Official Title: Pain Control with Regional Anesthesia following Pediatric Cardiac Surgery: A Randomized Double-Blinded Pilot Study

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Standard Research Summary

Purpose of the Study

Overall Aim: The overall objective of this study is to characterize the analgesic effect of a novel combination of bilateral Pecto-Intercostal Fascial Blocks **(PIFBs)** and a unilateral Rectus Sheath Block (**RSB**) in pediatric patients undergoing primary septal defect repairs. The *central hypothesis* is that together, bilateral PIFBs and a unilateral RSB provide superior pain control, reduce postoperative opioid use, and improve postoperative recovery compared to surgeon-delivered local anesthetic wound infiltration.

Aim 1. Assess postoperative pain intensity and opioid use in the first 48 hours after surgery. Patients will receive a standardized protocol-driven postoperative pain regimen in the Pediatric Cardiac Intensive Care Unit (PCICU). *Working hypothesis: PIFB/RSB-treated patients have statistically lower postoperative pain intensity and opioid use in the first 48 hours after surgery vs patients who receive local anesthetic infiltration. Expected outcome*: The analgesic effect of the proposed intervention will be greater than that of the control group.

Aim 2. Assess outcomes associated with improved postoperative recovery as defined by consensus guidelines for pediatric acute pain clinical trials (PedIMMPACT).

2A: Evaluate outcome measures associated with postoperative physical recovery. Early extubation, multimodal pain regimens, and prevention of postoperative nausea and vomiting are key metrics of ERAS protocols in children undergoing cardiac surgery. *Working hypothesis: Within the framework of a standardized ERAS protocol, PIFB/RSB-treated patients have earlier functional recovery compared to the control group. Expected outcome*: PIFB/RSB-treated patients will have a decreased time to mobilization and enteral intake, earlier removal of lines and drains, and shorter hospital length of stay.

2B. Evaluate additional measures of postsurgical recovery that are part of a comprehensive pediatric acute pain clinical trial. In addition to pain intensity and physical recovery, core outcome measures for pediatric acute pain trials include global satisfaction with treatment, emotional response to pain, adverse events (AEs), and economic factors. *Working hypothesis: Parental and patient satisfaction, the emotional response to pain, and unexpected AEs may also influence patient recovery*. *Expected outcome:* Comprehensive data on the effect of the intervention can be obtained based on consensus guidelines for pediatric acute pain clinical trials.

Outcomes Aim 1
Primary outcome: Opioid use in OMEs/kg during the first 12 hours after surgery
Secondary outcomes: 1) Opioid use in OMEs/kg at 3 additional time points: > 12 to 24 hours, > 24 to 48 hours and total during the first 48 hours after surgery 2) Pain intensity during the first 48 hours after surgery, as measured by averaging individual patient pain scores at 3 times points: within the first 12

hours, > 12 to 24 hours, and > 24 to 48 hours after surgery using developmentally appropriate assessment tools.

Outcomes Aim 2 (Exploratory)
Aim 2A Outcomes
Length of hospital stay (hours) defined by time of PCICU admission to time of discharge. Physical recovery outcomes from time (h) of PCICU admission to: 1) mobilization, defined as first time out of bed; 2) enteral intake, defined as ³50% of meal consumed by mouth; 3) removal of indwelling chest tube and arterial line.

Aim 2B Outcomes
1) Global patient and parental satisfaction with pain management and inpatient care; 2) emotional response in patients ³ 12 years of age 3) direct hospitalization costs 4) pain intensity 3 months after surgery; and 5) adverse events (AEs).

Background & Significance

Pediatric cardiac surgery patients are highly sensitive to hemodynamic and metabolic changes. Lack of compensatory mechanisms for pain-related tachycardia, hypertension, and tachypnea may lead to devastating post-surgical outcomes. Therefore, adequate pain control in this population is essential to ensure timely convalescence, particularly in the first 12 hours after surgery, when pain has been reported to be the highest.

