TITLE: Randomized Clinical Trial Comparing Analgesia and Plasma Pharmacokinetics of Lidocaine administered by Erector Spinae Plane Blocks vs. Intravenous Routes Following Open Heart Surgery: An Equivalence Study

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Protocol Outline

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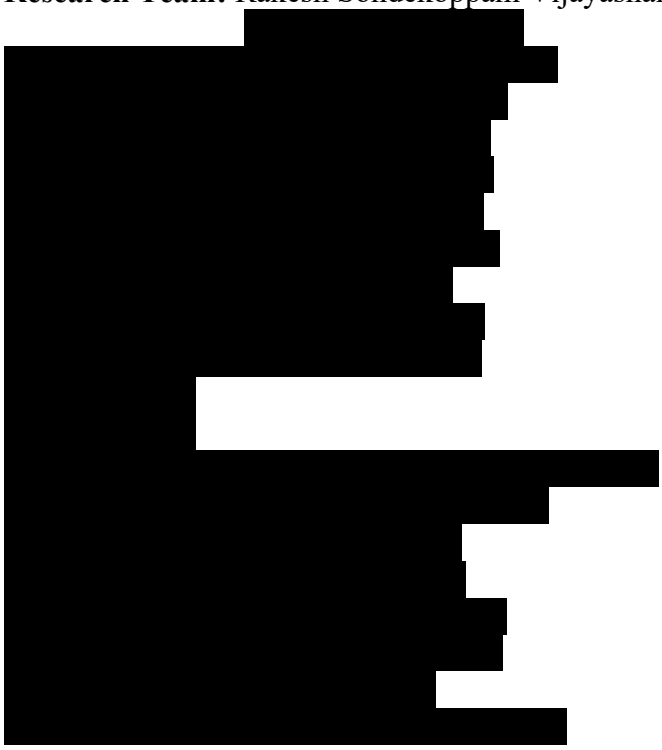


I. Abstract

Recently interfascial plane blocks have been developed for analgesia including erector spinae plane (ESP) block. The ESP block has been hypothesized to provide truncal analgesia by spread of local anesthetic into the paravertebral space. However, recent studies have shown that the spread of local anesthetic by this block procedure into the paravertebral space is unreliable. It has been established that interfascial plane blocks can result in systemic levels of local anesthetic that can achieve therapeutic concentrations similar to those observed by intravenous infusions of local anesthetic and could likely be the mechanism of action of the ESP block. Free and total plasma lidocaine levels will be measured until steady state levels are achieved with ESP blocks. Additionally, the safety of the ESP block using doses of local anesthetic has not been rigorously evaluated This study will evaluate both the analgesic efficacy and safety of ESP blocks in post-cardiac surgery

patients in comparison to intravenously administered lidocaine.

II. Background and Significance/Preliminary Studies

Postoperative pain is a significant issue following open heart surgery and poorly controlled pain can result in significant cardio-respiratory morbidity. A significant number of patients suffer from pain issues both at rest (49%) and on movement (62%) following open heart surgery via sternotomy (1,2) and adequate pain management requires closer re-assessment and treatment. The intensity of pain is noted to be higher in the first 48 hours post-surgery (3,4,5,6,7,8) and hence modalities to control pain may make the greatest difference in the first two days after surgery.

Enhanced recovery pathways utilizing multimodal analgesia have shown significant analgesic and opioid sparing benefit while minimizing ICU and length of hospital stays (9,10). Some such multimodal analgesic regimens have also incorporated regional anesthesia, but the optimal analgesic regimen is still elusive. Central neuraxial blocks such as epidural, intrathecal and paravertebral blocks have been utilized for cardiac surgery associated pain but given not widely adapted to practice due to concerns of altered coagulation status and the possibility of neuraxial hematoma. Additionally, there is a lack of clear guidelines to provide deeper regional nerve blocks in this patient population. A variety of interfascial plane blocks have been developed, among which the erector spinae plain (ESP) block has gained popularity recently. Given the non-neuraxial and superficial location of the structures of interest, more healthcare providers are offering ESP to provide analgesia following open heart surgery. Early evidence available from a clinical trial comparing ESP to no block and non-standardized multimodal anesthesia has shown variable pain reduction but consistent opioid sparing effects (11,12). The ESP block has been hypothesized to provide truncal analgesia by spread of local anesthetic (LA) into the paravertebral space (PVS). However, recent anatomical studies have contested this idea, showing unreliable spread of LA to the PVS. It is also well known that bilateral paravertebral blocks can result in higher than acceptable systemic levels of LA both in cardiac (13,14) and non-cardiac surgical patients and this may be true following bilateral ESP as well. Hence, the pharmacokinetic profile of administered local anesthetics is necessary given the lack of information about the local anesthetic systemic levels following bilateral ESP.

