PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	**Pecto-Intercostal Fascial Block for Postoperative Analgesia after Cardiac Surgery: A Pilot Study**
Principal Investigator	Balachundhar Subramaniam, MD MPH

B1. PURPOSE OF PROTOCOL

The purpose of this study is to determine whether administration of a pecto-intercostal fascial plane block (PIFB) with bupivacaine is a more effective therapy for postoperative analgesia after cardiac surgery as compared to patients who receive a sham block of normal saline.

Specific Aim 1: We aim to determine whether or not a PIFB with bupivacaine can reduce postoperative pain after cardiac surgery. This will be assessed through:
(*Aim 1A*) opioid consumption in the first 48 hours postoperatively
(*Aim 1B*) patient self-reported pain scores during their hospital stay

Specific Aim 2: We aim to estimate the effect size in order to obtain information that can be used to power future research on the use of regional modalities of analgesia for cardiac surgeries.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Over 80% of the patients undergoing cardiac surgeries experience moderate to severe postoperative pain [1]. Post sternotomy pain may lead to a number of complications. Pain elicits a neuro-humoral stress response, increasing the sympathetic outflow, which predisposes to cardiac ischemia, arrhythmias, hypercoagulable state in an already compromised patient. It also causes pulmonary complications by restricting breathing effort. Other complications include postoperative delirium and increased duration of ICU and hospital stay. Thus, pain impairs postoperative recovery. So, optimal pain management after cardiac surgery is of paramount importance. Undertreated pain may also lead to chronic pain conditions. Around 4% of the cardiac surgical population experience chronic sternal pain [2].

Currently, the main modality of postoperative analgesia is by systemic administration of opioids [1]. Opioids are given as either patient-controlled analgesia (PCA) or as nurse administered boluses until the patient can be weaned off to oral opioids. Other agents used are acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), though the use of NSAIDs in cardiac surgical population is controversial, considering the risk of hemorrhagic complications [2]. Systemic opioids may lead to a number of adverse events like nausea, vomiting, sedation, decreased bowel activity, urinary retention, delirium and life threatening complications like respiratory depression [2]. These factors lead to sub-optimal opioid dosing, and also directly prolong duration of ICU and hospital stay.

Regional techniques for analgesia are grossly underused in the cardiac surgical population. Neuraxial techniques such as intrathecal, epidural analgesic techniques are disregarded in most centers for the fear of epidural hematoma in a patient on anticoagulants [3]. Another concern is the associated sympathectomy and hemodynamic instability [4]. Some studies were not able to find a significant benefit of thoracic epidural analgesia on clinical outcomes after cardiac surgery [5].

Bilateral paravertebral block is being successfully used in some centers [6]. Many centers use local anesthetic infiltration at wound edges and drain sites. This provides analgesia for a limited period and is limited by the duration of action of the local anesthetic being used, unless a continuous infusion is being used or repeat blocks are administered [1].

Pain after cardiac surgery is multi-factorial. Apart from direct tissue trauma, inflammatory response to the trauma and neural sensitization play an important role in pain [7]. Somatic, musculoskeletal pain results from the skin incision, sternotomy, sternal retraction, lower limb venous harvesting, placement of drains and patient positioning. The sensory supply associated with skin incision and sternotomy is derived from T2 to T6 segments, and is carried by the intercostal nerves [7]. The visceral pain results from incision of the parietal pericardium, which is innervated by the phrenic nerve, sympathetic trunks and the vagus [7].

The intercostal nerves pass between the internal and innermost intercostal muscles for most of their course.

Nearthe sternum, they cross anterior to the internal thoracic vessels and pierce the transversus thoracis muscle, the internal and external intercostals, respectively, and the pectoral muscles to become the anterior cutaneous nerves supplying the thoracic wall. A single shot injection of local anesthetic in the plane between pectoralis major muscle and the external intercostal can effectively block the anterior thoracic cutaneous nerves. This is called the pecto-intercostal fascial block (PIFB) [8-10]. PIFB has been studied for analgesia after breast surgeries and also in thoracic trauma [8]. It is a promising option considering its efficacy and ease of administration.

PIFB might prove to be a useful analgesic technique, devoid of the systemic adverse events associated with opioids and the neuraxial and hemodynamic complications associated with neuraxial techniques. It is a relatively superficial plane block therefore it is very safe. It could prove useful in the acute setting of postoperative pain and even go a long way preventing chronic pain.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design
This is as a prospective, randomized, placebo controlled double-blinded trial of patients undergoing cardiac surgery at BIDMC. Patients meeting inclusion criteria with no exclusions will be approached to obtain written informed consent. Patients who decide to participate will receive a PIFB with either bupivacaine hydrochloride or placebo. Data will be collected in order to determine whether there is a difference in opioid consumption or pain scores following surgery.

