STUDY TITLE: Intermittent Bolus Versus Continuous Infusion Erector Spinae Catheters for Median Sternotomy Incisions: A Prospective Randomized Controlled Trial

NCT05642416

Protocol Version: 3

Protocol Date: 1/31/2025

1. STUDY AIM, BACKGROUND, AND DESIGN ABSTRACT

Open heart surgery is a commonly performed surgical procedure with the goal of correcting various cardiac abnormalities. Standard open-heart surgery typically requires a median sternotomy, sternal retraction, and placement of chest tubes and drains, all of which are associated with significant pain. Failure to properly manage this pain postoperatively can lead to cardiovascular sequalae (increased oxygen consumption, tachycardia), pulmonary complications (atelectasis, pneumonia, and stasis of bronchial secretions), as well as increased hospital length of stay [1][2].

Opioid analgesics are commonly employed in post-operative pain management strategies but can lead to nausea, vomiting, pruritus, and respiratory depression. Multiple modalities are currently used to help manage this acute post-operative pain, including IV analgesics, oral analgesics, as well as regional anesthesia. The advent of enhanced recovery after surgery (ERAS) protocols, including and not limited to regional techniques, has led to protocols aimed at reducing opioid use [3][4]. For example, Erector spinae plane (ESP) block, a relatively new block, has been shown to decrease opioid consumption for post-operative pain after open heart surgery [1][5]. Advancements in medication pump delivery systems has enabled automated intermittent boluses to be delivered through regional catheters. More recently, automated programmed local anesthetic (LA) boluses have been shown to provide superior analgesia compared to continuous LA infusions in various types of surgeries such as lung resections and painful foot surgeries, presumably due to more uniform local anesthetic spread [6]. These results show promising use in favor of programmed intermittent LA boluses in non-cardiac surgeries. A recent study by Vaughn et al. [7] demonstrated a shorter time to extubation, less opioid consumption, and shorter ICU stay in cardiac surgery patients that had continuous ESP catheters placed preoperatively. Limited data exists regarding the use of intermittent boluses and the clinical outcomes in cardiac surgery patients.

The purpose of this prospective randomized controlled trial is to compare the effectiveness of two different delivery methods for postoperative pain management following cardiac surgery requiring median sternotomy: intermittent programmed LA bolus versus continuous LA infusion through ESP catheters. Effectiveness of analgesia will be assessed based on the subjects' NRS pain scores and opioid consumption. The primary outcome measure will be the patients' opioid consumption over the course of the 72 hours following surgery. Secondary outcomes measures that will be evaluated include NRS pain scores, intensive care unit (ICU) length of stay, Quality of Recovery 15 (QoR-15) score, and time to first dose of antiemetic in the postoperative period. It is hypothesized that the use of intermittent programmed LA boluses will provide better analgesia compared to continuous LA infusion through ESP catheters. The findings of this study will provide guidance regarding the optimal method of delivery for postoperative pain management in patients following cardiac surgery.

2. SUBJECT POPULATION AND ELIGIBILITY

Subject Population

Adult patients undergoing elective cardiac surgery requiring median sternotomy for surgical exposure who receive pre-operative ESP catheters.

Inclusion Criteria

- Non-emergent elective cardiac surgery requiring median sternotomy for surgical exposure (i.e. CABG, aortic/mitral/tricuspid valve replacements)
- Age 18-90

Exclusion Criteria

- Placement and/or existence of cardiac assist devices (LVAD, RVAD, Balloon Pump, Impella)
- Neurocognitive dysfunction
- Patients who expire before extubation
- Non-English speaking
- Daily opioid therapy prior to surgery
- History of substance abuse
- BMI > 45

Enrollment and/or Screening

Eligible patients will be identified by manual review of the upcoming operating room schedule in the EPIC electronic medical record database. Patient's charts will be reviewed by study personnel at least a day prior to their scheduled surgery to verify that they meet study inclusion criteria. If eligibility criteria are met, patients will be called on the phone at least one day prior to their scheduled surgery by a study team member. If interested, they will be sent a copy of the Informed Consent Form to review via email or mail. Signature of the informed consent will take place in the preoperative area on the day of surgery.

3. STUDY PROCEDURES:

This study will be a double-blinded (both the subjects and nurses assessing their pain and dispensing their medications will be blinded), prospective, randomized controlled trial. Eligible patients will be identified by a study team member through a manual review of the upcoming surgery schedule in EPIC, and their charts will be screened to ensure that they meet inclusion criteria. Patients who meet eligibility criteria will be called on the phone at least one day prior to their scheduled surgery by a study team member. If interested, they will be sent a copy of the Informed Consent Form to review via email or mail. On the day of surgery, a study team member will approach the patient in the pre-operative holding area to thoroughly review the consent and answer any questions they might have.

