Paravertebral Nerve Blocks in Neonates and Infants Undergoing Repair of Aortic Coarctation, A Pilot Study

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Study Title: Paravertebral Nerve Blocks in Neonates and Infants Undergoing Repair of Aortic Coarctation, A Pilot Study

Short Title: Paravertebrals

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Abstract

Repair of aortic coarctation is a commonly performed operation. The repair is performed via thoracotomy which is a surgical incision that is commonly complicated by atelectasis, desaturation, and pain in the adult population. To prevent these complications, it has been shown that regional or neuraxial anesthesia can decrease the amount of pain the patient has, which allows for deeper breathing and fewer desaturations from atelectasis. We propose, in this study, to examine the benefits of paravertebral peripheral nerve block in the neonatal and infant populations. Regional anesthesia has the potential to decrease narcotic requirements in children undergoing painful operations, decrease ventilator time, and manipulate the stress response to surgery. [1] [2] [3]

One of the most severe morbidities associated with this operation is paraplegia. Paraplegia during this operation is thought to occur from decreased spinal cord perfusion, either during the cross-clamp period (the period when then aorta is clamped to allow for the repair to occur) or from compromised blood flow as a result of the repair. Though it is not typical to monitor spinal cord perfusion during repair of aortic coarctation, there is evidence that spinal cord perfusion can be monitored with near infrared spectroscopy (NIRS), a non-invasive light probe that measures regional oxygen saturation. [4]

The study population for this project will include neonates and infants (less than 1-year-old) who are undergoing repair of aortic coarctation via thoracotomy with no other simultaneous surgical procedure. The patients will undergo a standardized anesthetic. Patients in the experimental arm will receive a paravertebral nerve block for intraoperative and postoperative pain control supplemented with narcotic as needed while the control arm will receive standard of care, which will include additional narcotic as indicated and local anesthetic infiltrated into the wound after the procedure. Each group will have their spinal cord regional saturations measure with NIRS. Regional anesthetic techniques in children are relatively low risk endeavors and the primary concern is risk of regional block failure. More significant, but very rare complications could include local anesthetic systemic toxicity (LAST), tissue hematoma (bleeding), epidural hematoma (bleeding), unintentional epidural spread, and prolonged sensory blockade. [5]

The primary aim of this study is to determine the feasibility of studying whether a single-shot paravertebral nerve block is effective in providing intraoperative and postoperative pain control in infants undergoing a thoracotomy for coarctation of the aorta. This will be determined by comparing morphine equivalent consumption in the standard of care and intervention groups. Secondary outcomes include plasma epinephrine levels (three times per patient) to determine stress hormone response in both groups, NIRS values to monitor the difference in spinal cord oxygen supply between the intervention and control group, time to first feeding (another measure of pain control in this age group), and total ventilator time.

The following aims are proposed:

Primary Aim

1. Determine the feasibility of studying whether total narcotic administration is less in subjects who receive the peripheral nerve block versus standard of care.

Hypothesis: Patients undergoing the experimental technique, paravertebral nerve block, will have less pain and therefore will consume fewer morphine equivalents in the 48-hour post-op follow-up period. This difference will be measurable and provide sample size estimations for future studies.

Evaluation Method: All narcotics used in the 48-hour post-op period will be tabulated and converted to morphine equivalents. Other non-narcotic analgesics will also be tabulated, but can't be converted to morphine equivalents.

Secondary Aims

2. Measure whether spinal cord perfusion can be improved during aortic cross clamp by improving collateral blood flow with regional anesthesia techniques.

Hypothesis: Near infrared spectroscopy (NIRS) values will decrease in the control and study group during aortic cross clamp but values in the study group will be 41% higher than control due to increased collateral blood flow.

Evaluation Method: Continuous measurement of spinal cord NIRS values during repair of aortic coarctation, including the aortic cross clamp period.

3. Determine the total time required for post-op ventilation in each group.

Hypothesis: Post-op ventilation times will be lower in those patients undergoing the experimental technique, paravertebral nerve block, because these patients will have less respiratory splinting from better analgesia and be less sedated from less sedative and analgesic use.

Evaluation Method: Time until extubation.

4. Determine the time to first feeding in each group.

Hypothesis: Patients who undergo the experimental technique, paravertebral nerve block, will have earlier return to feeding since they will have better analgesia and less sedation from narcotics.