Enrollment
Study subjects will be identified from the perioperative information management system (PIMS), surgical consult lists, cardiac surgical clinic visit schedules and pre-admission testing (PAT) clinic visit schedules. After confirming eligibility, the patient will be approached by a research team member to discuss the study in detail. Written informed consent will be obtained before initiation of any study procedures.

Randomization
Enrolled subjects will be randomized to one of the two study groups, in a 1:1 randomization ratio (*Please see the table below)*. Patients randomized to Group 1, or the bupivacaine group, will receive 20cc of bupivacaine hydrochloride on each side (40ccs total at each time point). In Group 2, patients will receive 20cc of normal saline on each side. Use of placebo is a standard control procedure in clinical trials and will allow for the assessment of unbiased quantitative data on the efficacy across all treatment groups.

	Study Drug *(per side)*
Group 1	20cc bupivacaine hydrochloride on each side
Group 2	20cc placebo (0.9% NaCl) on each side

Administration of the Study Medications
Trained anesthesiologists will use ultrasound guidance to administer the PIFB in the plane between the external intercostal and the pectoralis major muscles. The block will be given as an injection on both sides of the chest at the following periods:

Time Point	**Administration Protocol**
Immediate Postoperative Period	The study drug/placebo will be given within ***two*** hours of the patient entering the ICU. A total of 40ccs (20cc on left, 20cc on right) will be administered at this time point.
Postoperative Day 1	The study drug/placebo will be given ***between 9 and 11 am***. A total of 40ccs (20cc on left, 20cc on right) will be administered at this time point.

The patient, anesthesia provider administering the block, nurses assessing pain and the study team members will

all be blinded for the group. In case of an emergency the randomization can be obtained from the research pharmacy.

Standard Therapy (Usual Care)
All preoperative care and intraoperative management will follow the current standard of care in all study participants. The current standard analgesic therapy in the post-cardiac surgical patients comprises of nurse administered boluses of IV opioids (intravenous morphine or hydromorphone or fentanyl) or oral opioids such as oxycodone titrated to pain relief. All patients will receive bolus doses of IV opioids (morphine/fentanyl/ hydromorphone) or oral opioids (oxycodone) as needed for breakthrough pain, as is the standard of care.

Data Collection, Outcomes and their Measurement
Patient comorbid conditions, surgery and anesthetic drugs used will be obtained from the patient's medical record, the Society of Thoracic Surgery database and the Anesthesia Information Management System. Data related to primary and secondary outcomes such as pain scores, opioid doses, duration of stay and complications will be obtained from the medical records.

Pain is routinely assessed in the postoperative period by nurses on an 11 point scale (i.e. patients are asked to rate their pain on a scale of 0 to 10). This is typically assessed every 4-8 hours by nursing staff and is readily available on the patient's electronic medical records.

The total dose of opioids consumed in the 48 hours post-operative period will be obtained from the patient's medical records. This will be converted to morphine equivalents for standardization of the outcome and for ease of analysis.

Daily 3D CAM assessment will also be performed on the study subjects in order to assess whether or not they are delirious. This assessment takes approximately 5 minutes to complete. If daily assessments are negative for 3 consecutive days (i.e. days 5, 6 & 7), they will then be completed every other day until date of discharge. In addition, these assessments will be done at the patient's convenience to ensure ability to finish the evaluations.

Data will be collected and stored in REDCap or on password protected computers. Any data collected on paper will be stored in locked study offices or file cabinets.

Adverse Event Reporting
Our patient population is by definition undergoing high risk surgery and is therefore critically ill. It is expected that they will have a number of unrelated adverse health events during the course of their hospital stay. Therefore, we will limit the scope of our AE monitoring and reporting to the following:

- All Serious Adverse Events, including unexpected death, believed to be related to the study
- Unexpected, Non-serious Adverse Events believed to be possibly or probably related to the intervention, including the pre-specified list below:
    - infection
    - hematoma
    - local anesthetic systemic toxicity

Evidence for adverse events will be assessed daily during the hospital stay, for a maximum of four postoperative days, which well exceeds the half-life of the study drugs.