The critical need for optimal acute postoperative pain control, ongoing development of evidence-based ERAS protocols in congenital cardiac surgery, and recognition that prolonged neuropathic pain may occur following sternotomy in children, have led to widespread interest in multimodal pain management strategies. In particular, regional anesthesia (specifically fascial plane blocks) for post-sternotomy pain has become routine practice in both adults and pediatric patients at many institutions. Commonly used fascial plane blocks include the Pectoral Nerve Blocks (ie, PECS1 and PECS2), Erector Spinae Plane Block (ESPB), Transversus Thoracic Plane Block (TTPB, also referred to as the deep parasternal intercostal nerve block), and the Pecto-Intercostal Fascial Block (PIFB, also referred to as the superficial parasternal intercostal nerve block).

Of these blocks, the 2 most studied in children undergoing cardiac surgery are the ESPB and the TTPB. There are 5 single center randomized controlled trials (RCTs) (3 ESPBs and 2 TTPBs) that include a cumulative total of 353 patients (TTPB: n = 174, ESPB n = 179), with half randomized to the control group. Ninety percent of patients in these studies underwent primary septal defect repair (n = 318). The results of these trials, regardless of block type, show significant decreases in opioid requirements and improved pain control in the postoperative period.

However, these prospective studies suffer from numerous limitations including 1) comparison to placebo with no active comparator (sham blocks only); 2) technical disadvantages of block placement; 3) no analgesia for chest tube pain; and 4) lack of relevance to contemporary practice of extubation in the OR for septal defect repairs. None of the trials compared block interventions to routinely used surgeon-administered local anesthetic infiltration; therefore, it is not possible to determine the strength of the analgesic effect of these interventions relative to current practice. Further, for block placement, the ESPB requires the patient to be moved into the lateral decubitus position, while the TTPB is performed in close proximity to the internal mammary artery due to its location within this plane, lung tissue and other deeper mediastinal structures. In addition, none of these studies have evaluated the analgesic response to a combination of block techniques addressing both sternotomy and chest tube pain. Finally, all 5 trials were performed in pediatric cardiac programs with varying extubation strategies and postoperative sedation requirements, potentially reducing generalizability.

The PIFB/RSB intervention proposed here has advantages over the TTPB and the ESPB. The PIFB effectively blocks the anterior cutaneous branches of the intercostal nerves in a superficial plane between the pectoralis major and the external intercostal muscles, and it can be performed efficiently in the supine position. It is an ultrasound-guided block with a specific well described fascial plane target and cannot be performed in the field by surgeons. Three recent prospective RCTs (cumulative total n=218 patients) in adult patients have demonstrated that bilateral PIFBs improves post-sternotomy analgesia, as denoted by lower pain scores and parenteral opioid administration in the first 12-24 hours after surgery. One study showed decreased time to extubation and length of stay in the hospital and ICU, and another reported that the average time of placement was 6 min.

We postulate that the proposed combination of regional anesthesia techniques will improve pain control, decrease opioid use, enhance recovery, increase satisfaction, and decrease costs in children undergoing septal defect repairs at our institution. If effective, this intervention may be reproduced at other centers and applied broadly for use for patients eligible for early extubation after pediatric cardiac surgery. Within the context of expanding ERAS protocols, the **impact** of this research will provide strong preliminary evidence to incorporate these pilot study results into enhanced recovery programs for pediatric cardiac surgery patients around the country.

Design & Procedures

We will conduct a single center, prospective, randomized, double-blind clinical trial with an active comparator arm. Subjects will be randomized 1:1 to either fascial plane blocks or surgeon-administered local anesthesia wound infiltration using randomization tables generated by The Biostatistics Group within the Department of Anesthesiology. Each subject will be assigned the next number.

Perioperative Care:
Anesthesia and surgical care will not be altered for this study except for randomization to the study intervention group. Oral or IV midazolam for anxiolysis may be given at standard dosing. Inhaled sevoflurane or intravenous agents will be administered at the anesthesiologist's discretion to induce general anesthesia.

Intraoperative Opioid Management: Since 2018, we have used a standardized weight-based intraoperative methadone protocol for all pediatric cardiac surgeries at our institution. This study will follow this well-established protocol. All patients will receive a dose of 0.1 mg/kg of methadone administered at 3 time points during the procedure: on induction of anesthesia, on incision, and on initiation of cardiopulmonary bypass (given to the perfusionist to administer). Per protocol, additional doses of 0.05-0.1 mg/kg methadone may be given at the discretion of the anesthesiologist following separation from bypass, up to 0.4 mg/kg total during the case. No patients will receive additional supplemental opioids intraoperatively.

