Bilateral Continuous Erector Spinae Blocks for Post-Sternotomy Pain Management: A Single Arm Interventional Study.

NCT04567407

10/25/2021

Boston Children's Hospital

CHeRP IRB Additional Protocol Information:

In addition to the CHeRP SmartForms, all protocols must include the following sections. If a section is not applicable for the current protocol please indicate why this is the case. Please note that a complete protocol consists of the CHeRP forms and the information provided in this form.*

TITLE:

Bilateral Continuous Erector Spinae Blocks for Post-Sternotomy Pain Management: A Single Arm Interventional Study.

A. Specific Aims/Objectives:

Overall Aim: To evaluate the efficacy of bilateral continuous erector spinae blocks (BESB) for postoperative analgesia in children and adolescents undergoing cardiac surgical procedures via sternotomy in the Early Recovery After Surgery (ERAS) program in a single arm, open label, interventional study.

Specific Aims:

1. Evaluate the utility of BESB in cardiac surgical patients by assessing the pain scores, opioid consumption, and complications related to BESB.
2. Compare intra- and postoperative opioid use in patients receiving BESB vs. matched historical controls who did not receive BESB in the ERAS program.
3. Compare clinical outcomes between the 2 groups: duration of mechanical ventilation, time to mobilization, pain scores (median pain score per period), intensive care unit length of stay (LOS), incidence of postoperative nausea and vomiting, postoperative complications, hospital LOS, readmissions, mortality, recovery to baseline activity and sleep post discharge, total and rescue opioid pain medication requirements.
4. Evaluate quality of sleep and activity with (Fitbit™) smart watch device of patients receiving BESB during the postoperative period.

Hypothesis: The investigators hypothesize that BESB is efficacious with respect to pain control and will lead to a 15% or greater reduction of consumed opiate equivalents at 12, 24 and 48 hours, and the 24-hour period preceding both 72 and

96 hours postoperatively compared to matched historical controls who received standard of care pain management (systemic opioid therapy).

B. Background and Significance:

Regional anesthesia—and pediatric regional anesthesia in particular—is a rapidly evolving subfield of anesthesia practice driven with considerable urgency by the growing recognition that even appropriate perioperative opioid administration can have significant deleterious long-term effects[1].

Regional anesthetics can provide targeted, continuous analgesia to select dermatomes with minimal additional patient risk and as such, have become routine components of opioid-sparing intraoperative and postoperative pain management plans for non-cardiac surgical patients at BCH. In addition to the postulated benefit of reducing overall opioid exposure (and potentially reducing the risk for long term physiologic and behavioral dependence upon opioids), regional anesthetics may allow for earlier extubation after selected surgeries, shorter intensive care unit (ICU) stays, shorter inpatient admissions, earlier mobilization, fewer gastrointestinal complications, and improved patient and care team satisfaction scores.

Historically, regional anesthetics have been avoided in cardiac surgery as most patients are pharmacologically anticoagulated during their procedures and are thus at increased risk for bleeding. [2-5] This is particularly worrisome in the pediatric cardiac surgical population as many of these children remain intubated for an extended period of time postoperatively and therefore may not have reliable neurological exams in the setting of neuraxial regional anesthetics—potentially resulting in unrecognized hemorrhage-related acquired neurological deficits.

Recently, the erector spinae block (ESB) has become popular for providing analgesia after a number of anterior chest and abdominal procedures.[7-10] This simple interfascial plane block can reliably provide unilateral chest and/or abdominal wall analgesia.[11] It has been described in numerous case reports and case series as an effective block for management of unilateral thoracotomies, unilateral rib fractures, unilateral abdominal incisions and most notably, for management of post-sternotomy pain when applied bilaterally.[12,13] New case reports and series involving the ESB are being published almost weekly with a growing number of manuscripts specific to cardiac surgical applications.[14,15] Indeed, numerous randomized controlled trials have investigated the analgesic efficacy of bilateral erector spinae plane blocks (BESB) compared with

conventional treatment for pain after cardiac surgery in adult patients and have been published recently (2018-2019) with promising results.[16]

As an interfascial plane block in a compressible anatomical space, the ESB is considered safe in anticoagulated (or recently anticoagulated) patients.[17] It is fast becoming a preferred anesthetic option at BCH for anticoagulated patients - as opposed to neuraxial (e.g. epidural) and paraneuraxial blocks (i.e. paravertebral) nerve blocks, which are largely contraindicated in this setting. Further, given its relative ease of placement, apparent efficacy and safety profile, it is increasingly becoming a standard option for patients undergoing a wide range of thoracic, abdominal and thoraco-abdominal procedures.

We are fortunate at BCH to have the largest pediatric cardiac surgical program in the United States. We also have an active, and well organized regional anesthesia service. We are in a unique position to more thoroughly evaluate the effectiveness and safety of regional anesthetics in children following cardiac surgery. Furthermore, we feel it is critical that institutions such as BCH take a leading role in documenting the effects of regional anesthesia on the most important outcome measures when considering perioperative medicine. These include: overall pain management, surgical healing, functional recovery, long term pain symptoms, and emotional/behavioral outcomes after surgery.

Indeed, given these considerations, our group recently investigated the feasibility of performing these blocks bilaterally in a pediatric cardiac surgical population undergoing sternotomy-based procedures (IRB-P00031524). At the conclusion of this 10-patient pilot, our group found that performing these blocks was technically feasible, requiring 30 minutes or less of OR time, resulting in no known complications. Furthermore, our data suggested an approximate 25% reduction in rescue opioid requirements in the first 48 hours amongst the erector spinae group ($p=0.048$).