B. Statistical Considerations

Sample Size Justification: In this study and we are looking at the effect of a sternal block on cardiac surgery patients' opioid consumption in the first 48 hours postoperatively (primary outcome). Based on historical data of analgesic use from patients at BIDMC, the average use of morphine per day is approximately 12 mg, or 24mg in 48 hours. Using a two-sided alpha of 0.05, power of 80%, expecting a 50% reduction in opioid use and standard deviation of 18 mg, we would need 36 patients per group in order to detect a difference. As it is possible that some patients may withdraw prior to administration of the study drug, ***we will aim to enroll 80 patients (40 per group)*** to account for this potential drop out. Data from study will be used to adequately power a larger trial, based on the treatment effect seen in this study.

Data Analysis: Analyses will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) or later. Descriptive statistics of the data will be performed. Continuous data (age, pain scores, and opioid consumption) will be represented using mean (± standard deviation) or median (interquartile range) for variables not normally distributed and compared using parametric or non-parametric t-tests as appropriate. Categorical data such as the proportion of patients who successfully completed the study protocol will be presented as frequencies or proportions and analyzed using a chi-square or Fishers Exact test. Linear and logistic regression will be employed as necessary to adjust for potential differences between groups that persist after randomization. All two sided p-values < 0.05 will be considered statistically significant.

The primary outcome of the study, opioid consumption in the first 48 hours postoperatively, will be assessed by review of the medical record. Other secondary outcomes include:

- Pain scores
- ICU length of stay
- Hospital length of stay
- Incidence of complications (including infection, hematoma, local anesthetic systemic toxicity directly related to the block or the drug used in the block)
- Incidence of delirium throughout the post-operative period

Electronic data will be stored on password-protected computers behind the BIDMC firewall or in REDCap directly. Data will be analyzed by a statistician at BIDMC.

C. Subject Selection

Inclusion Criteria

- Patients 18 years of age or older
- Undergoing cardiac surgery with sternotomy, limited to CABG, CABG+valve surgeries and isolated valve surgeries.

Exclusion Criteria

- Current participation in another interventional study
- Preoperative LVEF < 30%
- Use of mechanical circulatory support
- Emergent procedures
- Aortic surgeries, transplants ventricular assist device insertions, bentall, or grafts
- Minimally invasive cardiac procedures or those with thoracotomy approach
- Patients receiving other modalities of regional anesthesia like intrathecal morphine
- Chronic opioid use for chronic pain conditions with tolerance (total daily dose of an opioid at or more than 30 mg morphine equivalent for more than one month within the past year)
- Current use of TCA, gabapentin, or pregabalin
- Hypersensitivity to bupivacaine
- Women who are pregnant or breastfeeding
- Non English speaking

Drop-out Criteria

Prior to initiation of any study medications, the following criteria will be assessed. If the patient meets any of the following they will be excluded from the study.

- Unable to meet the standard Fast Track Criteria postoperatively, as determined by the surgical and ICU Physician Assistants
- Hemodynamically unstable (defined as HR > 120, SBP < 80, MAP < 50 within 30 minutes prior to drug administration)
- Abnormal chest tube output (1000cc in 2 hours)
- Oxygenation outside of normal limits (defined as PaO_2 < 60mmHg on an FiO_2 of 1.0 or SpO_2 < 85% within 30 minutes prior to drug administration)
- Received an infusion or bolus ≥ 0.05 mcg/kg/min of epinephrine
- Received an infusion or bolus ≥ 0.50 mcg/kg/min of milrinone
- Received an infusion or bolus ≥ 0.20 mcg/kg/min of norepinephrine

- Significant clinician or nursing concern

We will enroll patients without regard to gender, race, or ethnic distribution.

B4. POSSIBLE BENEFITS

There are no guaranteed health benefits to the patient being included in this study. An improved understanding, and potentially information as to whether or not this medication can provide symptom relief, may improve comfort after cardiac surgery for other patients in the future.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Risk of Bupivacaine
Bupivacaine is an FDA approved medication for the current indication. Cardiotoxicity, which includes arrhythmias, hypotension, bradycardia and cardiac arrest, is less common when the doses used do not exceed toxic limits. In the intensively monitored setting of cardiac ICU, any signs of impending cardiotoxicity can be identified early and managed effectively. Bupivacaine systemic toxicity can also manifest as seizures, which is less common in the doses used in the study. Further, other central nervous system reactions include restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors. Despite this, bupivacaine is effectively used in regional anesthetic techniques and the advantages of effective analgesia in terms of better patient recovery seem to outweigh the risks.

