1. **Protocol Title:** Paravertebral Block Versus Pectoral Nerve Block for Analgesia Following Mastectomy

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4. **Objectives:**

   I. Primary Objective: To determine if pectoral nerve blocks (PECs) achieve equal analgesia following mastectomy, partial mastectomy or lumpectomy, with and without reconstruction, when compared to paravertebral blocks (PVBs).

   II. Secondary Objective: To trend complication rates for PECs and PVBs.

5. **Background:**

   Postoperative pain control is essential following any major operative procedure. A variety of methods have been utilized to ensure adequate analgesia, each with its own advantages and risks. Increasingly, attention has focused on regional methods of analgesia, which may allow for reduction in systemic narcotic use and their associated complications [1]. Proposed benefits of regional analgesia and a resultant reduction in narcotic use include decreased risk of cancer progression, decreased length of stay, and decreased risk of ileus.

   The most common regional block used to achieve postoperative analgesia following mastectomy is the paravertebral block, during which local anesthetic is injected into the paravertebral space which contains the thoracic spinal nerves, between the costotransverse ligament and the pleura. At our institution there has been recent interest in an alternative regional block. The pectoral nerve block is performed by injecting anesthetic between the pectoralis major and the pectoralis minor (PECs I) or between the pectoralis minor and the serratus anterior (PECs II) [2]. A serratus plane block is a modification of the PEC block, in which a local anesthetic is injected between the serratus anterior and latissimus dorsi muscles.

   The proposed advantage of the pectoral nerve block for regional anesthesia during breast surgery is equal analgesic efficacy with fewer potential complications.

6. **Setting of the Research:**

   The study will take place at Spectrum Health Medical Center: Butterworth Hospital and Spectrum Health Blodgett Hospital with follow up through Spectrum Health Lemmen-Holton Cancer Pavilion and the Lake Drive locations.

7. **Resources Available to Conduct this Research:**

   Surgeries will be performed by the Spectrum Health breast surgeons. These surgeons perform approximately 300 mastectomies, partial mastectomies and lumpectomies per year. Even allowing for a percentage of patients who refuse participation, this should provide an adequate population base to recruit the required number of participants within 12 months.

   The regional anesthesia will be performed by the Anesthesia Medical Consultants' on-call pain physician. Subjects will be enrolled by Spectrum Health clinical research staff.

Dr. Marianne Melnik is a breast oncologist and surgeon who has been in practice for 26 years. She has a wealth of experience in research and served as the primary investigator of the Grand Rapids Research Consortium of West Michigan (then known as the Grand Rapids Clinical Oncology Program) from 2005-2008. Dr. Melnik has also been a lead physician in critical trial accrual for Spectrum Health. Dr. Melnik will plan to spend about 5% of her time on this project. She will be referring and following patients during the course of this study.

Dr. Jaklitsch is an anesthesiologist who is certified through the American Board of Anesthesiology and has been in practice since 2005. He is presently the Vice-Chairman of the Spectrum Health Department of Anesthesiology and has significant previous experience with research. Dr. Jaklitsch will plan to spend 5-10% of his time on this project, primarily in coordination and sharing information with other anesthesiologists who will be doing the blocks as part of standard of care.

The other investigators, Dr. Miller, Dr. Oostendorp, Dr. Paulson and Dr. Wright will be performing standard of care surgery. Their direct study involvement will be minimal, but they will be helping to screen and refer patients to the study as well as doing the standard of care follow-up visit two weeks post-surgery.

Dr. Erica Burkheimer is a general surgery_resident in her second_year of training. She will plan to spend about 5% of her time on this project.

The research study coordinators have clinical research and oncology experience. The lead research coordinator will plan to spend 25-30% of his or her time on this project.

This research project has been vetted by the research department and they have agreed to support it with resources. Physician time for the project is being donated.

8. Study Design:

a. Recruitment Methods

Patients will be referred by the Spectrum Health breast surgeons. If the patient is interested, the investigator or research staff will provide a copy of the informed consent for the patient to review. Spectrum Health research staff will then follow up with the patients to further discuss the study and confirm that the patient is interested in participation.

Patients will then be consented by a clinical research coordinator. Typically, this would occur at the hospital where they will be undergoing their surgery. The coordinator will review the consent with the patient (and family or significant other, as applicable) and have the patient sign it. The coordinator will make all reasonable attempts to keep the discussion as private as possible. In order to minimize coercion, it will be made very clear to patients that their participation is strictly voluntary and that not choosing to participate will in no way affect their present or future care at Spectrum Health.