During the short time required to complete our pilot study, several additional adult studies of improved size and quality have been published demonstrating favorable outcomes with this block for a variety of indications, including post-sternotomy care. As such, it has effectively become an accepted practice in the larger community and here at BCH as well, with surgeons, anesthesiologists, and families frequently requesting an ESB (unilateral or bilateral) as a part of the care they either provide or receive. We believe we have reached a point of clinical equipoise in relation to the existing standard of systemic opioid therapy and seek to evaluate the relative efficacy of this technique in a pediatric cardiac surgical population at BCH.

In order to best evaluate the efficacy of this block in the pediatric cardiac population, a blinded, randomized and controlled trial would be ideal. However, given that randomization could be challenging and the fact that blinding would not be feasible, we believe an observational prospective cohort study is most appropriate at this time.

As such, we propose to evaluate the comparative efficacy of BESB versus matched historical controls who received standard of care pain management (systemic opioid therapy) for patients undergoing cardiac surgery via sternotomy by means of a single arm, open label, interventional study that will compare as the primary outcome rescue analgesic requirements, rendered as opiate equivalents, at 12, 24 and 48 hours, and the 24 hour period preceding both 72 and 96 hours postoperatively. 'Efficacy' will be considered as a threshold of clinical significance being defined as a 15% difference). In addition to the primary endpoint, we plan to evaluate the duration of intubation, length of ICU stay, median pain scores, incidence of PONV (postoperative nausea and vomiting; 0-6h, 6-12h and overall), time to mobilization and adverse events between these groups. Postoperative data collected from standard clinical follow-up tools, such as return to baseline sleep and activity status as well as pain medication requirements at home, will also be compared. In addition, we plan to evaluate the quality of sleep and activity with a smart watch (Fitbit™) during the perioperative period in the BESB group only.

C. Preliminary Studies

While the paravertebral block and, increasingly, the ESB are commonly used for postoperative management of numerous thoracic procedures in adults and children, there is little prospective data available evaluating the efficacy of these blocks in this population and no prospective data evaluating the utility of such blocks for management of post-sternotomy pain in a pediatric population.

Retrospective studies and case reports exist that suggest that ESBs are efficacious and low risk, but very few prospective data exist. The ESB has been described as having utility in the adult perioperative environment for patients undergoing breast surgery[19], shoulder surgery[20], thoracotomy/thoracoscopic surgery[9,21], thoracic spinal surgery,[22] and ventral abdominal surgery[7]. Two case reports have also described its utility in treating patients with chronic pain in the thoracic dermatomes.[23] As noted above, there is at least one published prospective study in adults,[16] but similar studies in pediatric patients are yet to be undertaken. In general, there is much less published evidence in children; however, there are case reports and case series describing its use for patients undergoing thoracic and abdominal surgery[12,24-26].

Large retrospective analyses of multiple pediatric regional anesthesia registries consistently report a very favorable safety profile for the provision of regional anesthetics in the pediatric population. A recent (2015) consensus statement from the American and European Societies of regional anesthesia (ASRA and ESRA) reported the risk profile of administering regional anesthetics to anesthetized children, citing a risk of postoperative neurologic symptoms of 0.93/1000 cases (>90% of which resolve completely within 1 month) and a rate of local anesthetic systemic toxicity of 0.08/10000 cases.[27]

As previously noted, our group recently investigated the feasibility of performing BESBs in a pediatric cardiac surgical population undergoing sternotomy-based procedures at this institution. At the conclusion of this 10-patient pilot, we found that performing these blocks was technically feasible -- requiring 30 minutes or less of OR time -- and resulted in an approximate 25% reduction in rescue opioid requirements in the first 48 hours amongst the BESB group (p=0.048). There were no significant adverse events noted during this pilot with the exception of a single instance of a kinked (but useable) catheter.

While the numbers at BCH are relatively small, retrospective analyses of ESBs performed in this institution in non-cardiac surgery have demonstrated no evidence that this block type is associated with any greater risk than that demonstrated by aggregate block data from the various pediatric regional anesthesia registries. Information currently available suggests that regional blockade, when performed properly, carries a very low risk of morbidity and mortality in appropriately selected infants and children.[28] Furthermore, we have found no evidence of increased adverse events present in the ESB patients when compared to patients receiving other regional anesthetics in our local analysis. Indeed, two abstracts addressing the safety and efficacy of ESB blocks in BCH patients have recently been accepted for presentation at the major regional anesthesia conference.[29,30]

D. Design and Methods

(1) Study Design

We propose a single arm, open label, interventional study to compare the opiate requirements of 45 patients who consent to receive BESB catheters following cardiac surgery via sternotomy versus 90 matched historical controls who had similar surgical procedures but without BESBs.

Patients meeting eligibility criteria will be recruited and enrolled to have BESBs placed for postoperative pain control as a part of their perioperative anesthetic

plan. These patients will subsequently have a variety of preoperative demographic and functional data collected as well as data related to their surgeries and postoperative course all collected for later analysis. This enrolled group of patients will subsequently be compared regarding these outcome measures with a 1:2 matched, retrospective analysis of patients in the cardiac surgical ERAS program who did not receive regional blocks as a component of their anesthetic care. (The ERAS Cardiac program is a heart center perioperative evidence-based quality initiative. Retrospective data analysis of outcomes for patients in this program is performed for quality improvement purposes and outcomes research [IRB P00029161 – PI: Nathalie Roy MD, co-investigators: Roland Brusseau MD, Morgan Brown MD]). Children aged 2 years through 17 years meeting entry criteria will be screened and recruited for participation from the Boston Children's Hospital cardiac surgical program.

