Title:
The efficacy of pecto-intercostal fascial plane catheters for reduction of sternal pain in cardiac surgery patients with complete median sternotomy: A randomized, placebo-controlled trial

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1. Background and Significance

Post-sternotomy pain after cardiac surgery can be debilitating and associated with increased risk of complications, including poor respiratory mechanics and persistent post-sternotomy pain. (1–5) Sternal pain after cardiac surgery typically result in an average score of 3-7 on an 11-point numeric rating scale. (6–8) The sternum is innervated by the medial division of the anterior cutaneous branches of the T2-6 intercostal nerves (Figure 1). (1,9)

Concern for epidural hematoma in the context of systemic heparinization with cardiac surgery deters most institutions from utilizing neuraxial analgesia for post-sternotomy pain. (1,10) Parasternal regional blockades such as pecto-intercostal fascial plane block (PIFB) can provide a low-risk alternative. (1,11,12) PIFB consists of parasternal injection deep to the pectoralis major muscle and superficial to the internal intercostal muscle. (13) A superficial blockade such as PIFB may be safer and technically easier to perform than a deeper block such as the transversus thoracic plane block (TTPB), with theoretical risks of pleural puncture, internal thoracic artery (ITA) injury, and limited spread secondary to tissue plane disruption after ITA harvest. (11,14–17)

However, after a single-injection PIFB, spread may not be adequate. (14,18) Adequate spread can be achieved with multiple injections or multi-orifice catheters. (1,14,17,19) As post-sternotomy pain remains severe for two postoperative days (25), multi-orifice catheters may be more beneficial than single-shot injections with limited duration of action. (6)

This study aims to evaluate whether continuous local anesthetic infusion through multi-orifice PIFB catheters can reduce acute sternal pain after cardiac surgery via a complete median sternotomy. The 24 hour time point was chosen because it represents a time where both the post-sternotomy pain is rated as severe, especially with movement and coughing, and the patient is required to start actively participating in the postoperative rehabilitative process. (25)

2. Study objectives and hypotheses

2.1. Objectives

The primary objective is to evaluate whether PIFB catheters can effectively reduce sternal pain, on standardized coughing at 24 hours after cardiac surgery via complete median sternotomy.

2.2 Hypotheses

We hypothesize that a continuous ropivacaine infusion through PIFB catheters will be more effective than placebo in reducing sternal pain score on standardized coughing at 24 hours post-operatively.

3. Methods

3.1 Design:

This will be a prospective, randomized, double-blinded. placebo-controlled trial in which patients will be randomly allocated to two study groups in a 1:1 ratio:

1) Intervention Group:
   20 mL of ropivacaine 0.2% will be bolused through PIFB catheters on each side, followed by 3 mL/hour infusion of ropivacaine 0.2% for 48 hours each side.

2) Control Group:
   20 mL of normal saline will be bolused through PIFB catheters on each side, followed by 3 mL/hour infusion of normal saline for 48 hours each side.

3.2 Study population

The target population is adult patients undergoing scheduled cardiac surgery with complete median sternotomy. Patients who are likely to require prolonged postoperative intubation and sedation (See Section 3.2.2 *Postoperative Exclusion Criteria*) are excluded as they are unlikely to benefit from PIFB catheters.

3.2.1 Inclusion criteria

- Scheduled cardiac surgery patients
- Complete median sternotomy
- Adult (19 years old or older)
- English-speaking

3.2.2. Exclusion Criteria

Preoperative Exclusion Criteria:

- Patient refusal
- Emergent surgery
- Inability to provide consent
- Inability to follow up via telephone
- Known preoperative coagulopathy
  - i) Congenital coagulopathy
  - ii) Congenital platelet disorders
  - iii) Platelet count < 50 x 10^9
  - iv) INR or aPTT exceeding the upper range of normal in the absence of anticoagulant use
  - v) Does not include active anticoagulant or antiplatelet use
- Predicted post-operative therapeutic anticoagulation within 48 hours.
- Skin disease over block insertion site that would prevent catheter securement
- Immunodeficiency including uncontrolled diabetes, as defined by HbA1C more than 8.5% (20)
- Preoperative advanced liver failure (as defined by Child-Pugh B or C) (21)
- Preoperative advanced renal failure (as defined by eGFR < 30 mL/min/1.73 m^2)
- Opioid tolerance (as defined by morphine oral equivalent >60mg for a period of 7 days or longer pre-operatively) (22)
- Allergy to local anesthetic, acetaminophen, or hydromorphone
- Weight less than 60 kg