Intervention: At the end of the procedure prior to extubation, the following interventions will be administered using 0.2% ropivacaine. *Local infiltration group*: The surgeon will infiltrate the wound and skin around the sternotomy and chest tube site with 1.5 mL/kg per routine practice. *Regional group*: The patient will remain draped and in the supine position with the sterile field preserved. With ultrasound guidance, the anesthesiologist will inject 0.5 mL/kg bilaterally in the superficial parasternal intercostal plane at the level of the fourth costal cartilage. Patients whose height is > 125 cm will receive 2 injections per side at the third and sixth levels of the costal cartilage (0.25 mL/kg per injection per side). Using 0.5 mL/kg, an RSB will be performed on the side ipsilateral to the chest tube. The maximum volume of ropivacaine administered at all 3 sites will be 1.5mL/kg (3 mg/kg). We will use ropivacaine for this study because of its safety profile relative to bupivacaine. Liposomal bupivacaine is not approved by the Food and Drug Administration (FDA) in children < 6 years of age.

Following application of the surgical site dressing, all patients will be awakened from anesthesia, extubated in the operating room and transported to the PCICU.

Postoperative Care:
Pain Management: All patients will be managed postoperatively in the PCICU according to a standardized medication protocol that includes both opioids and scheduled acetaminophen and NSAIDs. Opioids: All children will receive morphine 0.025-0.05 mg/kg IV every one hour as needed (q1 hour IV pro re nata (PRN)) for the first 12-18 hours. Patients will only have 1 active IV PRN order, if additional break through medication is needed to treat pain beyond q1 hour dosing, a provider must be alerted to order additional medication. Following the initiation of enteral feeding (solids), patients will transition to oxycodone 0.1 mg /kg q6 hours PRN. At this time, morphine will be spaced to q3 hours PRN for break through pain. Opioid administrations will be based on assessments with validated pain scales.[34-35] Non-opioid adjuvants: All patients will receive scheduled non-opioid adjuvants including acetaminophen 15 mg/kg q6 hours (IV initially, then PO) and ketorolac 0.5 mg/kg q6 hours (for 48 hours) then ibuprofen 10 mg/kg q8 hours, throughout the hospital admission. NSAIDs will be used if the subject is greater than 6 months, platelet count is > 100,000/microliter, and creatinine is normal.

Management of PONV: All patients will be managed according to a standardized antiemetic protocol. Children > 12 years of age will receive a scopolamine patch preoperatively which will be continued for 72 hours. Patients > 3 years of age will receive 0.1 mg/kg of ondansetron q8 hours scheduled for 24 hours followed by PRN dosing.

Post Discharge: All patients will receive a IRB approved phone call at 3 months (± 2 week) after surgery to ask 4 questions (phone script uploaded) about the patient's ongoing medication use and pain as well as whether the subject required readmission or additional prescriptions.

Surveys: To collect data on global and treatment satisfaction and emotional response, we will use the following validated surveys:
1. Global satisfaction with inpatient hospitalization: CAHPS Child Hospital Survey (Child HCAHPS) will be completed by parents of all subjects[37]
2. Parent pain management satisfaction: American Pain Society Patient Outcomes Questionnaire – Modified (APS-POQ-M) will be completed by parents of subjects < 12 years[38-39]
3. Subject pain management satisfaction: The Pediatric American Pain Society Patient Outcomes Questionnaire (Pediatric APS-POQ) will be completed by subjects >=12 years[40]
4. Subject emotional response to pain: Adolescent Pediatric Pain Tool (APPT) will be completed by subjects >= 12 years[41]
For children >= 12, they will complete surveys 3 and 4 and parents will complete survey 1.
For children < 12, parents will complete surveys 1 and 2.

Selection of Subjects

Inclusion criteria (IC): All children (< 18 years of age, no lower age limit required) having primary isolated septal defect repair via sternotomy with signed, informed consent by a parent or a legal guardian. Subjects ³ 12 years of age must assent to participate. Post pubescent females must have a negative pregnancy test within 48 hours of surgery.