(2) Patient Selection, Inclusion/Exclusion Criteria and Recruitment Method

Patients from BCH who meet the criteria below will be considered for recruitment:

Inclusion Criteria:

1. Scheduled as part of the cardiac surgical ERAS program: Patients scheduled for elective surgeries for the following congenital anomalies, or similar: atrial septal defects (all types), partial anomalous pulmonary venous connection (non-obstructed), cor-triatriatum, VSD, partial AV canal, sub-aortic membrane resection, anomalous aortic origin of the coronary arteries, and pulmonary valve/conduit implantation

2. Scheduled to undergo a first time surgical pulmonary valve or right ventricle to pulmonary artery conduit change in anatomic position, in the context of previous complete repair.

3. Ages 2 years through 17 years.

Exclusion Criteria:

1. Single ventricle physiology.
2. Significant scoliosis or other anatomic contraindications to ESB.
3. Significant intraoperative hemodynamic instability or bleeding, as ascertained by clinicians taking care of the patient.
4. Patients with severe neurodevelopmental delays.

5. Patients with previous chronic pain syndromes.

6. Patients with a history of greater than 24 hours of postoperative or post-procedural opioid treatment at any point in the 2 months prior to surgery.

7. Lack of parental consent and/or child assent.

Recruitment Method:

We plan to include pediatric patients who are scheduled for inpatient surgery at BCH over a period of 2 years. Patients will be recruited by members of the study staff. We will contact all patients and/or families scheduled for an eligible ERAS procedure (see below for details of contact methods) and otherwise meet criteria.

Each morning, a designated member of the study staff will review the upcoming surgical schedule to identify pediatric cases that fit the study criteria (procedure type and age). If these criteria are met, the case will be sent to an investigator for further clinical review. A final eligibility decision will be made by the PI.

1. ***Outpatients*** *with procedures scheduled >2 weeks from identification:* Patients will be sent information on the study (cover letter, brochure, consent form) up to 2 weeks prior to their surgery or scheduled preoperative visit. This will be sent either by USPS mail or by secure electronic mail if an e-mail is on file.

2. ***Outpatients*** *with procedures scheduled 2 weeks or less from identification:* Patients will be contacted by secure electronic email and/or given informational materials at their preoperative visit if we are unable to send mailers reliably VIA USPS. We will allow at least a day for them to consider participating in the study.

3. ***Outpatient*** *telephone follow-up:* Patients sent information packets either by USPS or secure electronic email may be contacted by telephone to confirm receipt of the materials and answer any initial questions after such time as they would normally be expected to have received and reviewed the packets (the next week for USPS and no sooner than 1 day following email). If materials have not been received, patients will be given the opportunity to have those materials sent or be contacted at a preoperative visit.

4. ***Inpatients*** *with no planned discharge and/or preoperative clinic appointments:* Patients who are already inpatient will be approached on the

patient floor or other inpatient encounter with study information. We will approach as soon as we have confirmed eligibility and will provide them with recruitment materials prior to their day of surgery and allow at least 24 hours for a decision to be made.

5. ***International patients****:* For international patients meeting entry criteria, recruitment materials will not be mailed internationally. If an e-mail is available for an eligible international patient, a secure e-mail via BCH server will be sent to the family. The e-mail will include all approved recruitment documents. If we are unable to reach an international family via e-mail, eligible international patients and their families will be approached and provided materials in the preoperative clinic. At this time we will provide information about the study, answer all questions and allow at least 24 hours for them to consider participating in the study.

6. When feasible, consent will be obtained either at the time of the preoperative visit, on the day of surgery, or at the bedside for those who are inpatient (i.e. without pre-op appointments). When in person consent is not feasible, the research team will have the consent discussion by phone prior to the day of surgery and families will be asked to provide written consent following that discussion. Written consent may be done through the RCS e-consenting platform or by sending the consent to the home by mail or email and receiving a signed copy of the consent back by mail or email.

7. In the exceptional situation when bilateral erector spinae blocks are used clinically and the patient or family were not approached for the study because of changes in the surgical schedule or other special situation, the research team can approach the families to offer participation in the study if they meet entry criteria.

We have numerous recruitment strategies as cardiac surgical scheduling is very fluid, often with cases added only days before. Our recruitment scheme allows for physical and electronic mail, on-site (clinic, inpatient) encounters, and phone calls to assess interest. We allow ourselves a maximum of 3 patient contacts. Consent may be taken at any time a patient feels comfortable to do so, but never with less than a day for patients/families to think or (re)consider. While we do allow ourselves to take consent on the day of surgery, we would not endeavor to meet the patient, describe the study, and take consent all at once on immediately prior to being taken into the OR for the procedure and would ensure that this would be done a minimum of 24h prior.

It will be made clear to all eligible participants that while BESBs are used in other types of patient groups, they are not typically used for patients undergoing congenital cardiac surgery via a sternotomy at BCH, and are therefore considered to be under investigation in this study. Families will be informed that the study is being done to better understand if using ESBs bilaterally is an effective form of pain management for patients undergoing sternotomy when compared to a set of matched historical patients who did not receive BESBs, and whose pain management includes a multimodal pain strategy, cornerstone of the ERAS Cardiac program. Research staff will stress that if families elect not to participate, they will not receive the BESBs unless agreed upon with their primary anesthesia team, but instead the standard of care pain management at BCH (multimodal pain regimen including pain-score based systemic opioid therapy as part of the ERAS Cardiac program guideline and orderset).

