Short Title
PIFB with Perineural Adjuvants for Postoperative Analgesia Following Sternotomy

Full Title
Pecto-intercostal Fascial Block with Perineural Adjuvants for Postoperative Analgesia Following Sternotomy in Patients Undergoing Cardiac Surgery

Principal Investigators
Scott Coleman, DO, FASE

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Summary/Purpose/Rationale

Multimodal pharmacologic therapy is a mainstay of postoperative analgesia for patients undergoing cardiothoracic surgery involving sternotomy. Diligent control of postoperative pain for patients following cardiac surgery is essential for promoting early mobilization and improved respiratory mechanics, as well as decreasing the incidence of delirium, myocardial oxygen demand, and risk of developing chronic pain[1]. Emerging evidence suggests that pain after cardiothoracic surgery falls into four distinct trajectories, with over 50% of patients reporting moderate to high pain even on the 30th postoperative day[2]. Several regional anesthesia procedures have demonstrated improvement in postoperative pain after median sternotomy but remain underutilized[3,4].

While thoracic epidural catheters confer visceral and somatic analgesia and have long been considered the gold standard for management of postoperative pain following cardiothoracic surgery, there are notable concerns involving systemic heparinization following epidural placement increasing the risk of epidural hematoma, with potentially catastrophic neurologic sequelae, as well as one of the more common side effects of hypotension from sympathetic blockade, which can be deleterious for cardiac patients in the immediate postoperative period[5,6]. For these reasons, the field of regional anesthesia has progressed to investigating more peripheral targets for nerve blockade that are distant from the neuraxis and more targeted to the specific drivers of surgical pain. Fascial Plane Blocks (FPB) have become a common approach to blocking afferent sensory innervation of the chest wall for patients undergoing cardiothoracic surgery involving sternotomy, including Pectoral (PECS) blocks, Serratus Anterior Plane (SAP) blocks, and Erector Spinae Plane (ESP) blocks[4,7]. The Pecto-Intercostal Fascial Block (PIFB) is one such approach that anesthetizes the anterior cutaneous branches of the second through the sixth intercostal nerves, which innervate the sternum and overlying soft tissue, by injection of local anesthetic in the fascial plane between the pectus major and internal intercostal muscles. The PIFB has been demonstrated to reduce postoperative resting and dynamic pain scores, postoperative opioid consumption, time to extubation, duration of intensive care unit (ICU) stay, and incidence of postoperative nausea and vomiting (PONV) in patients following cardiac surgery[8,9].

Perineural adjuvants are commonly used in peripheral nerve blocks (PNB) to extend the duration of analgesia, but they remain relatively understudied in FPB. Specifically, the glucocorticoid steroid dexamethasone, alpha-2 adrenergic receptor agonists dexmedetomidine and clonidine, and the opioid receptor agonists nalbuphine and buprenorphine have been used to varying degrees of success for extending the duration of PNB[10-15]. Extending the analgesic duration of single shot PIFB is highly clinically-relevant, given that catheter-based techniques require deploying foreign bodies close to the surgical field of the sternum bilaterally, which create an additional nidus for infection and become at risk of displacement due to surgical retraction during the procedure. The ideal analgesic FPB for patients undergoing cardiac surgery with sternotomy would involve a single-shot technique with long-lasting sternal coverage to confer resting and dynamic analgesia of the chest wall to promote improved respiratory mechanics, allow for earlier extubation, facilitate earlier patient mobilization, and reduce opioid consumption. For this block to appropriately match the postoperative timeline, it would ideally last upwards of 24 hours to include the time surrounding extubation, as well as early respiratory physical, and occupational therapy sessions.