Exclusion Criteria (EC): 1) Patients on opioid therapy at the time of surgery 2) history of sternotomy 3) planned postoperative intubation, and 4) current diagnosis of a chronic pain syndrome.

If a consented subject can not be extubated in the OR, he/she will not receive a block or local infiltration and would be considered a screen failure.

Subject Recruitment and Compensation

Patients will be screened and properly identified by the principal investigator or member of the clinical research team via an IRB-approved review of the surgery schedule. An IRB-approved phone call may be conducted to introduce the study or patients may be approached on the day of surgery allowing sufficient time for explanation, questions and answers. If interested, parents or legal guardians may provide consent for the study in advance via an IRB-approved electronic Informed Consent Form or a paper consent may be obtained on the day of surgery.

Goal recruitment is 60 subjects to complete the study. Subjects will be compensated $20 gift card (mailed) for the time and effort to complete the surveys and phone call on day 30 after surgery.

Subject's Capacity to Give Legally Effective Consent

Parental/guardian permission will be sought first for study enrollment. In the case that subjects are 12 years and older, patient assent for enrollment in the study will then be obtained. If <12 years of age, only parental/legal guardian consent will be obtained for patient participation.

Study Interventions

The study related treatment is not investigational. Ropivacaine is a standard of care medication being used at standard doses.

Risk/Benefit Assessment

Recruitment and Informed Consent: The study will be conducted under appropriate Duke University IRB protocol and consent form approvals. The study will be conducted under the supervision of the PI, who is a Board-Certified pediatric anesthesiologist (Einhorn) with experience conducting clinical trials in children. Potential subjects will be identified through IRB-approved review of the surgical schedule prior to their surgery, at which time they will be contacted and asked if they are interested in participating. An IRB-approved phone screen will be conducted. Subjects that wish to participate may sign paper consent on the day of surgery when allowing sufficient time for explanations, questions and answers. If interested and willing, subjects may also be fully consented using IRB approved eICF. Informed consent must be given and signed by parents and/or legal guardian. Children greater than or equal to 12 years of age must provide verbal assent to be in the study.

Risks:
The safe and effective use of local anesthetics depends on proper dosage, correct technique, adequate precautions and readiness for emergencies.

Side effects of ropivacaine: dizziness, blurred vision, tinnitus, lightheadedness, pins and needles sensation, hypotension, nausea, vomiting, bradycardia.

Major peripheral nerve blocks may result in the administration of a large volume of local anesthetic in highly vascularized areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption, which can lead to high plasma concentrations.

The safety and efficacy of Naropin in pediatric patients have not been established.

Protections against Risk:
a) Dosing of local anesthetics has been established and these blocks have a track record of safety in pediatric patients with published peer reviewed data in the literature

b) Research subjects will receive pre-operative, intra-operative and post-operative monitoring by anesthesiology, pediatric cardiac critical care intensivists, advanced practice providers and nursing staff.

c) The risk of breach of protected health information will be minimized by limiting the number of people within the research group who have access to identified data which will be described in the data monitoring safety plan.

Potential Benefits:
Regional blocks may decrease the need for additional opioids in the immediate period after surgery, decrease possible side effects related to opioids, improve immediate postoperative pain relief and decrease the occurrence of chronic postsurgical pain.

Successful completion of this research is expected to result in improved pediatric surgical care, enhanced patient recovery, and optimized pain management.

Costs to the Subject

There will be no costs to subjects for participation in the study.

Data Analysis & Statistical Considerations

Sample Size Analysis: We have calculated that a sample size of 60 total patients provides > 80% power to detect an effect size (Cohen's d) of 0.9 with a significance level of $\alpha = 0.05$. For our primary outcome, opioid use during the first 12 hours postoperatively, a larger effect size of approximately 1.1 has been documented in our previous retrospective observational study, but a smaller effect size was chosen to allow for potential residual confounding. Based this primarily data, this effect size would correspond to a reduction in OME of approximately 0.32 mg/kg. The same retrospective study reported an estimated difference in LOS of 22 hrs with a pooled standard deviation of 24.4 hrs, corresponding to a Cohen's d of 0.9. For the secondary outcome of pain intensity, a Cohen's d effect size of 1.1 was demonstrated in our preliminary work, corresponding to a difference in pain scores of 1.7 points. In summary, our planned sample size of 60 patients provides 80% power to detect an effect with a Cohen's d effect size of 0.9, which is consistent with effect sizes seen in our preliminary data for opioid utilization, length of stay, and pain intensity.

