Prospective Randomized Trial: Pain Management after Pectus Excavatum Repair, Epidural vs PCA

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Protocol Version: 4.0 **Protocol Date:** 06/11/2019

1. STUDY OBJECTIVES/HYPOTHESIS

Primary Objective(s)

The objective of this study is to scientifically evaluate two different management strategies for post-operative pain after pectus excavatum repair.

The hypothesis is that pain management without an epidural decreases hospital stay without compromising comfort.

The primary outcome variable is length of hospitalization after the intervention.

2. BACKGROUND & RATIONALE

Pectus excavatum, the most common chest wall deformity, occurs in roughly one in 1000 children.[1] Operative repair of the anterior thoracic concavity has transitioned to the minimally invasive approach with substernal bar placement through small axillary incisions (Nuss procedure and multiple modifications). These procedures were quickly incorporated by high volume centers around the world including our own.[2-7] The operation is certainly quicker and associated with less blood loss than the open operation, but as opposed to most minimally invasive versions of an operation, patients do not leave the hospital sooner after bar placement and experience more post-operative pain.[6,7,8]

Pain during the post-operative hospital stay is the dominant management issue after bar placement. The sparse literature on the topic has suggested that a thoracic epidural is the most effective means for attenuating the pain during the first few post-operative days.[10-12] Therefore, most centers approach all patients undergoing a pectus deformity repair with an attempt at epidural placement under the assumption that this provides the most effective strategy for pain control.[3-9,13]

However, we conducted a retrospective evaluation to examine the validity of this assumption and to investigate whether there is a role for a prospective study to determine the optimum post-operative pain management of these patients.[14] We found length of stay was shorter with PCA and pain scores were similar. What we found certainly challenges the assumption that an epidural is the optimum management for these patients, and

convincingly answered the question as to whether there is a role for a prospective randomized trial.

We conducted the prospective, randomized trial in 110 patients.[15] We found the pain scores were better with epidural for the first 2 days and better with PCA the last 2 days. There was no difference in length of stay although it trended to favor PCA. Epidural group incurred far greater operation times and charges. The pragmatic interpretation was that we should just use PCA. The anesthesia interpretation is that we need a better epidural. Therefore, we have developed a better protocol for the transition to try to improve pain control the last 2 days. Further, we recognize several flaws in the last study; we included patients at extremes of age which don't represent a normal course. Second, we kept patients in the hospital until they had a bowel movement which may have prolonged the care unnecessarily in the PCA group. We will use the same sample size as last time since the difference in length of stay we were designed to detect was more than a day which is clinically relevant.

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3. STUDY DESIGN

This will be a multi-institutional, prospective, randomized clinical trial involving patients who undergo the minimally invasive repair of a pectus excavatum deformity with bar placement. This is intended to be a definitive study.

In epidural and PCA groups, the anesthesia protocols for premedication, induction and maintenance will be controlled to ensure uniformity across treatment groups.

Preoperatively, patients will receive either oral (0.5mg/kg up to 20 mg) or intravenous (0.025 - 0.05 mg/kg up to 4 mg) midazolam for anxiolysis prior to surgery or epidural placement under sedation. Oral midazolam will be administered 15 - 30 minutes prior to anticipated arrival to the operative room whereas intravenously midazolam will be given immediately prior to transport for surgery. General intravenous anesthesia will be induced using lidocaine (1-2mg/kg, max 100 mg), propofol (2-5 mg/kg, max 300 mg), and endotracheal intubation facilitated with rocuronium (0.6-1 mg/kg, max 60 mg) or vecuronium (0.1 mg/kg, max 10 mg). During surgery, anesthesia will be maintained using isoflurane or sevoflurane in 30%-50% oxygen. Intraoperative hypotension (defined as mean arterial pressure < 50 mmHg) will be treated with boluses of Lactated Ringers or Plama-lyte solution (10-20 ml/kg), phenylephrine (1-2 mcg/kg, max 100 mcg/dose) and/or ephedrine (0.05-0.3 mg/kg, max 10 mg/dose). At surgery conclusion, patients will receive the antiemetic ondansetron (0.1-0.15 mg/kg; max 4mg) and residual muscle paralysis will be antagonized if needed with neostigmine (50mcg/kg, max 5 mg) and glycopyrrolate (10 mcg/kg, max 1 mg).