Evaluation Method: Time until first feeding.

5. Measure stress response to surgery in the experimental and control groups.

Hypothesis: Patients who undergo the experimental technique, paravertebral nerve block, will have better suppression of the natural stress response to surgery.

Evaluation Method: Plasma epinephrine levels measured at baseline (before incision), postoperatively (just before transfer to the Intensive Care Unit), and 24 hours postoperatively.

Introduction, Background, and Significance to Our Mission

Repair of aortic coarctation is a commonly performed operation. The repair is performed via thoracotomy which is a surgical incision that is commonly complicated by atelectasis, desaturation, and pain in the adult population. To prevent these complications, it has been shown that regional or neuraxial anesthesia can decrease the amount of pain the patient has, which allows for deeper breathing and fewer desaturations from atelectasis. We propose, in this study, to examine the benefits of paravertebral peripheral nerve block in the neonatal and infant populations. Regional anesthesia has the potential to decrease narcotic requirements in children undergoing painful operations, decrease ventilator time, and manipulate the stress response to surgery. [1] [2] [3]

Pain remains a significant concern in the neonatal and infant populations. There is evidence that pain is often undertreated in order to accomplish other goals of medical management including earlier extubation. Furthermore, pain control with narcotic medications are an additional concern and withdrawal from narcotics can become an issue in those neonates and infants requiring long-term administration of these medications. Therefore, further study into alternative methods of pain control are warranted.

Significance:

Specific Aim #1:
Use of paravertebral nerve block in these patients may improve pain control for these patients and decrease the total burden of narcotic administered.

Specific Aim #2:
Use of regional anesthesia to encourage collateral blood flow may be spinal cord protective as evidenced by an improvement in the NIRS during aortic cross clamp in the experimental group.

Specific Aim #3:
Decreased time to extubation may be made possible in the experimental group, which would help to prevent ventilator associated complications including barotrauma, pneumothorax, pneumomediastinum and ventilator associated pneumonia.

Specific Aim #4:
Decreased time to first feeding may be facilitated by earlier extubation and less sedation in the experimental group.

Specific Aim #5:
Decreased stress response to surgery is generally associated with fewer physiologic perturbations and may be facilitated by the use of regional anesthesia compared to the standard of care group.

Experimental Design and Methods

Design:

This study is designed to be a prospective, randomized, non-blinded clinical trial. After informed and written parental consent, a total of 30 neonates and infants (<1 year old) will be enrolled. Subjects will be assigned to nerve block or SOC in a 1:1 ratio. Random treatment assignment

will be accomplished using a permuted block design with random block sizes of 2 or 4. Randomization will be done by study statistician using SAS v. 9.4 (Cary, NC).

Study Population:

A total of 30 neonates and infants, defined as children less than 12 months of age, will be enrolled in this study. The subjects will be scheduled for elective or semi-elective cardiac surgery at Children's Healthcare of Atlanta.

The following criteria will be used to determine patient eligibility:

Inclusion Criteria:

- Neonate or Infant (<12 months age) at the time of surgery
- >=2.5 kg at the time of surgery
- Undergoing aortic coarctation repair via left thoracotomy
- Parent or legal guardian willing to participate, and able to understand and sign the provided informed consent

Exclusion Criteria:

- Intubated prior to surgery (patients who have been intubated and subsequently extubated may be included)
- Ongoing septicemia or localized skin infection on the back
- Parent or legal guardian unwilling to participate or unable to understand and sign the provided informed consent
- Known coagulation defect
- Allergy to local anesthetics

Enrollment/Consent process:

The Institutional Review Board will approve informed consent documents prior to commencement of the study. Only those patients who meet the entry criteria will be considered as possible study candidates. A thorough discussion between the parents or legal guardian and the principal investigator, or the study coordinator will occur during the study consent process. No study related procedure will occur prior to obtaining appropriate informed consent.

All participants in this study will be neonates or infants (<12 months old). Patients will be enrolled consecutively as they present to Children's Healthcare of Atlanta. The parents or legal guardian of the neonate will be approached on the day prior to surgery or at presentation to the preoperative evaluation clinic by the investigators or the study coordinator to discuss the goals, benefits and risks of the project. Written informed consent will be obtained following this discussion. For the occasions when parents do not arrive at the hospital until the day of surgery, they will be approached only if there is sufficient time to allow for their full consideration.