(3) Description of Study Treatments or Exposures/Predictors

Participants will have their medical record reviewed following enrollment for demographic information including: gender, age, weight and height, procedure, surgeon, and current and historical medication use.

Any other routine standard-of-care data will be collected preoperatively as well in addition to research-specific data points.

All enrolled patients will have bilateral erector spinae blocks (with catheters for postoperative local anesthetic infusion) placed by the by a member of the BCH regional anesthesia team (under the supervision of a member of the research team) in a sterile fashion after the cardiac surgical procedure is completed. The placement is as follows:

- The patient is placed in a lateral decubitus position (left or right), with all pressure points padded in routine fashion.
- The area for intervention is prepped with a chlorhexidine solution, and sterile drapes are applied to demarcate the block placement area.
- The T4/5 transverse process on one side is identified with the ultrasound transducer in a parasagittal orientation.
- An 18g Tuohy needle is advanced to the target area under direct ultrasound visualization. The needle tip is advanced until it contacts the transverse process, just below the erector spinae muscle complex.
- Normal saline is injected to confirm appropriate needle tip position. The erector spinae muscle is visualized to be elevated up off of the transverse process with normal saline injection
- With confirmation of appropriate needle tip position, the initial local anesthetic bolus is injected using a standard, weight-based dosing protocol.

- Following the bolus injection, a catheter is threaded into the space occupied by the local anesthetic bolus.
- Catheter tip position is verified by one or more of the following: ultrasound visualization of the catheter tip, ultrasound visualization of instilled normal saline and/or ultrasound visualization of a small hyperechoic (i.e. bright on ultrasound) injection of air.
- With the catheter tip position identified, the catheter is tunneled to a cutaneous exit point approximately 2-3cm from the incision using a Crawford needle.
- The catheter is dressed in standard fashion with an adhesive catheter anchor, Dermabond, Mastisol, Tegaderm and tape.
- This is repeated for the contralateral side. To the extent possible, this will be done without repositioning in a contralateral decubitus position.
- A label indicating that each catheter is a nerve-block catheter with its laterality and date of placement noted is applied to each catheter.
- Catheter placement is complete.
- Postoperative infusion of local anesthetic (ropivacaine) via the nerve block catheter is initiated and managed by the Acute Pain Service (per standardized, clinical weight-based protocols).
- Procedural notes:
    - Minor deviations from the above procedure (e.g. small changes in sequence, needle entrance locations, amount of catheter deployed, etc.) are possible as the anatomy, positioning, etc. of individual patients varies. This is anticipated and allowable so long as such modifications remain within what is currently considered standard of care for the placement of these blocks and what is done in a given case is considered the appropriate standard of clinical care for that patient by the clinical providers placing the block(s).

All patients will have access to the multimodal pain regimen which is standard of care for all ERAS Cardiac patient and includes acetaminophen and ketorolac, when otherwise not contraindicated, as well as pain-score based opiate rescue medications as needed. All patients have access to postoperative pain management as needed by means of a standard opioid-based PCA/NCA demand protocols utilized at BCH if needed. In addition, all enrolled patients will be followed by the Acute Pain Service at BCH as is the standard of care for all patients receiving nerve blocks, enabling access to additional assessment, catheter and infusion management (where appropriate) and opioid treatment as needed 24 hours a day, 7 days a week. In addition, one of the primary investigators will be available to the

Acute Pain Service staff for consultation 24 hours a day regarding any desired consultation on study patients.

Possible risks related to the block include bleeding, infection, local anesthetic systemic toxicity, local anesthetic insensitivity and incomplete block and/or block failure. These risks occur at no greater (or lesser) frequency than when associated with the use of such blocks in routine clinical situations.

Intraoperative and postoperative anesthetic and surgical data, routinely collected for the Society of Thoracic Surgery (STS), will be collected from the EMR.

In addition to observational tools and subjective scoring, patient functional status (activity, sleep quality and other measures) will be assessed by actigraphic analysis using the Fitbit™ Charge 3 smartwatch. A Fitbit™ will be placed on the non-dominant arm, if possible, after extubation on the day of surgery. The Fitbit™ will remain on the patient until discharge from the hospital (which on average is about 5 days post-op) and the actigraphic data subsequently will be downloaded to the secure research database and the data wiped from the device. If a study subject had an unforeseeable complication and they no longer progressed along the standard recovery path (e.g. re-intubation, return to ICU), or if the watch was interfering in clinical care in any way, the Fitbit™ would be removed.

Following primary data collection for the enrolled subjects, each subject will be matched by surgical procedure using the STS procedure code, to 2 patients within the cardiac surgery ERAS program QI database (IRB #P00029161 which allows retrospective data analysis of outcomes) by the research team. All patients recruited for this study are themselves already part of the enhanced recovery after cardiac surgery clinical program [QIP]. Matching will be performed 1:2 with respect to surgical procedure and diagnosis using the STS codes, within 30% of the study patient's age and according to gender (if possible) and will be blinded to outcomes. Thus, up to 90 additional patients will be included in this study, retrospectively in addition to the 45 study patients from the single arm interventional cohort study (BESB).