Once the patient has been randomized to either PEC or PVB, the anesthesiologist on call for local blocks will see the patient and review that analgesic plan and the risks of that specific procedure with the patient. This meeting and explanation are standard, but they may also answer questions the patient may have related to the study.

We anticipate enrolling 128 total patients in the study, 64 in the PVB arm and 64 in the PEC arm.

There will be no payment to patients for inclusion in the study.

b. Inclusion and Exclusion Criteria

Inclusion Criteria:

i. Female patients ≥ 18 years of age
ii. Total mastectomy or partial mastectomy with or without reconstruction OR planned lumpectomy.
iii. Patient determined by their surgeon as medically able to receive a regional block for post-operative analgesia
iv. Patient agrees to participate in the study and signs informed consent

Exclusion Criteria:

i. Neoadjuvent radiation therapy
ii. Stage IV cancer
iii. Planned general anesthesia use during surgery
iv. Allergies to ropivacaine, midazolam, fentanyl, or propofol
v. Pregnant women
vi. Prisoners
vii. Adults unable to consent
viii. Non-English-speaking patients

c. Study Endpoints

Primary Outcome Variables:
Intraoperative narcotic use, Post Anesthesia Care Unit (PACU) narcotic use and postoperative narcotic use. We would expect that all variables will have a lower values in patients randomized to PEC versus PVB.

Secondary Outcome Variable(s):
Length of operation, estimated blood loss, incidence of postoperative nausea, subjective pain at two weeks (including patient's overall pain rating for the previous two weeks, the patient's stated last time they used pain pills) and number of calls to physician's office following hospital discharge.

d. Procedures Involved in the Research

This is a prospective, randomized study.
Following satisfaction of the inclusion/exclusion criteria and signed informed consent, patients will be randomized to paravertebral block or a pectoral nerve block. The randomization schedule will be set-up prior to study start using an Excel spreadsheet. Spectrum Health statisticians designed the randomization schedule to meet significance for the endpoints. Randomization is 1:1, PEC:PVB. If the patient is unwilling to be randomized to one or the other type of block, they will not be able to participate in the study. After each patient is consented, the randomization schedule will be checked and the data sheet with the type of block to be used will be placed in

the patient chart. The research coordinator will notify anesthesia of which block will be used on the patient.

Patients will proceed to surgery per usual standard of care. The PVB is performed along the spine utilizing ultrasound guided technique. The PEC is performed anteriorly, at the level of the axillary line, also utilizing ultrasound guided technique. Each block will be performed using 20-30 mL 0.5% Ropivacaine[1] per side. Midazolam and fentanyl will be used for sedation as needed. Intraoperatively, patients will undergo monitored anesthesia care with a propofol infusion (50-150 mcg/kg/min). Additional IV fentanyl will be given as needed. Anesthesia will be converted to general anesthesia if the patient is unable to tolerate the procedure with sedation and block anesthetic or if general anesthesia is preferred by the surgeon. This will not disqualify the patient, but the conversion will be noted in REDCap.

[1]Package inserts for these FDA-approved drugs are included as Appendix A to the protocol.

All post-operative care will be standard of care.

Data collected will include the following:

i. Demographics[1]
ii. Medical history[2]
iii. Surgical procedure performed & pain control technique(s) used
iv. Extra doses of narcotic and sedative medication used during surgery.[3]
v. Length of surgery
vi. Duration of hospital stay (measured in minutes)
vii. Total of extra narcotic and sedative medication used while in PACU and in the first 24 hours post-PACU (or until discharge, whichever comes first)
viii. Total does of anti-nausea medication used while in PACU and in the first 24 hours post-PACU (or until discharge, whichever comes first).
ix. Which anesthesiologist performed the procedure
x. Two-week post-operative visit pain rating (subjective information from the patient about their over-all pain rating for the previous two weeks, as well as the approximate last time they used pain pills)
xi. Number of phone calls to the surgeon's office for concerns about pain in the time post-discharge and prior to the office visit.