Study Description:

Participants in the study will be randomized to the control arm or experimental arm using computer-generated random assignment, which will be prepared at the start of the study and the assignments held in sealed envelopes. Once the participant is enrolled in the study and consent has been obtained the investigator will open the next consecutive sealed envelope which contains the patient's group assignment (experimental or control). If the participant is enrolled in the study and randomized to the experimental procedure an informed consent for treatment must be signed. This is the standard of care for this type of procedure.

Participants in the control arm will undergo an anesthetic consistent with the standard of care. The patient will be induced for anesthesia with propofol 3mg/kg or ketamine 2mg/kg (if there is intravenous access) or sevoflurane with 1 mcg/kg of fentanyl and 1.2 mg/kg rocuronium once IV access is established. The patient will be intubated; intravenous and intra-arterial access will be obtained and the patient will be positioned for surgery. A NIRS pad will be used for cerebral oximetry as well as another NIRS pad for spinal cord oximetry. Fentanyl may be used as needed for additional analgesia and anesthesia will be maintained with sevoflurane. The skin will be infiltrated at the conclusion of surgery with less than 1 mL/kg of 0.25% bupivacaine with epinephrine 1:200k. The patient will be returned to the ICU intubated unless the anesthesia provider considers them to be an excellent candidate for early extubation. Every patient will have an epinephrine level drawn pre-incision in the operating room, post-operatively upon arrival to the intensive care unit, and 24-hours post-operatively (unless there is no existing vascular access that allows the level to be drawn 24-hours post-operatively). The 24-hour post-operative time point will be defined as 24-hours after arrival to the CICU.

Participants in the experimental arm will undergo an anesthetic that includes the regional anesthetic technique, paravertebral nerve block. The patient will be induced for anesthesia with propofol 3mg/kg or ketamine 2mg/kg (if there is intravenous access) or sevoflurane with 1 mcg/kg of fentanyl and 1.2 mg/kg rocuronium once IV access is established. A NIRS pad will be used for cerebral oximetry as well as another NIRS pad for spinal cord oximetry. The patient will be intubated, and then will be positioned laterally for the nerve block at approximately the left T3-4 level. A 13-6 MHz, linear ultrasound probe with a sterile sheath will be used to provide imaging for the paravertebral nerve block. A Pajunk SonoPlex 50mm, 22 gauge, facet tip needle will be used. The injected solution will be 1 mL/kg of 0.2% ropivacaine with 5 mcg/mL (1:200k) epinephrine. Ropivacaine is a standard drug used in this patient population for regional nerve blocks and is non-experimental as part of this protocol. The paravertebral block needle insertion site and sterile field will be observed and the block will be performed or supervised by one of the study investigators. Fentanyl may be used as needed for additional analgesia and anesthesia will be maintained with sevoflurane. The skin will not be infiltrated with additional local anesthetic at the conclusion of the case. Every patient will have an epinephrine level drawn pre-incision in the operating room, post-operatively upon arrival to the intensive care unit, and 24-hours post-operatively (unless there is no existing vascular access that allows the level to be drawn 24-hours post-operatively). The 24-hour post-operative time point will be defined as 24-hours after arrival to the CICU.

Post-operative pain control in either the control or experimental (paravertebral nerve block) group will be accomplished with intravenous, rectal, and oral analgesics. Patients will receive scheduled rectal acetaminophen while intubated and oral acetaminophen once they have progressed to oral intake of formula. Intravenous fentanyl or morphine will be used for

breakthrough pain while intubated and until oral intake is tolerated. Once oral intake is resumed, the patient will be provided with oral oxycodone as needed for pain and additional doses of IV morphine as needed for severe pain.. If the patient is not yet ready for extubation and requires additional sedation, intravenous doses of midazolam may be required.

Sample Size/Statistics

This protocol is designed as a pilot study with limited-efficacy testing. The primary goal is to demonstrate the feasibility of a subsequent randomized clinical trial. In doing so, we will assess the capacity for recruitment and caregiver consent to random assignment. An additional exploratory aim is to evaluate the preliminary efficacy of using a single-shot paravertebral nerve block to decrease perioperative morphine consumption. Because this is a pilot study, the proposed study is likely underpowered to detect a statistically significant result. However, the results (i.e. effect sizes) from this study will be used in sample size and power calculations for a future, larger RCT. We expect that there will be a trend toward lower morphine equivalent consumption in the experimental group that will either reach statistical significance or provide a better estimation of necessary sample size for future funding from extramural sources.