Groups will be compared for demographic data, risk factors (from the STS database), diagnosis, procedure and cardiopulmonary bypass and clamp times to ensure their similarities

E. Definition of Primary and Secondary Outcomes/Endpoints

Primary:

- Analgesic requirements, rendered as opiate equivalents, at 12, 24 and 48 hours, and the 24 hours preceding both 72 and 96 hours postoperatively.

Secondary:

- Analgesic requirements, rendered as total opiate equivalents, at 12, 24 and 48 hours, and the 24-hour period preceding both 72 and 96 hours postoperatively.
- Duration of intubation following OR exit.
- Duration of ICU stay following OR exit.
- Duration of inpatient admission.
- Median pain scores collected per standard of care (VAS, NRS, INRS, or FLACC) at 0-3h, 3-6h, 6-12h, 12-24h, 24-36h and 36-48h.
- Incidence of postoperative nausea and vomiting during the following time ranges: 0-6h, 6-12h, 12-24h, and overall
- Time to mobilization (e.g. up to chair, ambulation).
- Quality/Quantity of mobilization and sleep via postoperative actigraphy.
- Outcome and satisfaction measures associated with routine perioperative questionnaire responses.
- Adverse events. – catheter, hemodynamic instability during placement (new inotrope or vasopressor – including Ca, volume > 5ml/Kg, variation 10% baseline SBP and MAP)
- All major Society of Thoracic Surgeons (STS) standard indices of morbidity and mortality

*Of note, all of the above data points are collected automatically (via the electronic medical record) for all patients, as a part of their routine clinical care, regardless of whether or not they participate in the study.

F. Data Collection Methods

All patients will be assigned a unique personal identifier that will not be linked to any patient identifying information. Data will be collected during the study in case report forms and then will be entered into a password-protected, secure database or automatically collected via the Regional Anesthesia Outcomes Database and uploaded to that same database.

With the exception of actigraphic data, all preoperative demographic information and intraoperative data will be extracted from the patients' EMR and loaded into the secure database.

Each subsequent day, appropriate data will be extracted from the EMR to the secure database for later analysis. In addition to the parameters described above, various other catheter-related and adverse outcome data points will be captured from the EMR and uploaded to the secure database for further analysis. Catheter boluses and catheter rate adjustments (if present) will be recorded as well.

Research information collected on paper (or other physical media) during the study will be stored in locked cabinets with access limited to the Principal Investigator and research personnel affiliated with the study. Information that has been generated as, or transferred to, electronic media will be kept on password protected, secured data servers. All health information is protected by HIPAA (Health Insurance Portability and Accountability Act) and all health records will be kept confidential. Patients' birthdate, name, and all other identifying information will be removed when analyzing and reporting the data. Any personal identifying information will be stored separately from the other information provided by or about the patient and no personal identifying information will be reported in any publications or presentations. Identifying information will be kept in a password protected, secure file with limited access by research personnel. Once data collection is complete, identifying information will be destroyed.

G. Data Management Methods

All relevant information retrieved from the electronic medical record, by the PI and/or a member of the research team will be translated into an electronic form. Data collected on paper case report forms will be entered into a standard, secured database for intake and checking, and will be protected by encryption and password. Only authorized users are permitted access to the data files, and daily server back-up activities are executed to ensure data safety. All data will be stored on a password-secured research computer, and all data entered into the computers will be password protected. Procedures to ensure accurate and reliable data collection will include well-designed data forms and training.

H. Study Timeline

We plan to enroll a total of 45 patients in this single arm, open label, interventional study. We anticipate that it will take approximately 2 years to complete enrollment and data collection for this study.

I. Adverse Event Criteria and Reporting Procedures

Adverse or unanticipated events will be reported as required to the Boston Children's Hospital IRB by the PI according to institutional reporting requirements.

An Adverse Event refers to any untoward medical occurrence whether or not it is considered intervention-related.

As noted above, analysis of the retrospective outcomes data for the 45 BCH patients treated with ESBs, the patients in our trial study, and the national and international literature demonstrates no evidence that this block type is associated with any greater risk than that demonstrated by aggregate block data from the various pediatric regional anesthesia registries. Information currently available suggests that regional blockade (including the erector spinae block), when performed properly, carries a very low risk of morbidity and mortality in appropriately selected infants and children.[28]

Nevertheless, as there exist little prospective outcomes data related to the ES block, we will implement a rigorous system to follow and report any adverse events, including interim analyses by a non-blinded statistician, as described below:

Adverse Event Monitoring:

Adverse outcomes will be carefully tracked for all patients enrolled in the study. Enrollment will be halted and the IRB informed by the PI if any of the following conditions are met:

- 1 of any of the following serious adverse events.
    - Patient death.
    - Pneumothorax directly resulting from placement or removal of the blocks and catheters as evidenced by: 1- lung puncture during placement resulting in a moderate to large pneumothorax on the side affected performed within 8 hours, and/or the development of a new air leak in an existing chest tube collection system. 2- The development of a new moderate to large pneumothorax within 8 hours after removal of Erector Spinae plane catheters.
    - Hematoma at the site of the catheter/block—causing pain or any neurological symptoms for the patient.
    - Persistent neurologic symptoms lasting more than 3 days after a single shot block or catheter is removed.