Planned Data Analysis: Descriptive statistics for each treatment group will be computed for patient demographic and characteristic variables. Since our randomization scheme will have balanced the age effect between treatment groups, we anticipate that the demographic and patient characteristic variables will be balanced across groups. For the primary and secondary continuous outcome measures including opioid use, pain scores, time to mobilization, time to enteral intake, time to removal of chest tube and arterial line, and length of stay, we will conduct two-sample *t*-tests to determine the difference in means (e.g., OME difference) between treatment groups. For continuous exploratory outcomes, including patient and parent satisfaction, hospitalization costs, pain 3 months after surgery, and emotional response, groups will be compared using Wilcoxon Rank-Sum tests. For the categorical exploratory outcome of adverse events, chi-square or Fisher's exact tests will be applied as appropriate. Results with $p < 0.05$ will be considered statistically significant. Point estimates and 95% confidence intervals (CIs) for the difference in means will be reported for all continuous outcomes, and odds ratios and associated CIs will be reported for categorical outcomes.

The Duke Children's Pediatric and Congenital Heart Center is the 10th largest pediatric and congenital heart program in the country. In order to recruit 60 patients during the 1-year grant period, we would need 60% enrollment. We believe this is feasible for our study because 1) the intervention is low-risk, 2) the surveys are brief; there are no painful procedures (blood draws); and follow up requirements are minimal; 3) the surgeons and PCICU team strongly support the study; 4) the research environment is robust, well established, and dedicated to clinical trial work; and 5) the study team is led by a well-supported PI and an experienced mentor who have successfully worked together on a prior pediatric pain RCT.

Data & Safety Monitoring

Data are collected and stored via REDCap. The REDCap servers are securely housed in an on-site limited access data center managed by the Division of Biostatistics. All web-based information transmission is encrypted, and the data is stored on a private, firewall protected network. No identifiable data will be stored on personal computers or laptops. Data will be exported from REDCap for statistical analysis with patient identifying information removed. The consent form, medical information, and case report forms will be stored under lock and key (office, file cabinet) and only the PI, physician investigators, and research team will have access.

As noted above, all patients will receive continuous invasive monitoring postoperatively in the PCICU as per standard of care. Local anesthetic doses are standardized and chosen to prevent local anesthetic systemic toxicity (LAST). We have completed over 100 of these blocks in this population since June 2021. There has been no concerns of LAST and this regional block was specifically chosen to avoid a fascial plane with large blood vessels; however, in a suspected case of LAST, Intralipid 20% would be given as per standard protocol with weight based dosing. Signs and symptoms of LAST typically occur in the first 1-5 minutes after delivery of local anesthetic; therefore this rare complication would likely occur while the patient is still in the operating room.

Any potential study related AE will be immediately reported to the PI, study team, CRU practice managers, and IRB.

Unblinding Procedures:
Emergency Unblinding is appropriate in the unlikely situation of a medical emergency (as determined by the PI or treating physicians, APPs) where knowledge of the treatment allocation is likely to have a significant effect on the clinical management of the enrolled subject and would be instrumental in immediate treatment decisions. In an emergency, it may not be feasible to obtain prior approval from the PI. Unblinded research staff, the attending surgeon, and attending anesthesiologist are all unblinded in this study. The contact information for these individuals as well as the PI will be available at the bedside for the medical care team if emergency unblinding is required. In this case, after the subject is successfully unblinded, there must be clear documentation explaining why unblinding was necessary. The PI, IRB, and Research Practice Manager will be notified as soon as possible.

Accidental Unblinding: If a subject is accidentally unblinded, clear documentation of events must be recorded, as well as communication with the PI and Research Practice Manager. An accidental unblinding may occur if an unblinded study research staff member or unblinded surgeon/anesthesiologist/OR nurse accidentally shares information with the blinded care team or parent. The treatment assignment must not be revealed to any other members of the study staff, pharmacy staff, or to the subject, unless written approval from the study sponsor is obtained. Every effort should be made to maintain what remains of the blind. In this case, a protocol deviation should be reported to the IRB of record.