Our group has previously demonstrated that the addition of perineural dexamethasone to long-acting local anesthetics in PNB increases the duration of analgesia that is not replicated with IV dexamethasone administration, as directly assessed by sensitivity to pinprick[10,16]. Clonidine is another commonly-used perineural adjuvant known to safely extend the analgesic duration of regional procedures and is well-tolerated in many of our PNB and FPB[12,17-19]. Epinephrine has long been used as a perineural adjuvant that extends analgesic duration of PNB by causing localized vasoconstriction that limits systemic uptake of local anesthetics and has an added safety benefit of being a marker of intravascular injection[20]. While concern has been raised about the potential toxicity of perineural adjuvants when studied *in vitro*[21], data from *in vivo* studies, as well as years of experience from our group have demonstrated safety and tolerability of perineural epinephrine, clonidine, and dexamethasone when used in the context of safe block performance techniques, such as appropriate patient selection with exclusion of those with pre-existing neurologic deficits, monitoring of injection pressure, and the addition of peripheral nerve stimulation to ultrasound guidance for blocks with motor nerve components[16,22].

Objectives

The purpose of this randomized, triple-blinded, prospective, feasibility study is to compare postoperative analgesia provided by PIFB when performed with local anesthetic solution with or without perineural adjuvants in patients following cardiac surgery involving sternotomy. We hypothesize that the patients receiving PIFB with bupivacaine with epinephrine, clonidine, and dexamethasone will have lower dynamic pain over the first 24 hours compared to those receiving PIFB with just bupivacaine and epinephrine. The primary outcome will be the 24 hour area under the curve (AUC) pain scores, based on patient-reported dynamic NRS pain scores with incentive spirometer (IS) use measured at 6, 12, 18, and 24 hours after block placement in patients that are extubated. We set a minimally clinical important difference (MCID) to be 10% for AUC pain scores with IS use. Secondary outcomes will include patient-reported NRS pain scores at rest at 6, 12, 18, and 24 hours after block placement; cumulative 24 hour opioid consumption; time to first postoperative opioid administration after extubation; time to extubation; duration of ICU admission; incentive spirometry volumes at 6, 12, 18, and 24 hours after block placement;

nausea incidence; vomiting incidence; postoperative delirium incidence; and patient-reported NRS satisfaction with the analgesic regimen.

Risks to Subjects

The PIFB has been shown to be a safe block, given its superficial target plane between the pectoralis major and internal intercostal muscles. Although the intended location is not intrathoracic, but rather, superficial to it, the relative proximity to the parietal pleura makes pneumothorax a potential risk of the PIFB. The transversus thoracis muscle is deep to the intended fascial plane and constitutes a safe "backstop" in case of needle advancement farther than intended, before arriving at the parietal pleura. The presence of the internal mammary arteries and veins, which reside in the deeper plane between the internal intercostal and transversus thoracis muscles, are also theoretically potentially at risk of needle puncture, although they are easily visualized and avoided during PIFB performance. Another FPB that similarly targets the anterior cutaneous branches of the upper intercostal nerves, called the Transversus Thoracis Plane (TTP) block, entails advancing the needle to this deeper plane, where the internal mammary vessels lie. Given the intrathoracic location of this deeper block, and attendant risks of pneumothorax and internal mammary vessel injury, our institution has opted to avoid TTP block placement, in favor of the PIFB, as the latter is generally regarded as a safer block. To date, there have been no incidences at our institution or in the literature of any identified pneumothorax or internal mammary vessel injury occurring as a result of PIFB placement.

The risks will be minimized by continuous, real-time, in-plane ultrasound guidance of our echogenic block needles only after identifying the correct anatomy, using color Doppler function on our ultrasound machine as appropriate to more readily identify vascular structures and avoid them. Blocks will be performed by anesthesiologists well versed in performance of the PIFB, or by trained anesthesiology residents or fellows directly supervised by them.

The use of local anesthetics always bodes a potential risk of local anesthetic systemic toxicity (LAST) as a result of systemic uptake from intravascular injection, rapid vascular absorption, or overdose of local anesthetic solution. We employ a multifaceted approach to minimize the risk of LAST by including local concentration and dose in the context of the patient's weight during the regional timeout procedure, using epinephrine as both an intravascular marker and local vasoconstrictor to limit systemic uptake of local staying below the recommended upper limit of local anesthetic dose of 3mg/kg for bupivacaine with epinephrine, and aspirating frequently, including before any injection of local anesthetic solution, and in between each aliquot of 5cc of local before proceeding with dosing. This study has an exclusion criterion such that minimum body weight must be above 50kg for inclusion, so that no patients in whom the prescribed local anesthetic dose would be higher than the recommended upper limit of bupivacaine dosing will be enrolled, as detailed below.