Postoperatively, patients in both study arms will receive ketorolac 0.5 mg/kg (maximum dose 30 mg) every 6 hours for the first 96 hours postoperatively (16 doses total). Upon completion of scheduled ketorolac doses, ibuprofen (10 mg/kg, max 600mg) will be scheduled every six hours until hospital discharge. Oral or intravenous acetaminophen (15 mg/kg, max 1g) will be scheduled every 6 hours (IV form will only be used while patients not tolerating PO) throughout the study period. Patients with postoperative emesis or nausea will be treated with ondansetron (0.1-0.15 mg/kg; max 4mg). An intravenous infusion of naloxone (1 mcg/kg/hr, max 100 mcg/hr) will be routinely ordered for both groups as prophylaxis against narcotic induced side effects and will be discontinued when patients transition to oral analgesics. Pruritis will be managed by the administration of po or IV diphenhydramine (0.5-1.0 mg/kg; max 50 mg) and/or naloxone (1-2 mcg/kg, max 100 mcg/dose). In addition, oral or intravenous valium will be available as needed for anxiety or muscle spasm (0.05-0.1 mg/kg, max 5 mg) every 6 hours. All patients will be started on Miralax, (17g in 8oz water or juice) and Colace (100mg) by mouth every day beginning the day after surgery.

PCA Group
In the PCA arm, patients will receive fentanyl (2-5 mcg/kg, max 250 mcg) at anesthesia induction. Additional fentanyl may be administered intraoperatively as indicated hemodynamic response to surgical stimulation (greater than 20% increase in heart rate or systolic blood pressure) from baseline. Patients who are $\geq$ 35 kg (in keeping with current FDA approved labeling) will receive a clonidine 0.1 mg/day transdermal patch to the deltoid immediately after induction of anesthesia and 1-1.2 mcg/kg (max 100 mcg) of clonidine IV prior to surgical incision. Upon arrival to the post anesthesia care unit, patients will be placed on a patient controlled analgesic (PCA) pump (hydromorphone: loading dose (given intraoperatively or on arrival to post-anesthesia care unit (PACU)) 10-20 mcg/kg (max 2 mg); 4-5 mcg/kg (max 300 mcg) continuous infusion; 4-5 mcg/kg (max 300 mcg) six minute demand dose). An additional nurse-administered hydromorphone dose (8mcg/kg, max 500 mcg) will be available every 2 hours for pain scores of > 4/10 throughout the duration of PCA use. Patients will also receive clonidine 1.5 – 1.7 mcg/kg (max 150 mcg, 3 doses total) orally every eight hours for the first 24 hours post-operatively to account for the slower onset time of transdermal clonidine. Patients will be converted from PCA to an oral regimen (see below) when tolerating a full-liquid diet. The oral regimen will consist of extended-release oxycodone (Oxycontin) 10mg initiated every 12 hours. For reported pain scores > 4, the dose will be increased by 10mg with each subsequent dose, up to a max of 40 mg. Oxycodone 0.05-0.15 mg/kg (max 10 mg) every 3 hours will be available for breakthrough pain.

Epidural Group
The epidural study arm will be structured in the following manner. Upon arrival to the operating room, patients will have a thoracic epidural (T 6-8) placed. If for any reason, the anesthesiologist feels that an "awake, sedated" epidural placement is not optimal for a particular patient, the epidural will be placed after induction of general anesthesia, as is also standard practice in our operating rooms. All epidural catheters will be inserted 3-5 cm within the epidural space and will be placed by attending anesthesiologists. Patients will receive midazolam (0.025 – 0.1 mg/kg IV, max 5mg) and/or fentanyl (0.5 – 2 mcg/kg IV, max 150 mcg) in divided doses for comfort during the procedure. Once the epidural is placed, the patient will be positioned for surgery. After confirming the absence of blood or cerebrospinal fluid upon epidural catheter aspiration, the anesthesiologist will administer a 0.1 ml/kg (max 3 ml) test dose of lidocaine (1.5%) with epinephrine (1:200,000); patients will be observed for a hemodynamic or electrocardiographic response to rule out an intravascular injection and an unintentional intrathecal injection will be ruled out by lack of an extensive sensory block and/or hemodynamic data. The epidural catheter will be initially bolused with 0.3ml/kg of ropivacaine 0.20% (max 5 ml), fentanyl (1 mcg/kg, max 100mcg) and clonidine (1.5 - 2mcg/kg, max 100 mcg). An infusion of ropivacaine 0.20%, fentanyl 2 mcg/ml and clonidine 1.5 mcg/ml will be initiated immediately at the rate of 0.3ml/kg/hr (max 8ml/hr). Intraoperatively, patients will receive intravenous fentanyl if indicated by a hemodynamic response to surgical stimulation (greater than 20% increase in heart rate or systolic blood pressure) from baseline.