    - Local anesthetic systemic toxicity (any symptoms leading to this diagnosis by a study team participant)
- >2 of any of the following minor/moderate adverse events in a given patient or >10 in aggregate:
    - Persistent bleeding at the site of the catheter insertion or block placement.
    - Leakage of local anesthetic from the catheter insertion site that leads to discontinuation of the catheter infusion.
    - Redness or superficial infection of the catheter site or site of the block placement.
    - Skin irritation at the site of the catheter insertion or block placement that results in greater than 3 cm of induration or is associated with pain.

In addition to these stoppage rules, we plan to have Dr. Meena Nathan MD (Director of Quality and Safety, Cardiac Surgery, BCH) independently review the case outcomes, etc. to ensure patient/subject safety in a way that may not be captured by the above stoppage rules. This monitor will make such assessments for each cohort of 15 patients. As Dr. Meena is not a part of the study team, these reviews need not be blinded/redacted/etc. in any way. Any concerns raised by Dr. Meena will be brought to the attention of the PI directly and the IRB as well in a timely fashion.

If there is a pause for any of the above reasons, continuance of the protocol will be at the discretion of the IRB in consultation with the study team. No individual care data will be reported unless there is a serious adverse effect. Reports will be done in an aggregated fashion.

Special note regarding ropivacaine:

Ropivacaine use constitutes the standard of care at BCH for all nerve blocks and regional anesthetics, including cardiac surgical ERAS patients. Known potential adverse consequences of this mode of delivery of this medication include hypersensitivity, allergic reaction, hypotension and cardiac arrhythmias if injected intravascularly. The presence of any of these will be assessed by the primary anesthesiologist intraoperatively and treated appropriately at the time of block placement and initial bolus and further assessed for such daily by members of the research team and Acute Pain Service. Any occurrence of a possible adverse event or events will be documented and reported to the DSMB, the IRB and the Department of Anesthesia Quality Assurance Physician as appropriate. In the event

of a serious adverse event, it will be reported to the DSMB and IRB immediately and the study halted until a thorough investigation into the cause can be made.

The relative safety of ropivacaine for use in regional anesthesia is supported by the information contained the Pediatric Regional Anesthesia Network (PRAN) database. The PRAN is a consortium of major pediatric centers in North America that manages a prospective data registry on pediatric regional anesthesia. From their database, which at this time comprises more than 130,000 pediatric regional anesthetics from numerous major centers in the US and Canada, ropivacaine is documented to be used in greater than 85% of pediatric regional with a safety profile at least equivalent to, if not better than, bupivacaine.[31]

Further, ropivacaine is very well studied in pediatrics. There is an extensive body of prospective clinical trials and clinical outcomes studies on ropivacaine pharmacokinetics, safety and clinical outcomes from infancy through adolescence. Our prescribing practices at BCH in the Regional Anesthesia and Acute Pain Services are derived from that body of PK information and consensus recommendations.

We therefore regard ropivacaine as the established standard of care for pediatric regional anesthesia and have selected it for use in this study.

J. Quality Control Method

Data quality control will be assured through automated and manual methods. The study database enhances data quality through required entry fields for critical data and automatic flags for missing or out-of-range data. Efforts will be made to minimize data entry error by the development of a user-friendly database and all data entry will be double-checked with the source files. Data will be audited for accuracy by investigators after being entered into the database.

K. Data Analysis Plan

At the time of data analysis, de-identified datasets will be downloaded from the secure database and merged into secure statistical analysis tool for purposes of analysis. Missing data will be accounted for when the data is coded into respective variables.

Descriptive statistics will be generated in order to summarize demographic characteristics of patients enrolled. Data will be tested for normality using the Shapiro-Wilk test. Data will be presented as total n (%), means and standard deviations (SD) if the distribution appears normal, or medians and range when not.

Assuming normality, t-tests will be conducted to investigate the differences between the two exposure groups (to compare total opioid equivalents, time required to place the block, time to extubation, and time to discharge, etc.). If data does not appear to be normal, Wilcoxon Rank Sum/Mann-Whitney tests will be used for group comparisons. Repeated measure analysis will be used to compare pain scores over time between groups and when compared to baseline values. Adverse events and complications (if any) associated with the blocks will be recorded and categorized. Fisher's exact test will be used to compare the proportion of patients who reported adverse events between the two groups. $P<0.05$ will be considered statistically significant.

Should a clinically significant effect be demonstrated, healthcare costs related to the surgical encounter for both groups will be approximated and compared in order to better assess the added value of the intervention in a more global fashion.

L. Sample Size Considerations

In order to evaluate the efficacy of BESB in this cardiac surgical population compared to those who did not receive blocks, we have defined 'efficacious' as denoting an at least 15% difference in the total opioid consumption at 96hours based on the historical rescue opiate data in the matched cohort. Assuming an alpha of 5%, 80% power, and the mean opiate requirements found in our pilot study, we estimate that a total sample size of 38 patients undergoing sternotomy with BESBs and 76 matched controls are needed to demonstrate efficacy of the new treatment (BESB).

Table 1 (below) demonstrates that, using a 1:2 ratio of BESB:standard ERAS patients, 38 BESB and 76 standard ERAS patients are required to detect a 0.18 mean difference (15% relative reduction associated with BESB) in square-root Total (96-hr) OME between groups with 80% power using a two-sided 0.05-level test. Because the coefficient of variation for 48-hour OME is somewhat smaller, this sample size will provide 87% power to detect a 15% relative reduction (0.16 mean difference) in square-root 48-hr OME between groups using a two-sided 0.05-level test.