[1] Include distance the patient lives from the Lemmen-Holton Cancer Pavilion, their self-reported ethnicity and age.
[2] Include stage of tumor, outpatient chronic use of narcotics, diagnosis of chronic pain, ASA classification, current diagnosis, major comorbidities and BMI.
[3]Defined as total amount of narcotic/sedative medication given during surgery, in milligrams,

Standard of care follow-up will occur at 2 weeks with the physician who performed the surgery. Patient will be asked about pain pill use; those units will be converted to morphine equivalents. This information may also be obtained through a phone call.

This trial is registered on clinicaltrials.gov

Schedule of Events:

Study Requirements	Pre-Surgery Visit	Day of Surgery	PACU	1st 24 hrs. post-surgery	Post-Surgery Visit (2 wks after surgery, +/- 1 week)[3]

Eligibility Criteria	**X**				
Consent	**X**[1]	**X**			
Randomization		**X**			
Surgery, using PEC or PVB		**X**			
Data Collection[2]		**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**	**X**

[1] Consent may be done either prior to the day or surgery or on the day of surgery, depending on timing and patient preference.
[2] Includes patient demographics, medical history, block procedure used (PVB or PEC), method of pain control used during surgery, extra narcotic/sedative use during surgery, length of surgery, extra narcotic and sedative use in PACU, name/total dosage of narcotic use during post-op hospitalization, duration of hospitalization
[3] Data collected from this time period may be done over the phone as well as at the surgeon's office.

e. Data Management

Data to be collected are detailed in Appendix B (pdfs of REDCap database for this study). Data will be managed by Spectrum Health research staff and kept in a locked cabinet or a limited-access electronic drive.

f. Provisions to Monitor the Data for the Safety of Subjects

The Principal Investigator will oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events (see "Adverse Events" below).

g. Withdrawal of Subjects

A patient may be withdrawn from the study prior to the expected completion of that subject for failure to adhere to protocol requirements. Patients may choose to withdraw from the study at any time. Data that have already been collected on these patients will still be used.
The primary investigator may remove a patient at any time from this research study if it is felt to be in the best interest of the patient.

9. Statistical Plan:

a. Sample Size Determination
The primary outcome variable for this study is the difference in narcotic use between the PEC group and the PVB group during the first 24 hours following surgery. If we define a clinically important effect as the mean narcotic use in the PVB group is twice that seen for the PEC group, with a standard deviation equal to the mean of the PVB group, with $\alpha=0.05$ and $\beta=0.20$, we will be able to detect a statistically significant difference with 64 subjects in each group, using the unpaired t-test. Complication rates will also be compared between the two

groups, although with an anticipated rate of only 5% in the PVB group, it is unlikely with the projected sample size that we will find a statistically significant effect for this variable.

b. Statistical Methods
Summary statistics will be calculated. Quantitative data will be expressed as the mean + SD, while nominal data will be expressed as a percentage. Comparisons between groups for quantitative variables will be performed using the t-test. Nominal variables will be evaluated using the Chi-Square test. The data will be analyzed as intention to treat. Significance will be assessed at $p<0.05$.

10. Risks to Subjects:

Risks of both procedures are very low – less than 5% for each risk listed here.

PEC

a. Vascular puncture
b. Inadequate analgesia
c. Intraneural injection, resulting in transient neuropathy
d. Incomplete nerve block
e. Infection

PVB

a. Pneumothorax
b. Vascular puncture
c. Incomplete nerve block
d. Hypotension secondary to intrathecal or epidural spread with subsequent sympathetic blockade.
e. Infection

Possible risks related to either PEC or PVB will be discussed with each patient by the anesthesiologist prior to their scheduled surgery and will be address in a separate consent form as part of routine care.
Adverse Events (AEs)

An adverse event is defined as "…an unfavorable and unintended sign, symptom or disease associated with a subject's participation in this research study." AEs will be monitored until the follow up visit with the surgeon postoperatively. All adverse event information will be recorded and the clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Since pain is an expected side effect of surgery, and we will be monitoring post-op pain medication usage and post-op pain levels in research subjects, pain will not, in and of itself, be considered an AE for this study. As defined by the Common Terminology Criteria for Adverse Events, Version 4.0 (May 28, 2009), pain will not be considered an AE unless it has reached a "Grade 3," defined as "Severe pain; limiting self-care and activities of daily living."

We will specifically track any instances of track pneumothorax or hypotension, since those are potential side effects of PEC.