It is well known that interfascial plane blocks can result in systemic levels of LAs that achieve therapeutic concentrations (15) similar to that observed by intravenous infusions of LA (16,17). This is very likely the case for the ESP block, especially since the clinical and anatomical studies have conflicting findings regarding the loco-regional effects. Although intravenous lidocaine has shown some promise to prevent post-operative cognitive dysfunction (18,19), its effect on postoperative pain is not well studies. One study utilizing low dose lidocaine failed to show improvement in pain scores or opioid consumption, but the study did not utilize standardized multimodal analgesia

regimen (20). It is currently unknown whether the analgesic benefits of interfascial plane blocks are due to the multimodal analgesic regimen, the loco-regional benefits of the blocks, the systemic levels of local anesthetics following the block performance or a combination of all. We hypothesize that the mechanism by which the ESP block produces analgesia in the background of multimodal analgesia is probably related to the systemic absorption of local anesthetics. In addition, the safety of the ESP block using high doses of LA in cardiac surgery patients has not been rigorously assessed. We propose a pragmatic study to address both unknowns, the mechanism and safety of ESP following cardiac surgery.

III. Study Aims

1. The hypothesis of this study is that the analgesic effects of ESP can be attributed to its systemic distribution rather than its locoregional effects. A finding that lidocaine administered by ESP block achieves plasma concentrations in the analgesic range (2-5 ug/ml) at steady state will support our hypothesis whereas inability to reach analgesic levels will suggest that systemic distribution of local anesthetic is not a significant contributing factor of analgesia.

2. Despite the use of clinically acceptable doses, plasma concentrations of local anesthetic have been known to reach toxic levels following bilateral paravertebral blocks. This may also be true of ESP blocks. This study will address this concern and help establish a safety profile for ESP blocks in the cardiac patient population.

IV. Administrative Organization

University of Iowa Hospitals and Clinics—CVICU and Laboratories

V. Study Design

i. Experimental design of the study (e.g., single-blind, double-blind): Randomized

ii. Study population general description: Adults undergoing elective cardiac surgery for coronary artery bypass graft (CABG) or valve surgery via sternotomy

iii. Sample size determination and power analyses: 70 adult patients as determined using an online calculator available at: https://www.sealedenvelope.com/power/continuous-equivalence/

iv. Study outcomes/endpoints:

1. Arterial blood samples will be drawn and assessed for lidocaine concentrations
2. Pain scores will be collected from EPIC electronic medical record or directly from the subjects.
3. Opioid doses will be assessed and reported in morphine equivalents

VI. Study Procedures

a. Subject selection procedures

i. Inclusion: Any patient >18 years and <81 years undergoing elective cardiac surgery for CABG or valve surgery via sternotomy and surgical procedure is not greater than 12 hours

Exclusion: Allergy to study medications; major livor or kidney dysfunction; BMI <20 or >50; revision surgery; Off-pump coronary artery bypass surgery; surgery via thoracotomy; narcotic dependent (opioid intake morphine equivalent > 10 mg/day for more than 3 months); other sources of chronic pain such as fibromyalgia; patients with associated significant central nervous system, liver, renal or respiratory disease; coexisting hematological disorder or deranged coagulation parameters; lack of informed consent; preoperative neurological deficits; and emergency surgery (E1, E2 and E3 classifications only).

ii. Recruitment procedures

1. **Where will recruitment occur?** Pre-surgical clinic or Day of Surgery Admissions (DOSA)
2. **Where and when will consent be obtained?** DOSA prior to surgery or in pre-surgical clinic
3. **Who will obtain consent?** Anesthesia team
4. **What is the advertising plan, if applicable?** N/A
5. **What recruitment materials will be provided to the potential participant (brochures/information sheets/video presentation)?** None.

iii. Screening procedures

1. **What procedures are required for screening?** Prior to the surgical procedure, the anesthesia team will review eligibility criteria: Allergic to study medication; diagnosed with major liver or kidney dysfunction; any bleeding disorders; in females verify non-pregnant state.
2. **What is the screening schedule (number of visits, length of visits)?** This will occur only on the day of surgery and will last approximately 30 minutes.
3. **Which screening tests/procedures are part of standard care and which are for research purposes only?** All screening procedures listed above are part of standard of care.
4. **What happens with screen failures (including any data gathered during screening)?** A screening

log will be maintained and will be destroyed at upon study completion.