Methods/Measurements

Design

This will be a randomized, triple-blinded, prospective, feasibility trial that will take place after approval from our Institutional Review Board. Investigational New Drug Exemption has been obtained from the US Food and Drug Administration for use of the perineural adjuvants and is filed as FDA IND Exemption 165506. Written informed consent will be obtained from all study participants prior to randomization. This trial has been registered on www.clinicaltrials.gov as NCT05676814.

Selection Criteria

Inclusion: Adults between 18 and 90 years of age undergoing cardiac surgery involving sternotomy at Atrium Health Wake Forest Baptist, and who have consented to participate and lack any contraindications to PIFB for postoperative analgesia will be recruited for participation in the study.

Exclusion: Patients with any contraindications to regional anesthesia, such as history of allergy to amide local anesthetics or any of the perineural adjuvants; existing neurologic deficit in the chest wall; remaining intubated at the six hour point after block placement; weight under 50kg; undergoing emergency surgical procedures or urgent return to the operating room; active endocarditis or mediastinitis; moderate to severe right ventricular function before or after cardiopulmonary bypass; reliance on mechanical circulatory support devices, such as intra-aortic balloon pump or Impella; reliance on extracorporeal membrane oxygenation; localized or systemic infection; chronic use of high dose opioid analgesics (defined as daily use greater than 30 oral morphine milligram equivalents (OMME) for over one month prior to surgery); as well as those who are pregnant, will be excluded from participation. Intraoperative opioids will be limited to fentanyl, therefore patients who receive any other opioids will be excluded. Additionally, any administration of ketamine, methadone, and dexmedetomidine during intraoperative and postoperative settings will exclude the subjects from the study. Furthermore, postoperative administration of tramadol, NSAIDs, muscle relaxants, and Haldol will exclude the subjects from the study. Any patients who refuse enrollment or withdraw their consent will also be excluded and any of their information already collected will be destroyed.

Setting

Patients between 18 and 90 years of age, scheduled to undergo cardiac surgery involving sternotomy at Atrium Health Wake Forest Baptist will be screened for eligibility. These patients will be approached for enrollment by research staff either during their preoperative assessment clinic visit prior to their surgery date, or when admitted as inpatients and scheduled for surgery. During this visit, the study will be discussed in detail, and eligible participants will be offered the ability to ask any questions and sign consent forms at that time, or decide at a later time prior to surgery. Study staff will also review the surgical schedule and offer to call eligible participants to discuss the research study to determine their interest. At that time, if interest is shown, the consent will be emailed to them for review prior to their hospital admission to allow adequate time for consideration. Those subjects will then be seen on the morning of surgery to obtain a written informed consent. All patients will be provided with a signed copy of their written informed consent for their records.

Study Protocol

Baseline data collection
After time of consent, enrolled patients will be informed on the appropriate use of an incentive spirometer (IS), asked to rate their baseline verbal pain score both at rest and with use of an incentive spirometer (IS) on the eleven-point numerical rating scale (NRS: 0-10, where 0 represents no pain and 10 represents the worst imaginable pain). Maximum effort IS volumes will be measured in triplicate and averaged, and patient characteristics will be recorded, including age, gender, height, weight, BMI, ASA physical status classification score, surgeon, planned surgical procedure, as well as preoperative opioid use and doses.

Randomization
Subjects will be randomized on the day of surgery, specifically prior to the start of their procedure. Surgery will proceed as scheduled, and patients will be anesthetized and monitored per our usual cardiac anesthesiology practice with general anesthesia. At the end of the cardiopulmonary bypass circuit run, patients will be reassessed for the aforementioned exclusion criteria before the randomized block is placed. Patients will be blinded to their treatment arm assignment, as will all research personnel who be responsible for collection of outcome data, as well as the surgeons performing the cardiac procedure, and the critical care staff caring for the patients in the postoperative period. PIFB will be performed after skin closure and before transport from the operating room to the CVICU. For patients who are randomized at enrollment but later excluded due to exclusion criteria prior to block placement, their randomization assignment will be replaced at the end of the initial recruitment.