Once the patient has awoken in the PACU, a sensory level will be assessed (using ice in standard fashion) by the recovery room nurse. If an inadequate sensory level is obtained, catheter efficacy may be tested with 1-2% lidocaine (max 5 ml), or catheter may be pulled back 1-2 cm (for unilateral block) by the attending anesthesiologist in PACU. The postoperative epidural infusion will be started in PACU: 0.3 ml/kg/hr 0.2% ropivacaine, 2 mcg/ml fentanyl and 1.5 mcg/ml clonidine (max 8 ml/hr basal rate), 0.05 ml/kg (max 3 ml) bolus available every 20 minutes (hourly max including basal 14 ml/hr); maximum ropivacaine dose will not exceed 0.4 mg/kg/hr. Patients with breakthrough pain refractory to epidural boluses will receive appropriate intravenous narcotics (hydromorphone 5-10 mcg/kg, max 500 mcg/dose) IV every six minutes) to establish pain control and the narcotic doses administered in the recovery room will be tracked.

Once transferred to the inpatient unit, patients with refractory pain despite using the maximum allowable dosing may have epidural catheter efficacy interrogated as in the PACU by the attending anesthesiologist on the Acute Pain Service. Patients with breakthrough pain refractory to an epidural bolus will receive appropriate intravenous rescue narcotics at same dosing as PACU. At any point if the epidural is felt to be not working, with no discernable epidural level, the epidural will be discontinued and the patient placed on a PCA. This will not influence their group assignment.

Epidural catheters will be discontinued on the third postoperative day. Upon discontinuation of epidural medication, patients will be administered a single dose of intravenous methadone (0.1 mg/kg, max 5 mg). They will also receive the same oral regimen as the PCA group: extended-release oxycodone (Oxycontin) 10mg initiated every 12 hours. For reported pain scores > 4, the dose will be increased by 10mg with each subsequent dose, up to a max of 40 mg. Oxycodone 0.05-0.15 mg (max 10 mg/dose) every 3 hours po will be available for breakthrough pain. If they are not adequately comfortable after 24 hours, they may be started on a PCA per the same protocol of the other treatment arm.

After operation, the patients will undergo chest x-ray and transfer to a hospital bed on the surgical service after recovery per routine where they are allowed to rest in bed the day of surgery. This is a floor status bed. This is current clinical standard practice as is the remaining clinical care outlined below here in section K.
Post-operative day 1, all patients will be asked to attempt ambulation and/or get up to a chair when ambulation is not feasible.
The patient in both groups will have a Foley catheter placed in the operating room. In the PCA group, this will be removed when the patient is ambulating and beginning to require fewer narcotics. In the epidural group, this will be removed 4 hours after the catheter is discontinued except when the catheter is removed early due to dysfunction in which case the removal criteria will be the same as the PCA group.
Oxygen therapy will be weaned to discontinuation on the basis of persistent oxygen saturation levels at or above 92% as determined by standard pulse oximetry.
Diet will be advanced as tolerated.

Patients will be discharged from the hospital when they have transitioned to oral pain medications only with adequate pain control and have adequate oral intake to not require intravenous support.

Patients and parents will be asked to complete a pain evaluation questionnaire on the day of discharge.

4. TARGET STUDY POPLUATION SPECIFICS

Patients who are scheduled for a pectus excavatum repair via the minimally invasive technique will be considered. Informed parental permission/patient assent or patient consent will be obtained by a named individual on this IRB form prior to the operation. After permission/assent is obtained, the randomization sequence will be utilized to define patient treatment.

We are asking for 121 patients to be sure of obtaining 110 who will complete the study.

- Inclusion Criteria

Patients undergoing a pectus excavatum repair with bar placement.

Exclusion Criteria

- Open repair
- Re-Do operation
- Known allergy to a pain medication in the protocol
- Existing contraindications to epidural catheter placement
- Requirement for 2 bars to be placed (rare)

5. DATA COLLECTION

Data Collection Procedures

The primary outcome variable is the post-procedure number of days until the patient meets discharge criteria.