Postoperative Exclusion Criteria:

- Postoperative bleeding at time of randomization as defined by initial chest tube loss of >350 mL, >200 mL per hour loss, > 2 mL/kg/hour loss for 2 consecutive hours, or requiring return to the operating room for surgical management (23)
- Hemodynamic instability, as determined by CSICU attending anesthesiologist
- Anticipated mechanical ventilation of more than 24 hours
- Anesthesiologist unavailable to insert PIFB catheter within 4 hours of CSICU arrival

3.2.3. Withdrawal Criteria

- Hemodynamic or respiratory instability, as determined by CSICU attending anesthesiologist
- Inability to follow commands to initiate cough as per standardized script, and to provide NRS pain score

4. Study Centre

All study procedures will take place at St. Paul's Hospital, Vancouver. There are approximately 1000 annual scheduled cardiac surgeries involving median sternotomies at St. Paul's Hospital, of which approximately 850 involve complete sternotomies, providing sufficient patient population size to conduct this study.

5. Recruitment and Informed Consent

Patients will be identified in the Pre-Assessment Clinic by an anesthesiologist or nurse, who is part of the patient's circle of care. Patients will be asked for permission to be approached by a research assistant regarding the study. If permission is granted, a research assistant will explain the purpose of the study, confirm eligibility and propose enrolment. Some patients may be admitted to St. Paul's Hospital prior to their scheduled cardiac surgery and will not be seen at the Pre-Assessment Clinic. In such cases, an anesthesiologist or ward nurse, who is part of their circle of care, will ask for the patients' permission to be approached by a research assistant instead. During current times, telephone consultation with patients may be utilized. In such cases, patient consents forms will be exchanged securely via approved email accounts (BC Health Authority and affiliated BC University email accounts).

Recruited patients will be informed of the study interventions, the chances of being assigned to one of the two groups, the risks and benefits of participating, and their right to withdraw from the study at any time without adversely affecting their clinical care. If the patient decides that they would like to participate, they will be asked to sign the consent form. The investigators will provide the patient with a copy and will retain the original consent form. It will be emphasized that the patients may not eventually receive pecto-intercostal fascial plane catheters if they meet aforementioned exclusion criteria postoperatively.

Consent will be verified on the day of surgery in surgical day care prior to the operation.

6. Group Allocation and Randomization

Participating patients will be randomly allocated to one of two study groups, as detailed in section 3. Patients will be randomized using a computer-generated sequence of random numbers. A clinical-trial pharmacist will develop the randomized sequence list. A copy of this list will be kept with the St. Paul's Hospital pharmacy for the purposes of randomization.

Within 4 hours of CSICU admission, or in the cardiac surgery operating room after skin closure, patients will be checked for postoperative exclusion criteria. Eligible patients will be randomized

into the study. The physician performing the block will alert the pharmacist, who will assign the patient to the next sequential participant number and corresponding study arm. Pharmacy will send the randomized de-labeled study solution of either ropivacaine 0.2% or normal saline. Time zero is at the first bolus of study solution through the catheters.

7. Blinding
This study observes blinding of the patients, anesthesiologists, surgeons, nurses, outcome collectors, and data analysts.

7.1 Patient Blinding
Patients will be informed that they will receive one of two solutions (ropivacaine or saline), without disclosing which group they are allocated to.

7.2 Anesthesiologists, Cardiac Surgeon, Nurses, Nurse Practitioners, Acute Pain Service Team
Anesthesiologists, cardiac surgeons, CSICU nurses, ward nurses, nurse practitioners, and acute pain service team will be blinded to assignments.

7.3 Blinding of Assessors
Assessment of patients, data collection, and follow-up will be conducted by team members (i.e. research assistant, anesthesiologist, CSICU nurses, and ward nurses, acute pain service team) who are blinded to group allocation.

7.4 Blinding of Data Analyst
The data analysts will be provided a table with two groups of the unique numbers, but which group corresponds with ropivacaine and which corresponds with normal saline will not be revealed until the data analysis has been fully completed.

8.0 Patient Management

8.1 Preoperative and Intraoperative Phases:
After the patients have been recruited, the research assistant will educate recruited patients on the use of IV Patient-Controlled Analgesia (IV PCA) and NRS pain scores. Otherwise, preoperative and intraoperative management, including the use of sedatives and analgesics, will be up to the discretion of the anesthesiologist in accordance with standard practice.