Serious Adverse Events (SAE's)

A serious adverse event is defined as "an adverse event that results in death, is life-threatening, requires initial or prolonged hospitalization, results in a congenital anomaly or requires a medical or surgical intervention to prevent permanent impairment or damage." SAE's will be reported to the Spectrum Health Institutional Review Board (IRB) in accordance with IRB policies and procedures, within five business days. Copies of each report and documentation of Spectrum Health IRB notification and receipt will be kept in the study records.

11. Potential Benefits to Subjects:

There is no direct benefit to the patients that participate in this study. It is possible that a PEC block will offer equal analgesic efficacy in comparison to paravertebral blocks with potential reduction in adverse events including pneumothorax and perioperative hypotension. This research may also benefit others in the future by contributing information to the body of knowledge about surgical pain control.

12. Provisions to Protect the Privacy Interests of Subjects:

The study, including potential risks and benefits of treatment, will be discussed thoroughly with potential subjects in a space where he/she is comfortable. Efforts will be made to get a copy of the informed consent to the patient ahead of time, so he/she can review it at his/her own pace. The consent will be reviewed and patients (and others, as applicable) will be allowed adequate time to ask questions. Voluntariness will be emphasized. Efforts will be made to keep the discussion private. Reported data will not contain identifiable information. No vulnerable populations will be included in this study.

13. Provisions to Maintain the Confidentiality of Data:

Patient data will be entered into an electronic data capture system, created in REDCap. Only study staff will have access to these records. Any paper records will be stored in hard copy in a locked filing cabinet in the research office. Data will be analyzed by the Spectrum Health Research Department statistician and will not be sent outside the system. Only study staff will have access to the research data. Data will be stored after study completion per Spectrum Health Research standards. The collection of sensitive information will be limited to the amount necessary to achieve the aims of the research study. Study-related monitoring, audits and inspections by the Spectrum Health IRB and government regulatory agencies will be permitted, as required.

All study staff will have training through the Collaborative Institutional Training Initiative (CITI), including training on Good Clinical Practice (GCP) practice standards.

14. Medical Care and Compensation for Injury:

If patients are injured or made sick from taking part in this research study, medical care will be provided in accordance with current standards of care. No funds have been set

aside to pay the patient in the event of a research related injury. The patients may contact the investigator for more information.

15. Cost to Subjects:

Since both PEC and PVB are both standard of care procedures, costs for the surgery, including the blocks, will be billed to the patient and/or their insurance company. Study subjects will be responsible for any co-pays. Study subjects should not incur any extra charges related to the research study.

16. Consent Process:

The study investigators (Spectrum Health Breast Surgeons) will introduce the study to the patients at their pre-surgery visit. They will fill out and sign an eligibility checklist for the research coordinators. The research coordinators will then reach out to the patient to confirm interest in the study and will give the patient a copy of the informed consent, if they have not already received one. The coordinator will then review the consent with the patient and family (as applicable). Adequate time will be allotted for the patient and/or family and friends to ask questions. Enough time will also be allowed for both the patient and the coordinator to feel that there is an adequate understanding of the study and the responsibilities involved. Subjects will be informed that the research study is voluntary. If the patient is still interested, they will sign a copy of the research consent. A copy of the consent will be given to the patient and a copy will be placed in their medical chart. On the morning of surgery, when the anesthesiologist comes in to discuss anesthesia and pain control with the patient, he or she will also discuss the research study with the patient.

17. Vulnerable Populations:

This study will not include any vulnerable populations.

18. ***Sharing of Results with Subjects:***

There are no plans to share study results with the research subjects.

19. References:

1. Glissmeyer, Johnson, Sherman, et al. Effect of paravertebral nerve block on narcotic use after mastectomy. American Journal of Surgery. 2015. article in press
2. Wahba, Kamal. Thoracic paravertebral block versus pectoral nerve block for analgesia after breast surgery. Egyptian Journal of Anaesthesia. 30.129-135. 2014.
3. Sopena-Zubiria, Fernandez-Mere, Arias, et al. Thoracic paraverteberal block compared to thoracic paraverteberal block plus pectoral nerve block in reconstructive breast surgery. Revista Espanol De Anestesiologia Y Reanimacion. 2012 Jan; 59(1): 12-7
4. Bashandy, Abbas. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Regional Anesthesia and Pain Medicine. 2015 Jan; 40(1): 68-74

5. Study data were collected and managed using REDCap electronic data capture tools hosted at Spectrum Health.[1] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. [1]Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr;42(2):377-81.