After patients have consented to participate in the study, they will be randomized into one of two treatment groups by a study team member using the randomization tool in REDCap. The two groups will receive treatment as follows: Group A (control): will receive continuous infusion of

local anesthetic postoperatively, Group B (treatment): will receive intermittent boluses through their ESP catheter postoperatively.

ESP catheters will then be placed by staff regional anesthesia team members preoperatively per the institutional standard block protocol. The regional anesthesia team managing the peripheral nerve catheters will be informed which group the patient has been randomized into by a member of the study team. For both group A and B, an ambIT® PIB-IL infusion pump (Avanos Medical, Inc, Alpharetta, GA) will be used to administer the local anesthetic. For Group A (control) the continuous setting will be selected to administer 0.2% ropivacaine at a rate of 10mL per hour (5mL per side per hour), and for Group B (treatment) the bolus setting will be used to administer a 30mL bolus of 0.2% ropivacaine every three hours. The nursing staff and intensive care unit physicians collecting postprocedural pain scores and dispensing medications will be blinded to the treatment group.

Postoperative pain scores and opioid consumption will be obtained from the electronic medical record in EPIC. As part of standard practice, postoperative pain scores are recorded by nursing staff using a numeric pain rating scale (NRS) from 0 to 10. These pain scores will be collected starting no sooner than postoperative day (POD) 1 and continue until POD 3 and will be recorded every 4-8 hours in the ICU and general practice unit, according to standard practice. The ESP catheters will stay in place during this time frame. Total opioid consumption will be defined as oral morphine equivalents doses (OME) administered in the same time period from POD 1 up until POD 3 and reported in 4-hour intervals. A member of the study team will administer the validated Quality of Recovery-15 (QoR-15) questionnaire on POD 1, POD 2, and POD 3 [8]. The data collection is expected to be finished within 16 months and the results are expected to be published within two years following the IRB approval date.

The collection of personal patient information will be limited to the amount necessary to achieve the aims of the research. Only study personnel will collect the data. Data will be stored using an HFHS REDCAP database. Following data collection, data will be de-identified prior to data analysis. The de-identified data will be provided to an HFHS biostatistician for statistical analysis. The data will be retained per the IRB retention policy for two years and then will be destroyed. The provisional investigation is projected to be completed in two years.

The following data will be obtained from the patient's medical charts in HFHS EPIC:

- MRN
- Last Name, First Name
- Sex
- Age
- Race
- Height
- Weight
- BMI
- Date of surgery
- Number and location of chest tubes placed intraoperatively and on what postoperative day they were removed

    - These will be documented because of their potential influence on pain scores
- Conditions associated with chronic pain not managed by chronic opioid medications (i.e. fibromyalgia, chronic pain syndrome, chronic low back pain)
- Pain Scores – Numeric rating scale (NRS) pain scores on a scale of 0-10, obtained from flowsheet in EPIC electronic medical record
    - The pain scores will be recorded every 4-8 hours on POD 1, POD 2, and POD 3.
- Total Opioid Consumption – Patient total opioid consumption, converted to oral morphine equivalents (OME) on POD 1, POD 2, and POD 3.
- ICU length of stay – Duration of time, in days, that patient spends in ICU from post-operative day 0 until they are downgraded to a lower level of medical care.
- Quality of Recovery-15 (QoR-15) Score on POD 1, POD 2, and POD 3
- Opioid-related side effects:
    - Total antiemetic dosage (in mg)

Statistical Analysis Plan:

The time weighted average (TWA) of the NRS will be calculated for every post-operative day (POD 1 through POD 3). The TWA of pain scores, opioid medication (intravenous and oral use), and antiemetic medications will be recorded every day (POD 1 through POD 3) during the study period. Data will be summarized overall and between the two treatment arms. Continuous variables be compared using Student's t-test or Wilcoxon rank sum test. Categorical variables will be compared using chi-squared or Fisher's exact test, as appropriate. A linear model or generalized linear model will be used to evaluate the treatment effect on primary and secondary outcomes. An intention to treat (ITT) approach will be utilized for all analyses, regardless of adherence to study protocol or crosstalk between treatment arms. Statistical significance is considered to be p value<0.05. Dr. Franklin Dexter from The University of Iowa will be performing the statistical analysis of data. All identifiers (names, MRNs, and admission dates) will be removed from the data set prior to giving it to Dr. Dexter.