8.2 Postoperative Phase and Study Intervention
Within 4 hours of CSICU admission, or in the cardiac surgery operating room (OR) after skin closure, a member of the PIFB catheter placement team will be contacted. Each member is a staff anesthesiologist or anesthesiology fellow with previous experience performing the PIFB. The patient will then be checked for postoperative exclusion criteria. If no exclusion criteria are present, the patient will be randomized as previously described. Randomized solutions (ropivacaine 0.2% or saline) will be sent to CSICU or OR from pharmacy accordingly.

While the patient remains sedated and intubated, bilateral PIFB will be performed under ultrasound-guidance. The InfiltraLong 600T (Pajunk, Geizingen, Germany), a 19-gauge, 600 mm multi-orifice catheter (45 orifices in the first 100 mm) will be inserted parasternally using a 17-gauge, 6-inch Tuohy needle. The needle approach will be caudal-to-cranial, 2 centimeters away from the sternal border, extending from T6 to T2.

Up to 5 mL of D5W per side may be given via the Tuohy needle for catheter placement. 20 mL of randomized solution per side will be given through the catheter at time zero. Each catheter will then be connected to a CADD Solis Pump, set at a continuous infusion rate of 3 mL per hour of the study solution. The catheters will be removed after 48 hours.

All patients will be provided standard post-operative pain control regimen:

1) Acetaminophen 1300 mg PR within 2 hours of admission to CSICU
2) Acetaminophen 650 to 975 mg PO QID regular

3) NSAIDs will not be used in the first 48 hours
4) Prior to extubation and PCA initiation (Discontinued with initiation of IV PCA):
   a) Hydromorphone IV 0.2-0.4 mg q5min PRN for pain
5) After extubation with resumption of cognition to utilize IV PCA:
   a) Hydromorphone (0.6 mg/mL) IV PCA, set at 0.2 mg bolus (Range: 0.1-0.3 mg, titrated as clinically indicated), 6-minute lockout, and no continuous infusion. 0.3 mg clinician bolus q10min PRN, with maximum 3 clinician boluses per hour.

Patients will be assessed daily by the Acute Pain Service team for PCA management.

8.3 Postoperative Management at CSICU and 5B

Standard post-operative management on CSICU:
- Continuous monitoring of invasive blood pressure, central venous pressure, heart rate, ECG, ETCO2, SpO2 and respiratory rate
- Regular monitoring of temperature, Richmond Agitation Sedation Scale (RASS), Behavioural Pain Scale (BPS), peripheral pulses, and pupillary status
- Hourly fluid input and output (urine and chest tube losses)
- Ventilatory support with appropriate tidal volumes and SpO2 target >92%
- Inotropic/vasopressor support at the discretion of the attending Anesthesiologist
- Maintenance of sedation with propofol or dexmedetomidine
- Correction of anemia, coagulopathy and electrolyte abnormalities at discretion of attending Anesthesiologist
- Management of nausea with antiemetics as per existing protocol

Extubation criteria:
- Stable respiratory and hemodynamic status
- Intact airway reflexes and effective cough
- Richmond Agitation-Sedation Scale (RASS) score ≤ +1 and Behavioural Pain Scale (BPS) score ≤ 6
- Absence of pulmonary pathology on Chest X-ray (CXR)
- Normothermia

Chest tube removal criteria:
- Chest tubes in-situ for 6-8 hours and drainage less than 100ml in past 4 hours
- No evidence of air leak
- Stable respiratory and hemodynamic status
- Weaned from mechanical ventilation
- Coagulation studies within normal limits

Criteria to transfer to 5B ward from CSICU:
- Stable, unsupported hemodynamic status
- Stable respiratory status on no/minimal oxygen therapy
- At least 4 hours after extubation, 1 hour after CVC/arterial line removal, 1 hour after first beta blocker dose
- Protected airway
- Incision intact and sternum stable
- Adequate urine output
- Pain controlled

Postoperative management will otherwise be at the discretion of attending CSICU intensivist or cardiac surgeon without influence from this study.

Nursing staff will be directed by a detailed protocol to identify any symptoms of local anesthetic systemic toxicity (ie. perioral numbness, tinnitus, visual and auditory disturbance, twitching/tremors, seizures, apnea, arrhythmia, cardiovascular collapse). If such symptoms were noted, the CSICU intensivist will be alerted. If blinding needs to be broken in case of suspected local anesthetic systemic toxicity or other concerning symptoms, pharmacy will be called to access the randomized sequence list to determine which arm the patient has been allocated to.