The most similar study available for comparison examined the use of paravertebral nerve catheters in infants undergoing thoracotomy to repair long-gap esophageal atresia. This study was retrospective and several days of morphine consumption were observed. In this retrospective trial of 17 patients, the authors observed a decrease of 36% in morphine consumption per day ($p<0.001$).[6] If such a dramatic decrease in morphine consumption is observed during our prospective study, then it is adequately powered at current sample size 15 in each arm, total 30 patients.

Descriptive statistics will be calculated for all variables of interest and include means and standard deviations, medians and ranges or counts and percentages, as appropriate. Summary measures will be tabulated overall and by treatment group. Recruitment and consent rates will be calculated with associated 95% confidence intervals. Primary and secondary outcomes will be compared between the two intervention groups. Continuous measures will be compared between groups using two-sample t-tests or Wilcoxon rank-sum tests while categorical variables will be compared using Chi-square tests or Fisher exact tests. Because this is a pilot study, effect sizes will be calculated for all outcomes and will include difference in means, difference in rates, or risk ratios with associated 95% confidence intervals. Analysis will follow the intention to treat principal where all subjects are analyzed based on their randomly assigned treatment whether or not they received the treatment. A p-value less than 0.05 will be considered statistically significant and all statistical testing will be two-sided, unless otherwise noted. Analysis will be conducted using SAS v. 9.4 (Cary, NC) and under direction of the pediatric biostatistics core.

Adverse Event Reporting

Monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs) is an important aspect of data collection. The study subjects will be reviewed on a case-by-case basis. The principal investigator will determine the seriousness of each adverse event and whether or not the event

was related to the study. Adverse events potentially associated with paravertebral nerve blocks include (from most to least common): block failure, vascular puncture, deep tissue hematoma (SAE), epidural hematoma (SAE), hypotension, lung puncture, pneumothorax, and local anesthetic systemic toxicity (SAE). Hypotension will be defined as a mean arterial pressure less than 30 mm Hg during the first 24 hours after arrival to the CICU.

Generally, paravertebral nerve blocks are felt to be safe in the pediatric population. They have an adverse event rate comparable to other regional anesthesia blocks, less than is reported with thoracic epidural analgesia. The incidence of local anesthetic toxicity is 0-0.015%, paresthesia 0.004-0.17%, and infection 0-0.5%. Overall, Vecchione *et al* report a major complication rate of 1 per 2,390 paravertebral nerve blocks and a minor complication rate of 13.2%, largely associated with catheter malfunctions rather than single-shot paravertebral nerve block complications.[7] Pneumothorax has only been reported in adult literature and basically becomes irrelevant in the setting of thoracotomy (as pneumothorax cannot develop during an open chest procedure). [8] There has also been publication demonstrating efficacy of paravertebral nerve block catheters in infants who need long-term mechanical ventilation after long-gap esophageal atresia repair with no significant morbidity related to paravertebral nerve block catheter placement. [6]

After enrollment, the principal investigator or designee will collect the adverse experiences from the medical record. Serious Adverse Events (life-threatening, requiring intervention) will be reported to the IRB within guidelines set by the IRB.

The amount of blood drawn for this study should not affect the transfusion requirements of the surgical procedure (total 6mL per patient). Standard of care will be followed for all lab draws to ensure there is no increased risk of infection from phlebotomy.

Data Safety Monitoring Plan

A potential risk of this study is related to patient confidentiality since protected health information is included in the study data. This risk will be minimized by only recording information absolutely necessary to fulfill the study's objectives. Information directly identifying patients will be excluded (names, addresses, telephone numbers, social security numbers, e-mail addresses, and account numbers). Once lab samples are collected, they will be identified only by the study number assigned to the patient. Additionally, in the research database, patients will be identified only by their assigned study number. The database, along with the code linking a subject's identity to an assigned number, will be locked in the office of the principal investigator or designee.

The study subjects will be reviewed on a case-by-case basis by the entire pediatric cardiac anesthesia division and pediatric cardiac surgery division in a weekly quality conference. Quarterly, experienced cardiac anesthesiologists not involved in the study will review each study subject's reported adverse events and assess whether or not the event could be related to the study.

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