appropriate records will be made in the patient chart, and the patient will be treated as needed by the operating physician.

Any unforeseen injuries that may occur to the subjects while enrolled in this study will be treated as needed by the operating physician. No provision has been made for financial payments or other forms of compensation (such as lost wages, medical cost reimbursement, lost time or discomfort) with respect to such injuries**.** No arrangement has been made for further compensation from UMMC. However, patients do not waive any legal rights by signing a consent form.

Benefits:
There are no benefits to you from your taking part in this research. We cannot promise any benefits to others from your taking part in this research. However, possible benefits to others include pain relief and possibly shorter hospital stay with decreased risk of complications. The only alternative post-operative pain treatment options include intravenous or oral opioids. During the study period, any subject who prefers not to be involved in this study will be treated appropriately as determined by the surgeon and anesthesiologist. There will be no alteration in the post-operative program for those that decline enrollment in this study.

No parties will receive any specific direct benefits from this study with the exception of the patient. The physician and medical community at large may indirectly benefit from learning more about the post-operative pain options for these patients.

Precautions and corrective actions: All treatment arms will have the same post-operative protocol. All complications will be noted by the operating physician and reported to the IRB and research staff. Appropriate records will be made in the patient chart and the patient will be treated as needed by the operating physician.

Project Medications: All medications will be provided by the hospital pharmacy, and will be noted in the medicine administration record in the chart. No experimental medications will be evaluated in this study.

Specimens to be collected: None

Data collection: The surgeon, anesthesiology staff, and research staff will collect data. The data will be comprised of outpatient notes, inpatient records, operative reports, intra-operative photos and assessments, questionnaires, study follow-up evaluations. In addition to the surveys used to measure subjective and objective outcome, other data will be collected during patient interviews including:

- Demographic data
- Age
- Weight
- ASA class
- Type and duration of surgery
- VAS Score at 1, and 6, 24, , 48, , and 72 hours after surgery
- Length of stay in recovery room
- Amount of opioids given preop,intraoperatively and post-operatively
- Rate of conversion to general anesthetic
- Satisfaction with treatment
- Quality of recovery survey on 72 hours post-injection
- OBAS at 72 hours
- Chronic pain (pain disability index) at 3, 6, 12 months
- At 72 hours the following will be recorded:
    - Any persistent need for analgesics
    - Total length of stay
    - Total Use of opioids per day
    - Amount of opioids left over after 3 days
    - Presence of nausea/vomiting in 3 days post operatively
    - Occurrence of any subsequent re-admission over the ensuing 1 month and any complications

The collected data will be compared between groups on a regular basis in order to evaluate the safety and efficacy of the study. All data will be stored in secure locations in the Research Office. Research coordinators working with physicians to collect data at appropriate intervals will ensure complete follow-up. Research coordinators will periodically check physician schedules to ensure that patients being seen for follow-up complete all required questionnaires. Monthly meetings will also be conducted to ensure all patients needing to be evaluated are seen at the appropriate time intervals and that all data is being entered into the appropriate database.

Data Safety Monitoring: Authorized study staff and investigators who have gone through HIPAA, CITI, and other data security training through the University of Minnesota will be collecting, managing, and analyzing data. All serious adverse events will be brought forward to the Anesthesia Data Safety Monitoring Board that is comprised of various senior staff anesthesiologists. A formal determination concerning the severity of the risk and the recommended actions required will be submitted in writing to the principle investigator. This report will be submitted to the Institutional Review Board along with the required UPIRTSO documents.

Statistical Considerations: The primary outcome measurement used in this study is total opioid use

A sample size of 112 (56 per group) will be enrolled in order to power our study at 80% to detect a 35% decrease in total post-operative opioid usage for our treatment group versus the control with an α=0.05. This sample size was estimated based on previous estimates for postoperative analgesic consumption from similar trials reported in the Tam (2015)[1] meta-analysis paper.