9. Outcome

9.1 Outcome Assessment

Baseline information including age, weight, height, BMI, sex, cardiac surgery type, duration of surgery, and ASA classification will be collected. Relevant co-morbidities, including coronary artery disease, valvular disease, congestive heart failure, respiratory conditions such as asthma or COPD, diabetes, and chronic pain will also be recorded.

CSICU nurses will be responsible to assess and record NRS sternal pain scores at rest and on coughing every 8 hours until the 48th hour after time zero. Once the patient has been transferred to the 5B ward from CSICU, the nurses from 5B will record this data until the 48th hour.

9.2 Follow Up

At 48 hours, the research assistant will administer patient questionnaire of QoR-15 and EQ-5D-5L.

After patient's discharge from hospital, medical record will be reviewed for narcotic usage and complications of sternal wound infection, local anesthetic systemic toxicity, and nausea or vomiting.

Patients will be followed up by the research assistant via telephone at 3 and 6 months to administer EQ-5D-5L as well as determine the presence and severity of chronic sternal pain.

10. Study Outcomes

10.1 Primary Outcome Assessed

The primary outcome is NRS sternal pain score on coughing at 24 hours. Coughing will be elicited with a standardized script for a sitting patient:

"Please use both hands to hold on to the pillow in front you to hold your chest in, and give me three forceful coughs in a row"

Patient will be considered a reliable reporter if they are able to follow the directions in 10.1 and subsequently report an NRS pain score.

10.2 Secondary Outcomes Assessed

1) Cumulative opioid consumption (in IV morphine equivalents) at 24 and 48 hours
2) Nausea or vomiting within 48 hours
3) Quality of Recovery-15 score at 48 hours
4) Chronic sternal pain at 3 and 6 months postoperatively
5) Quality of Life as measured by EQ-5D-5L at 3 and 6 months postoperatively

11.0 Sample size calculation

The sample size is estimated based on previous finding the mean NRS on coughing at POD1 was 6.45 with a standard deviation (SD) of 2.96 (8). Using 2-sample t-test, a type I error of 0.05 and a type II error of 0.80, and assuming a reduction on NRS at 24 hours of 2.1 to be significant (24) in patients treated with PIFB catheters, 33 patients per group would be required. Accounting for a 20% attrition rate, 40 per group (n=80 total) would be required. Sample size calculations were conducted using the "pwr" package in R.

12.0 Analysis plan

The primary outcome will be analyzed using 2 sample t-test, with both an intention-to-treat and per-protocol analyses. Patients with missing outcomes (i.e. pain score at 24 hours) will have their last value prior to 24 hours carried forward. Cumulative opioid consumption and Quality of Recovery-15 scores will be compared using t-tests or Mann-Whitney U test, as appropriate, after applying the Shapiro-Wilk test as a confirmation of normality. Frequency of nausea or vomiting will be compared using Fisher's exact test.

There are no plans for an interim analysis due to the relatively small sample size. Data will be analyzed using RStudio (ver. 1.3.1093).

13.0 Feasibility

The study centers perform an average of 1000 annual scheduled cardiac surgeries involving midline sternotomy, of which 850 involve complete median sternotomies. Assuming 75% of those are eligible for the study, 20% approve the study, and assuming 50% of approved patients get randomized due to logistical issues, 64 patients can theoretically be recruited annually. As such, the entire study can be completed within 1.5 years.

14.0 Confidentiality

All printed study data will be kept in a locked file cabinet in the St. Paul's anesthesia office, accessible only to research personnel; all digital study data will be kept on encrypted USB key or REDCap. Patients will be assigned study ID numbers to maintain confidentiality during data entry and analysis. Any presentation or publication of research results will be done using aggregate data with no identifiable patient information.

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Appendix

Figure 1. Innervation to the Sternum (Reprinted with permission from Liu et al.)