Interventions
Once the surgical team is finished with skin closure, bilateral PIFB will be placed by a faculty anesthesiologist well-versed in the performance of ultrasound-guided regional anesthesia and performance of PIFB blocks, or by a trained anesthesia resident or fellow directly supervised by them. This will be done by obtaining a longitudinal, parasagittal view of the costal cartilage 1-2cm lateral to the sternum at the level of the fourth or fifth rib and guiding a block needle in the cephalad direction in plane to the fascial plane between Pectus Major and Internal Intercostal muscles, with the goal of obtaining cephalad spread along the plane over multiple costal cartilage levels, as described previously[23]. PIFB will be performed bilaterally using a volume of 30cc of local anesthetic solution per side, with dosing in 5cc aliquots only after confirming aspiration is negative for blood and that a small aliquot of local solution demonstrates spread in the intended plane. We will repeat aspirations in between each aliquot of 5cc of local anesthetic, as is our standard practice, to monitor for intravascular needle position.

Patients randomized to the control arm will receive bilateral PIFB with a total of 60cc of 0.25% bupivacaine with 2.5mcg/cc epinephrine (1:400,000 dilution), and those in the experimental arm will receive bilateral PIFB with a total of 60cc of 0.25% bupivacaine with 2.5mcg/cc epinephrine (1:400,000 dilution), 1.67mcg/cc clonidine, and 0.1mg/cc preservative-free dexamethasone.

Patients will be monitored throughout block placement using standard ASA monitors including telemetry, heart rate, blood pressure, pulse oximetry, and end-tidal capnography. Following placement of bilateral PIFB, patients will be transported still intubated to the ICU with propofol infusion for sedation, as per institutional protocol for routine postoperative care.

As is our current practice, patients will be managed with ICU nursing-administered titrated boluses of IV fentanyl for analgesia before extubation based upon signs of nociception, including hypertension, tachypnea, facial grimace, and motor agitation. Patients will have as-needed doses of oxycodone and/or hydromorphone ordered for analgesia after extubation, unless they have a contraindication or allergy, in which case a suitable alternative at equianalgesic doses will be ordered.

Materials

Ultrasound guidance for imaging the relevant anatomy will be obtained using a linear ultrasound probe. All PIFB will be performed in a sterile manner, using sterile gloves, sterile ultrasound probe cover, sterile short-bevel block needle, and skin cleaning using an aseptic cleaning solution prior to placement. All products used are FDA-approved for the above-mentioned procedures, and an Investigational New Drug (IND) exemption has been obtained for use of the study medications used in this protocol under FDA IND165506.

Measurements

The time of block placement will be documented as the zero hour time point for the purposes of measurements. As described above, to collect data for the primary outcome, research staff will elicit patient-reported NRS pain scores with use of incentive spirometry at 6, 12, 18, and 24 hours post block placement. If patients are not yet extubated at the 6 hour point, they will be excluded from the study as mentioned above. Research staff will also collect data for secondary outcome measures including, but not limited to: eliciting resting NRS pain scores at 6, 12, 18, and 24 hours after block placement; measuring incentive spirometry volumes in triplicate at 6, 12, 18, and 24 hours; measuring the time after extubation to first opioid administration; time to extubation; duration of ICU admission; calculating incidence of nausea and vomiting based on the administration of the antiemetics ondansetron, metoclopramide, prochlorperazine, and promethazine; assessing delirium based on bedside ICU nurse documentation using Confusion Assessment Method in the ICU (CAM-ICU) in the first 24 hours post block placement; and measuring patient-reported NRS satisfaction with the analgesic regimen at the 24 hour point (0 represents completely unsatisfied and 10 represents completely satisfied).

For the NRS pain scores and measurement of incentive spirometer volumes at each 6, 12, 18, and 24 hours interval, there is a grace period of 1 hour. This is to give the research staff/ ICU nurse the flexibility of completing these tasks.

The cumulative 24 hour opioid consumption will be abstracted from the EMR. All opioids will be converted to oral morphine milligram equivalents (OMME) to allow for appropriate comparison using a widely available dose conversion table. These metrics will be accessed, abstracted, de-identified, and analyzed by research personnel who are blinded to group allocation.