Sample Size/Power Justification

Sample size calculation was performed based on the primary outcome of the study, which is the cumulative opioid consumption (in OME) from the start of POD 1 to the end of POD 3.[7] A 20% reduction in OME is considered clinically significant. Assuming a mean OME of 220 mg with a standard deviation of 108mg for patients receiving continuous infusion, a total of 192 patients from both arms (96 per arm) will provide a statistical power of at least 80% to detect the projected effect size using a t-test for two independent samples, with a two-sided significance level of 0.05. Adjusting for a 20% drop-out rate, 240 patients (120 per arm) will be required in both arms.

Funding will be obtained from internal funding sources and possible grant funding through Avanos Medical, Inc.

4. ANTICIPATED RISKS

The only anticipated risk to participants in this study is a breach of confidentiality. Every effort will made to maintain the confidentiality of study records. The collection of personal patient information will be limited to the amount necessary to achieve the aims of the research. Only study personnel will collect the data. Data will be stored using an HFHS REDCAP database. Following data collection, data will be de-identified prior to data analysis. The de-identified data will be provided to an HFHS biostatistician for statistical analysis. The data will be retained per the IRB retention policy for two years and then will be destroyed.

5. ANTICIPATED BENEFITS

There are no anticipated benefits to participants in this study. Future patients may benefit, regarding post-operative pain management, from data collected during this study.

6. RENUMERATION/COMPENSATION

You will not be compensated for your participation in the study.

7. COSTS

There will be no cost to the participants in this study.

8. CONSENT PROCESS AND DOCUMENTATION

Patients who meet eligibility criteria will be called on the phone at least one day prior to their scheduled surgery by a study team member. If interested, they will be sent a copy of the Informed Consent Form to review via email or mail. On the day of surgery, a study team member will approach the patient in the pre-operative holding area to thoroughly review the consent and answer any questions they might have.

9. WITHDRAWAL OF SUBJECTS

Patients may be withdrawn from the study if they continue to be intubated past POD 1. Patients may also be withdrawn if reintubation occurs during the study time period or if there is displacement of the peripheral nerve catheters noted by the clinical team. Other circumstances that may lead to patient withdrawal is the need for premature catheter removal such as MRI studies.

In the event of suspected catheter failure (observed catheter dislodgement, unable to flush medications through catheter), we will continue to follow with the intention to treat (ITT) until the last study day. It is anticipated that 20-25% of patients will have suspected catheter failure. Their information will still be included in the analysis and reported in the results, as we will assume catheter failure is distributed equally between the two randomized groups.

10. PRIVACY AND CONFIDENTIALITY

Every effort will made to maintain the confidentiality of study records. The collection of personal patient information will be limited to the amount necessary to achieve the aims of the research. Only study personnel will collect the data. Data will be stored using an HFHS REDCAP database. Following data collection, data will be de-identified prior to data analysis. The de-identified data will be provided to an HFHS biostatistician for statistical analysis. The data will be retained per the IRB retention policy for two years and then will be destroyed.

11. DATA AND SAFETY MONITORING PLAN

The data will be thoroughly evaluated for accuracy on a monthly basis by the PI. The PI will be responsible for the quality check of source document as well as adherence to data confidentiality and accuracy. Protocol deviations/amendments will be communicated to the IRB within one week of the incident by Katherine Nowak via email. Information will be stored securely in REDCAP.

10. THE INVESTIGATOR(S)

Dr. Patrick Forrest is the Division Head for Regional Anesthesia and the Quality Assurance Chair for the Henry Ford Health System Department of Anesthesiology, Pain Management, & Perioperative Medicine. He was voted "Anesthesiologist of the Year" in 2017 at Harper University Hospital in Detroit Medical Center. Dr. Forrest is serving as PI of a new quality improvement project focused on preventing post-induction hypothermia by using a pre-warming protocol and a non-invasive temperature patch (IRB pending). He is also serving as a sub-investigator a study evaluating an opioid-free post-cesarean-section pain management protocol using liposomal bupivacaine (IRB pending).

12. REFERENCES

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7) Vaughan BN, Bartone CL, McCarthy CM, Answini GA, Hurford WE. Ultrasound-Guided Continuous Bilateral Erector Spinae Plane Blocks Are Associated with Reduced Opioid Consumption and Length of Stay for Open Cardiac Surgery: A Retrospective Cohort Study. J Clin Med. 2021;10(21):5022. Published 2021 Oct 28. doi:10.3390/jcm10215022

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