[1] Tam, K., Chen, S., Huang, T. et al. Effect of wound infiltration with ropivacaine or bupivacaine analgesia in breast cancer surgery: A meta-analysis of randomized controlled trials. International Journal of Surgery 2015. Vol 22: 79-85.

Outcome Measurements:

Outcome measures include both clinical assessments and subjective outcome measures reported by the subject on different rating scales.

Distribution of the scores and the clinical evaluations will be examined and cut-points may be assigned to create categorical data. Statistical analysis of parametric data will be done using ANOVA techniques with corrections for repeated measures (when necessary); non-parametric data will be analyzed with Chi-squared techniques. Statistical significance will be defined as $p < 0.05$. Power is expected to be 0.8. Data stratification will be done where appropriate. Stratification variables include: pre-operative pain modality.

Stopping Criteria:

This study will be stopped if 5% of the subjects experience local toxicity. If $\geq$ 10% of the subjects develop an infection at the injection site, the protocol will be discontinued. Additionally, if any patient experiences a serious adverse event as a result of the study medications as determined by the principle investigator, they will be discontinued from the study.

Local anesthetic toxicity is defined as patients who experience local anesthetic toxicity symptoms such as new onset of tinnitis, metallic taste in mouth, numbness around lips, seizures, heart block or new arrhythmia after injection of local anesthetic for up to monitoring period of 5 days.

Notification: When a study participant, voluntarily or involuntarily, is eliminated from the study protocol, the Principal Investigator and Associate Investigators will be notified.

Adverse reactions: Adverse or unexpected occurrences resulting from the treatment utilized in the protocol will be reported to the Principal Investigator and the Associate Investigators. These individuals will discuss these reactions or untoward events and implement changes in the protocol accordingly. Investigators will meet regularly to discuss problems encountered with the study protocol.
Modifications to protocol: Alterations that may become necessary in the protocol during the study period will be made by agreement of the investigators. Patients will be notified of any relevant protocol changes.

Definition of Adverse Event (AE):
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgement about causality. An AE can arise from any use of the drug (e.g., off-label use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE can be any unfavorable and unintended change in a body structure or body function. Adverse events include any clinically significant deterioration of a subject's medical status. The AE may involve any organ or system and can be represented by the new onset or the deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change after the subject signs the ICF, including frequency or pattern changes for a fluctuating condition (e.g. migraine) is considered an AE.

An AE that occurs after the ICF has been signed and before the start of the study drug administration is identified as a pretreatment AE (PTAE). An AE that occurs after the administration of a study treatment is considered a treatment emergent AE (TEAE).

Definition of Adverse Reaction:
Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Definition of Suspected Adverse Reaction:
Any AE for which there is a reasonable possibility that the drug cased the AE. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. Suspected adverse reactions are a subset of all AEs for which there is a reasonable possibility that the drug caused the event.

Severity of Adverse Events:

Relationship of Adverse Events to Study Drug:

The Investigator will assess the relationship of the AE to study drug after careful medical consideration, on a case-by-case basis. General guidelines are provided as follows:

Not Related: A causal relationship between the study drug and the AE can be easily ruled out (e.g., based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause).

Related: There is a reason to conclude that the drug caused the event (i.e., there is a reasonable possibility based on evidence to suggest that the drug caused the event).

Definition of a Serious Adverse Event:
Definition of a serious adverse event (SAE). An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity
- Congenital anomaly/birth defect
- Medically significant

Any Serious Adverse Event will be reported to the local IRB within 5 days

Use of information and publications arising from the study: Information gained from the interpretation of the data collected in this study will be used for the preparation of a scientific publication, and a presentation to a peer review journal and scientific meetings.

Prior to submission of information for publication or presentation, a written assessment of the data will be presented to the Primary Investigators at UMMC.

References

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4.Leiman D, Barlow M, Carpin K, Pina EM, Casso D. Medial and lateral pectoral nerve block with liposomal bupivacaine for the management of postsurgical pain after submuscular breast augmentation. Plastic and Reconstructive Surgery. 2014;2:e282-e282.