Because the larger SD of the two groups from background data (see **Table 2**) was used in these calculations, and because the groups will be matched on several patient characteristics which will minimize variation, these assumptions are conservative and power to detect the effect sizes shown in Table 1 may be even higher than shown.

Table 1. Required Sample Size to Detect BESB vs. ERAS Group (1:2 Ratio) Reductions in 48- and 96-hour OME (square-root transformed) assuming two-sided α=0.05, 80%/85% Power, 48-hour mean sqrt OME 1.05 and 96-hour mean sqrt OME 1.23 in ERAS Group.

Outcome (sq. root)	SD	%Reduction	Group Difference	Power	BESB N	ERAS N
48 hr OME	0.26	15%	0.16	80%	32	64
48 hr OME	0.26	15%	0.16	85%	36	72
48 hr OME	0.26	20%	0.21	80%	19	38
48 hr OME	0.26	20%	0.21	85%	21	42
96 hr OME	0.32	15%	0.18	80%	38	76
96 hr OME	0.32	15%	0.18	85%	43	86
96 hr OME	0.32	20%	0.25	80%	20	40
96 hr OME	0.32	20%	0.25	85%	23	46

Table 2. Background Data

Group	N Obs	Variable	N	Mean	Std Dev	Median
ERAS	20	sqD0N0D1N1	20	1.050	0.181	1.049
		sqtotalome	20	1.231	0.211	1.227
		D0N0D1N1_OME	20	1.134	0.390	1.100
		Total_OME	20	1.557	0.540	1.505
BESB	10	sqD0N0D1N1	10	0.890	0.261	0.898
		sqtotalome	10	1.120	0.320	1.157
		D0N0D1N1_OME	10	0.854	0.528	0.810
		Total_OME	10	1.346	0.724	1.340

Given the possibility of patient withdrawal due to procedural changes, intraoperative exclusionary events, etc., we plan to enroll 45 patients for the BESB intervention group and 90 matched historical controls from the cardiac ERAS database (IRB P00029161).

M. Study Organization

Drs. Roland Brusseau, Nathalie Roy, and Morgan Brown will serve as principal investigators. Patient screening, recruitment, enrollment, and data collection will be performed by a designated member of the research team.

N. Potential Benefits

It is possible that, as a result of receiving these blocks, a patient might a) be exposed to less narcotic and benzodiazepine than might otherwise be the case, b) be extubated sooner and as such be at less risk for ventilator-associated pneumonia, and/or c) mobilize earlier and therefore avoid numerous possible postoperative complications. These are just putative benefits known to be associated with regional anesthetics and thus may occur in study participants.

Results from our pilot study suggested an approximate 25% reduction in opioid requirements in the first 48 hours following surgery, but the study was too small to draw any significant conclusions. Currently no data exists to recommend these blocks over conventional management in congenital cardiac surgery via a median sternotomy. The results of this study may allow the investigators to develop an appropriately powered, randomized controlled trial to evaluate the utility of this intervention which might be used to inform such management decisions for future patients.

O. Privacy Provisions

Information will only be made available to individuals who are part of the research team. Medical information collected for this study will only become part of the child's medical record if the information is determined to be pertinent to the care the child is receiving at Boston Children's Hospital. Disclosure of personal information may occur only when required by law.

P. Confidentiality Provisions

All identifying information such as dates of birth, names, and medical record numbers will be removed from the study database. All patients will be assigned an ID number that will not be linked to any patient identifying information. All data will be electronically secured in a password protected private folder. Only research investigators and personnel affiliated with the study will have access to patient information.

Every effort will be made by research staff to keep patient information confidential. To ensure patient confidentiality, all research data will be secured in locked filing

cabinets in a locked office. Any publications that result from this study will not be linked with personal identifiable information that would disclose the identity of study subjects.

Q. References

1. Harbaugh CM, Lee JS, Hu HM, McCabe SE, Voepel-Lewis T, Englesbe MJ, Brummett CM, Waljee JF. Persistent Opioid Use Among Pediatric Patients After Surgery. Pediatrics. 2018 Jan;141(1). pii: e20172439. doi: 10.1542/peds.2017-2439. Epub 2017 Dec 4.
2. Hemmerling T, Choiniere JL, Basile F, Prieto I. Regional anesthesia in cardiac surgery and immediate extubation after cardiac surgery: a different view. Can J Anaesth 2005;52:883.
3. Djaiani G, Fedorko L, Beattie WS. Regional anesthesia in cardiac surgery: a friend or a foe? Semin Cardiothorac Vasc Anesth 2005;9:87-104.
4. Riedel BJ. Regional anesthesia for major cardiac and noncardiac surgery: more than just a strategy for effective analgesia? J Cardiothorac Vasc Anesth 2001;15:279-81.
5. Mychaskiw G, 2nd, Heath BJ. Regional anesthesia and pediatric cardiac surgery. Anesth Analg 2000;91:1562.
6. Peterson KL, DeCampli WM, Pike NA, Robbins RC, Reitz BA. A report of two hundred twenty cases of regional anesthesia in pediatric cardiac surgery. Anesth Analg 2000;90:1014-9.
7. Chin KJ, Adhikary S, Sarwani N, Forero M. The analgesic efficacy of pre-operative bilateral erector spinae plane (ESP) blocks in patients having ventral hernia repair. Anaesthesia 2017;72:452-60.
8. Chin KJ, Malhas L, Perlas A. The Erector Spinae Plane Block Provides Visceral Abdominal Analgesia in Bariatric Surgery: A Report of 3 Cases. Reg Anesth Pain Med 2017;42:372-6.
9. Forero M, Rajarathinam M, Adhikary S, Chin KJ. Erector spinae plane (ESP) block in the management of post thoracotomy pain syndrome: A case series. Scand J Pain 2017;17:325-9.
10. Forero M, Rajarathinam M, Adhikary S, Chin KJ. Continuous Erector Spinae Plane Block for Rescue Analgesia in Thoracotomy After Epidural Failure: A Case Report. A A Case Rep 2017;8:254-6.
11. Ivanusic J, Konishi Y, Barrington MJ. A Cadaveric Study Investigating the Mechanism of Action of Erector Spinae Blockade. Reg Anesth Pain Med 2018;43:567-71.