There will also be a 30-day post-block phone call follow-up for ongoing opioid use/last use, such as frequency and dosage, and pain levels in their day-to-day activities.

Statistical Analysis

Power Analysis

We define a minimum clinically important difference (MCID) to be a 10% reduction in area under the curve for our primary outcome. Given that no current data exist on the anticipated duration of PIFB with perineural adjuvants at our institution, we have decided to recruit 10 patients per arm for a total of 20 patients in this feasibility trial. Based on prior studies involving the use of perineural adjuvants with long-acting local anesthetics, we have noted an average duration around 20 hours for peripheral blocks performed at other sites with bupivacaine containing perineural adjuvants epinephrine, clonidine, and dexamethasone. We have therefore chosen 24 hours as the final time point, with serial checks starting at 6 hours post block placement to represent clinically important pain trajectories for patients recovering from cardiac surgery with sternotomy.

Data Analysis

Demographic information will be collected as mentioned above and compared between the groups to verify that randomization balanced important baseline variables between the control and experimental groups. For the primary outcome of AUC pain scores with use of incentive spirometry for the first 24 hours post block placement, we will compare mean and standard deviations of the overall integrated area under the curve using the trapezoid rule. For secondary outcomes with continuous variables, such as intubation or ICU duration, t-tests and confidence intervals will be calculated. For continuous variables with serial measurements, repeated measure analysis of variance (RMANOVA) will be used. Further assistance with statistical analysis is being elicited from the Clinical and Translational Science Institute (CTSI), and this IRB protocol will be updated with further details after final review with a statistician.

Missing Data Points

Missing data points for the primary outcome will be imputed by a mixed effects modeling framework that allows us to use all available data points to tests hypotheses about differences between the two groups at each time point. Models will be implanted using the ‘lme4’ package in R statistical software.

Human Subjects Protection

Subject Recruitment Methods

Potential candidates for the study will be identified based on the posting for the surgical procedure of cardiac surgery involving sternotomy as mentioned in the inclusion criteria as above, provided they lack any of the exclusion criteria. Patients will be approached during their preoperative assessment clinic visit, via telephone call, or during their inpatient admission if they are scheduled for surgery the following day, and told about the study in detail, including any known or possible risks, benefits, and alternatives. They will be advised there will be no

financial incentive to participate, but potential benefits may include reduced surgical pain for the first 24 hours postoperatively. Written informed consent will be obtained and scanned into the EMR during that visit, if they consent, or on the day of surgery, if they need more time to deliberate on enrolling. Ample opportunity to ask questions will be given both during this preoperative visit and on day of surgery. All patients meeting the aforementioned eligibility criteria, regardless of gender, age, race, and ASA physical status, will be offered to participate.

Informed Consent

Confidentiality and Privacy

Confidentiality will be protected by collecting only the requisite information required to assess the study outcomes, minimizing the collection of any information that could directly identify subjects. Each patient will be assigned a unique study identifier that will appear on the data collection form, and any protected health information that may directly identify the patient corresponding to the unique study identifier will be kept secure with access limited to designated study personnel. Following collection of all data, subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous data set for analysis. All patient information collected will be kept confidential during recruitment as well as the remainder of the study. All identifying protected health information will be de-identified in the electronic database during data collection, which will be encrypted and secured in the Atrium Health Wake Forest Baptist private servers and only accessible by two-factor authenticated, password-protected computers. Only selected research personnel who are specifically enrolling patients or collecting or analyzing data will have access to the dataset. No reference to any individual participant will appear in reports, presentations, or publications that may arise from this study.

Data and Safety Monitoring

The principal investigators will be responsible for overall monitoring of the data and safety of study participants and will be assisted by other members of the research personnel in the identification of any safety concerns.

Reporting of Unanticipated Problems, Adverse Events, or Deviations

Each participating attending anesthesiologist will report to the principal investigators about any protocol violations, unanticipated problems with the protocol, or adverse events, which will promptly be reported to the IRB and corresponding government agency, if appropriate.

Resources/Citations

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