Risks Associated with Block Administration
PIFB is a relatively superficial block and is devoid of complications like pneumothorax, especially when performed under ultrasound guidance. Infection secondary to the invasive procedure is rare because of the sterile aseptic precautions used to administer the block. There is a minor risk of hematoma associated with any regional block but the pecto-intercostal fascial plane is a relatively avascular plane and the use of ultrasound guided visualization further reduces the risk of hematoma.

Risk of a Confidentiality Breach
Any patient participating in a research study runs a small risk of breach of confidentiality. All study staff for this trial are well trained in HIPAA regulations and BIDMC confidentiality standards. Patient data will stored in locked cabinets and will be password protected computers on BIDMC network secure servers or in REDCap directly.

Risk/Benefit Ratio
The local anesthetic used in this study is approved by FDA for regional analgesia. When administered at recommended safe dosages and when monitored in the intensive care setting, the risks of local anesthesia systemic toxicity associated with bupivacaine are far too small compared to the benefits of decreased pain and enhanced recovery following cardiac surgery.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment
Prescreening will be accomplished by reviewing the operating room schedule and surgical consult lists. Patient medical records will be reviewed for inclusion and exclusion criteria. All patients who meet inclusion criteria with no exclusions will be approached in the cardiac catheterization holding area, PAT clinic, cardiac surgery clinic, or in the preoperative holding area for full written informed consent.

Consent
Written informed consent will be obtained prior to the scheduled surgery in a private, secure location. Consent will be obtained by one of the approved study team members. At the time of consent, all study procedures will be explained in detail, including the associated risks and benefits. The subjects will have the opportunity to ask any and all questions, and will be reminded that participation is voluntarily. All subjects will be consented with curtains drawn or the door closed, assuring patient privacy. Written informed consent will then be obtained prior to surgery and initiation of any research procedures. If a physician investigator is not available to meet with the proxy in person to obtain written consent, he/she will be available by phone for any questions. Another member of the study team, as approved by the CCI, will obtain consent on-site. This will be documented in a consenting memo.

The research staff undergoes a rigorous consent training process. Within the Center for Anesthesia Research Excellence (CARE) at BIDMC, this training includes: didactic sessions, mandated attendance at CCI/HSPO seminars related to the informed consent process, shadowing of informed consent in a variety of contexts, trainee-

led informed consent conversations with the aid of consenting checklists and accompanied by senior staff member and/or PI, robust feedback sessions, and clear communication when the team member is skilled enough to engage in informed consent discussions without direct supervision.

Subject Protection
It is unlikely that patients will be vulnerable to coercion or undue influence in this study. Patients will be informed that their decision to participate or not to participate will in no way affect their relationship with their health care provider. Patients have the ability to discontinue their participation at any time.

B7. STUDY LOCATION

Privacy
All efforts will be taken to ensure patient privacy. Patient interactions including consent will take place in private clinical settings with curtains/doors closed so as to provide privacy and comfort. Throughout the study, only the minimum required information will be collected, assuring patient privacy during the study protocol as with usual patient care. Data collection from chart extraction will occur only on password-protected computers secured by the BIDMC firewall or in REDCap directly. Data collected will be limited to only the minimum necessary to accomplish the stated research purposes.

Physical Setting
All patients will be enrolled at BIDMC. Consent will be obtained from eligible participants in the cardiac catheterization lab holding area, PAT clinic, cardiac surgery clinic, or in the preoperative holding area. Study procedures, including administration of the PIFB will be performed in the operating room, the subject's inpatient room in the intensive care units, or in the ward at BIDMC. Data will be abstracted from the patients' chart and will be stored on password-protected computers behind the BIDMC firewall or in REDCap directly. All data collected on paper will be maintained in locked study offices accessible to only the study team.

B8. DATA SECURITY

Data will be stored on password-protected computers behind the BIDMC firewall and entered into a computer database (REDCap). Computers and data collected on paper will be stored in locked rooms. For all analyses subjects will be identified only by their unique coded study ID number assigned for the sole purpose of this project. Limited information will be retained on patients who are prescreened and do not qualify, or who are approached and declined, for the purposes of generating a CONSORT diagram for the trial.

B9 Multi-Site Studies

N/A – Single Center Study

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Patients will be thanked for their time throughout the study. Because study results are likely to be published a few years after a given subject's participation, study investigators are concerned that mailing the published manuscript and an additional thank-you note years after participation risks violating subject privacy, as mailing addresses are increasingly likely to change with passing time. It is out of the scope of this study to continue tracking mailing addresses after study completion.

B11 References

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