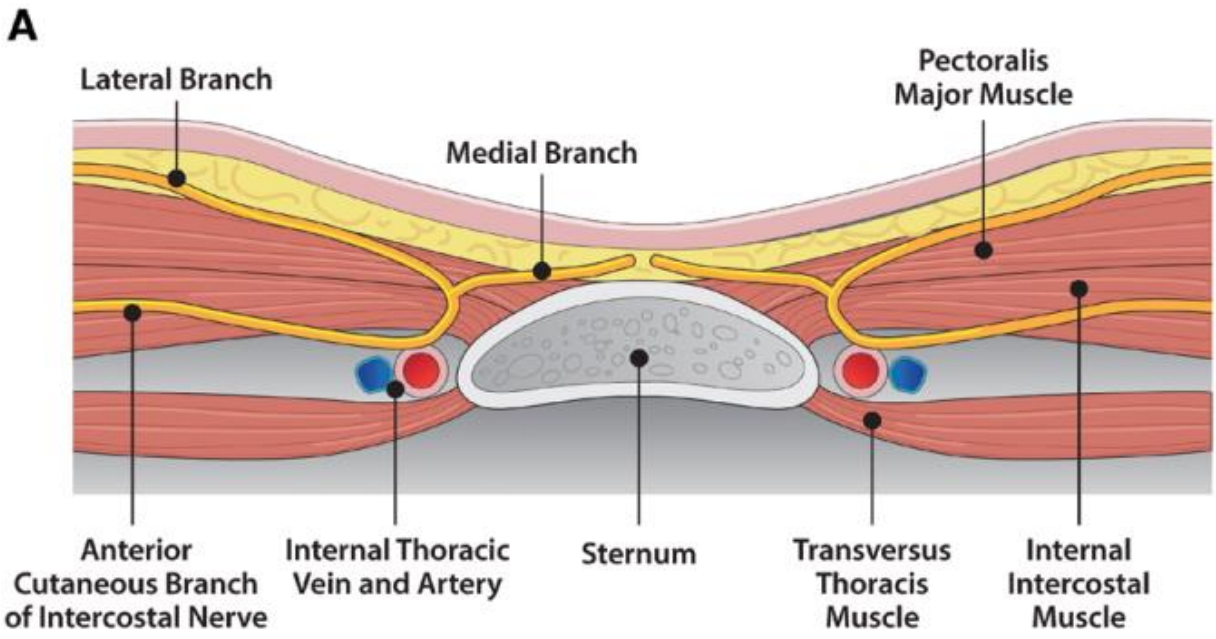
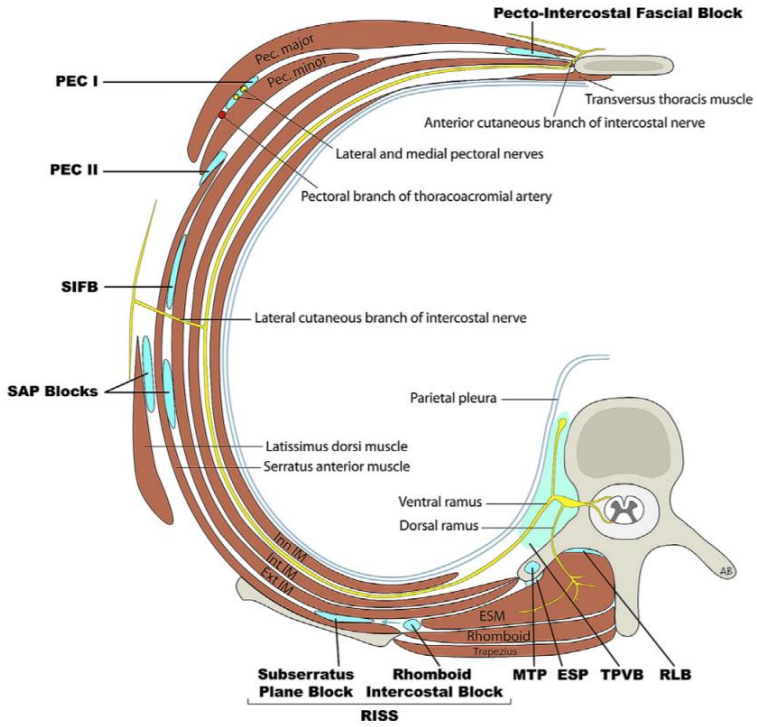

A
Lateral Branch
Medial Branch
Pectoralis Major Muscle
Anterior Cutaneous Branch of Intercostal Nerve
Internal Thoracic Vein and Artery
Sternum
Transversus Thoracis Muscle
Internal Intercostal Muscle

Figure 2. Possible areas of nerve blockade for post-sternotomy pain



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