Secondary outcomes variables include total time in the operating room, time in the operating room from patient entry to incision, time to urinary catheter removal, time to regular diet, time to removal of oxygen support, amount of narcotic pain medication taken, time to transition to oral pain medications, pain and sedation scores after the operation, wound infections, revisions, procedure charges, anesthesia charges, hospital charges, total charges and pain survey results.

Prior to the intervention, age, sex, height and weight, and Haller index will be recorded.

During the intervention, success of epidural, technique used, anesthesiologist, total time in the operating room, time in the operating room from patient entry to incision, and operative time will be recorded.

After the intervention, length of stay, time to urinary catheter removal, number of days on PCA or epidural, time to regular diet, time to removal of oxygen support, nature of oxygen therapy, maximum daily temperature, time to beginning transition to oral pain medications, time to complete transition to oral pain medication, rest and maximum pain scores on exit from the PACU and each 12 hour interval (am and pm) after the operation, prn antiemetic and antipruritic use, wound infections, revisions, calls to Anesthesia and Surgery, reason for the call and intervention provided, procedure charges, anesthesia charges, and hospital charges will be recorded.
Upon follow-up, time until oral narcotics were no longer required will be recorded. This will terminate their involvement in the study.

Parents and patient will be asked to complete a pain survey on the day of discharge.

Records to be kept

Information will be collected on a data collection sheet (attached) and stored in a password protected database/spreadsheet. A master linking list will be maintained that links the subject's medical record number with their study number. This will include medical record number, pt name and date of consent.

Secure Storage of Data

The research record generated will consist of an excel sheet. Only the data points listed in the attached data collection sheet will be entered into the research record. Security measures include: storage of the excel sheet on a password protected computer in a restricted assess departmental folder limited to only study personnel listed.

6. STUDY DURATION/STUDY TIMELINE

Unknown at this time as rates of pectus surgeries varies greatly.

7. STATISTICAL CONSIDERATIONS

Power calculations based on the known length of hospitalization listed above with $\alpha = 0.05$ and power of 0.8 show the need for 55 patients in each arm. The primary end point will be reached during the hospital stay therefore we expect a very small amount of attrition and will intend to recruit 110 (while asking for 121 subjects to ensure 110 complete the study).
One group will undergo an attempt for epidural regional analgesia (epidural) for post-operative pain control. The other groups will receive patient controlled intravenous systemic analgesia (PCA).
Both groups will have the same management algorithm.

All data will be analyzed on intention-to-treat basis

8. HUMAN SUBJECTS (Note the text in this section are examples only)

Institutional Review Board (IRB) Review and Informed Consent

This protocol, and any subsequent modifications, will be reviewed and approved by the Pediatric IRB at The Children's Mercy Hospital & Clinics.

Potential subjects will be determined by Surgery's schedule of pectus operations. Once general eligibility is determined, potential subjects will be approached by study staff. Subjects will be approached in pre-operative clinic or at the time of surgery. If a researcher considers it appropriate, final permission/assent agreement may be obtained by phone within a few days of surgery. Prior to drawing any blood or performing any other procedures related to this study, the permission/assent form or consent form will be reviewed carefully with the participant (and parent) in person.

Subject Confidentiality

Linking List Example: All records will be kept in a locked file cabinet. Human subject's names will be kept on a password protected database and will be linked only with a study identification number for this research. There are no patient identifiers recorded in the research record. All computer entry and networking programs will be done using study identification only. All data will be entered into a computer that is password protected. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the OHRP, the Sponsor, or the Sponsor's designee. Data will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study.

Waiver of Consent at Age 18

We are requesting a Waiver of Consent at Age 18. The fact that the subject turns 18 during the study does not substantially change the risks or benefits of the study as they were originally presented to the subject and parents during the initial Permission/Assent process. Furthermore, study activities for subjects that have turned 18 are limited to chart review and data collection of previously received medical treatment. This ongoing chart review data collection was described in the Permission/Assent form signed during study enrollment, and the continuation of such data collection after the subject turns 18 remains consistent with the procedures described during the Permission/Assent process. No additional patient contact or procedures for this study are involved after the age of 18.

Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the Sponsor, the OHRP, the FDA or other Government agencies as part of their duties to ensure that research subjects are protected.

9. PUBLICATION OF RESEARCH FINDINGS

Unknown at this time