12. Kaushal, B., et al. "Efficacy of Bilateral Erector Spinae Plane Block in Management of Acute Postoperative Surgical Pain After Pediatric Cardiac Surgeries Through a Midline Sternotomy." J Cardiothorac Vasc Anesth 2020; **34**(4): 981-986..
13. Wong J, Navaratnam M, Boltz G, Maeda K, Ramamurthi RJ, Tsui BCH. Bilateral continuous erector spinae plane blocks for sternotomy in a pediatric cardiac patient. J Clin Anesth 2018;47:82-3.
14. Leyva FM, Mendiola WE, Bonilla AJ, Cubillos J, Moreno DA, Chin KJ. Continuous Erector Spinae Plane (ESP) Block for Postoperative Analgesia after Minimally Invasive Mitral Valve Surgery. J Cardiothorac Vasc Anesth 2018;32:2271-4.
15. Monahan A, Guay J, Hajduk J, Suresh S. Regional Analgesia Added to General Anesthesia Compared With General Anesthesia Plus Systemic Analgesia for Cardiac Surgery in Children: A Systematic Review and Meta-analysis of Randomized Clinical Trials. Anesth Analg 2019;128:130-6.
16. Krishna SN, Chauhan S, Bhoi D, et al. Bilateral Erector Spinae Plane Block for Acute Post-Surgical Pain in Adult Cardiac Surgical Patients: A Randomized Controlled Trial.
17. De Cassai A, Tonetti T. Local anesthetic spread during erector spinae plane block. J Clin Anesth 2018;48:60-1.
18. Tsui BCH, Navaratnam M, Boltz G, Maeda K, Caruso TJ. Bilateral automatized intermittent bolus erector spinae plane analgesic blocks for sternotomy in a cardiac patient who underwent cardiopulmonary bypass: A new era of Cardiac Regional Anesthesia. J Clin Anesth 2018;48:9-10.
19. Kimachi PP, Martins EG, Peng P, Forero M. The Erector Spinae Plane Block Provides Complete Surgical Anesthesia in Breast Surgery: A Case Report. A A Pract 2018.
20. Forero M, Rajarathinam M, Adhikary SD, Chin KJ. Erector spinae plane block for the management of chronic shoulder pain: a case report. Can J Anaesth 2018;65:288-93.
21. Adhikary SD, Pruett A, Forero M, Thiruvenkatarajan V. Erector spinae plane block as an alternative to epidural analgesia for post-operative analgesia following video-assisted thoracoscopic surgery: A case study and a literature review on the spread of local anaesthetic in the erector spinae plane. Indian J Anaesth 2018;62:75-8.
22. Ueshima H, Otake H. Clinical experiences of ultrasound-guided erector spinae plane block for thoracic vertebra surgery. J Clin Anesth 2017;38:137.
23. Ramos J, Peng P, Forero M. Long-term continuous erector spinae plane block for palliative pain control in a patient with pleural mesothelioma. Can J Anaesth 2018;65:852-3.

24. Hernandez MA, Palazzi L, Lapalma J, Forero M, Chin KJ. Erector Spinae Plane Block for Surgery of the Posterior Thoracic Wall in a Pediatric Patient. Reg Anesth Pain Med 2018;43:217-9.
25. Munoz F, Cubillos J, Bonilla AJ, Chin KJ. Erector spinae plane block for postoperative analgesia in pediatric oncological thoracic surgery. Can J Anaesth 2017;64:880-2.
26. Holland, E. L. and A. T. Bosenberg. "Early experience with erector spinae plane blocks in children." Paediatr Anaesth 2020; **30**(2): 96-107.
27. Ivani G, Suresh S, Ecoffey C, et al. The European Society of Regional Anaesthesia and Pain Therapy and the American Society of Regional Anesthesia and Pain Medicine Joint Committee Practice Advisory on Controversial Topics in Pediatric Regional Anesthesia. Reg Anesth Pain Med 2015;40:526-32.
28. Polaner DM, Drescher J. Pediatric regional anesthesia: what is the current safety record? Paediatr Anaesth 2011;21:737-42.
29. Foz C ES, Alrayashi W, Kordun A, Cravero JP. Erector Spinae Plane block in children undergoing coarctation of aorta repair. American Society of Regional Anesthesia. Las Vegas, NV2019.
30. Eklund SE FC, Alrayashi W, Kordun A, Cravero JP. Erector Spinae Plane Blocks in Patients Undergoing Periacetabular Osteotomy. American Society of Regional Anesthesia. Las Vegas, NV2019.
31. Suresh S, De Oliveira GS, Jr. Local anaesthetic dosage of peripheral nerve blocks in children: analysis of 40 121 blocks from the Pediatric Regional Anesthesia Network database. Br J Anaesth 2018;120:317-22.