b. Randomization procedures (if applicable)

Participants will be randomized to IV or ESP groups using a computer-generated block randomization sequence and the allocation concealment will be ensured using a sealed envelope technique. The randomization sequence will be available with the PI and the research team.

c. Study Intervention

iv. For Drug/device studies:

1. **Active study agents:** Lidocaine
2. **Placebo study agents:** None
3. **Blinding/labeling/preparation of agents:** Drug will be provided through the UIHC Investigational Drug Service
4. **Storage:** Room temperature. Protect from light.
5. **Administration:** Per study, either through ESP catheter or intravenously.
6. **Toxicities and guidelines for adjustments:** Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution.

Management of Local Anesthetic Emergencies The first consideration is prevention best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as underventilation or apnea due to unintended subarachnoid injection of drug solution, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to the use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of

circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

d. Study Assessments and Activities

i. Describe all study procedures, assessments, and subject activities

Procedures Affecting Both Groups

A. Pre-Operative Phase (Standard of Care)

• Pre-operative fasting and carbohydrate treatment. Patients are kept NPO for 8 hours before surgery except for an oral carbohydrate beverage given 2 - 4 hours before procedure.

• Pre-operative multimodal analgesic is initiated. Gabapentin and acetaminophen will be given pre-operatively and continued postoperatively at regular intervals.

• Anxiolytic medications. Minimal anxiolytic medications given before surgery including midazolam given by anesthesia provider.

B. Intra-Operative Phase (Standard of Care - At discretion of Anesthesia Provider)

• Intraoperative opioid administration. Fentanyl IV given as needed for pain but typically < 1 mg for procedure.

• Hydromorphone 0.5 - 1 mg given near completion of procedure

• Intraoperative multimodal analgesia. If time since preoperative acetaminophen dose significantly exceeds 6 hours, acetaminophen 1000 mg IV, or via NG route is considered

• Postoperative sedation initiated. Near the end of the procedure, dexmedetomidine or propofol infusion is begun for postoperative sedation in ICU while intubated

• All patients will receive dual post-operative nausea and vomiting (PONV) prophylaxis in the form of ondansetron and dexamethasone at appropriate time periods.

If the surgical procedure takes longer than 12 hours, the subject will be withdrawn from the study.

C. Block Performance/Procedure

• Upon arrival to the CV-ICU, patients will be assessed for eligibility to extubate based on hemodynamic and pulmonary stability on a case-by-case basis with the aim to extubate as early as possible. When appropriate, extubation will proceed following the CV-ICU Fast Track Extubation protocol that is already in place. Extubation is not required prior to the administration of study drug via IV or ESP catheters route. Participation in the study can proceed as long as after assessment by clinicians, the subject is extubated or ready to be extubated.

D. Group ESP (Study Procedures)

• Bilateral ultrasound guided erector spinae plane (ESP) catheters will be inserted either pre- or post-operatively.

• After confirming that there are no contra-indications, the subject will receive lidocaine via ESP catheter.

• Patients will receive lidocaine at a dose of 2 mg/kg ideal body weight (IBW) as bolus divided equally between the two ESP catheters.

• Subjects will then lie in a supine position.

• Lidocaine infusion via ESP catheters either through 2 dedicated pumps or via a single pump and a y-connector at a rate of 2 mg/kg/hour for approximately 48 hours.

• Blood samples will be drawn at 5, 30, 60, 120 minutes, 6 and 24 hours and assessed for lidocaine concentration.

• Pain scores (resting and with movement/cough) will be collected from bedside record and EPIC medical record. Standard assessment protocol already in place has this charted every 2 - 4 hours by ICU nursing staff.

• All patients will receive continued oral multimodal analgesia

• When not eligible to receive oral medications (e.g. NPO), pain analgesia will be provided through an IV route. This can include an IV PCA pump using hydromorphone 0.2 mg with a lockout of 10 minutes and a maximum dose of 6 mg in 4 hours continued postoperatively.

• If oral medications are insufficient to provide pain relief, and the subjects are not receiving medications via PCA, pain medications

will be provided IV. • Opioid doses (both oral and IV) will be assessed and reported in morphine equivalents.

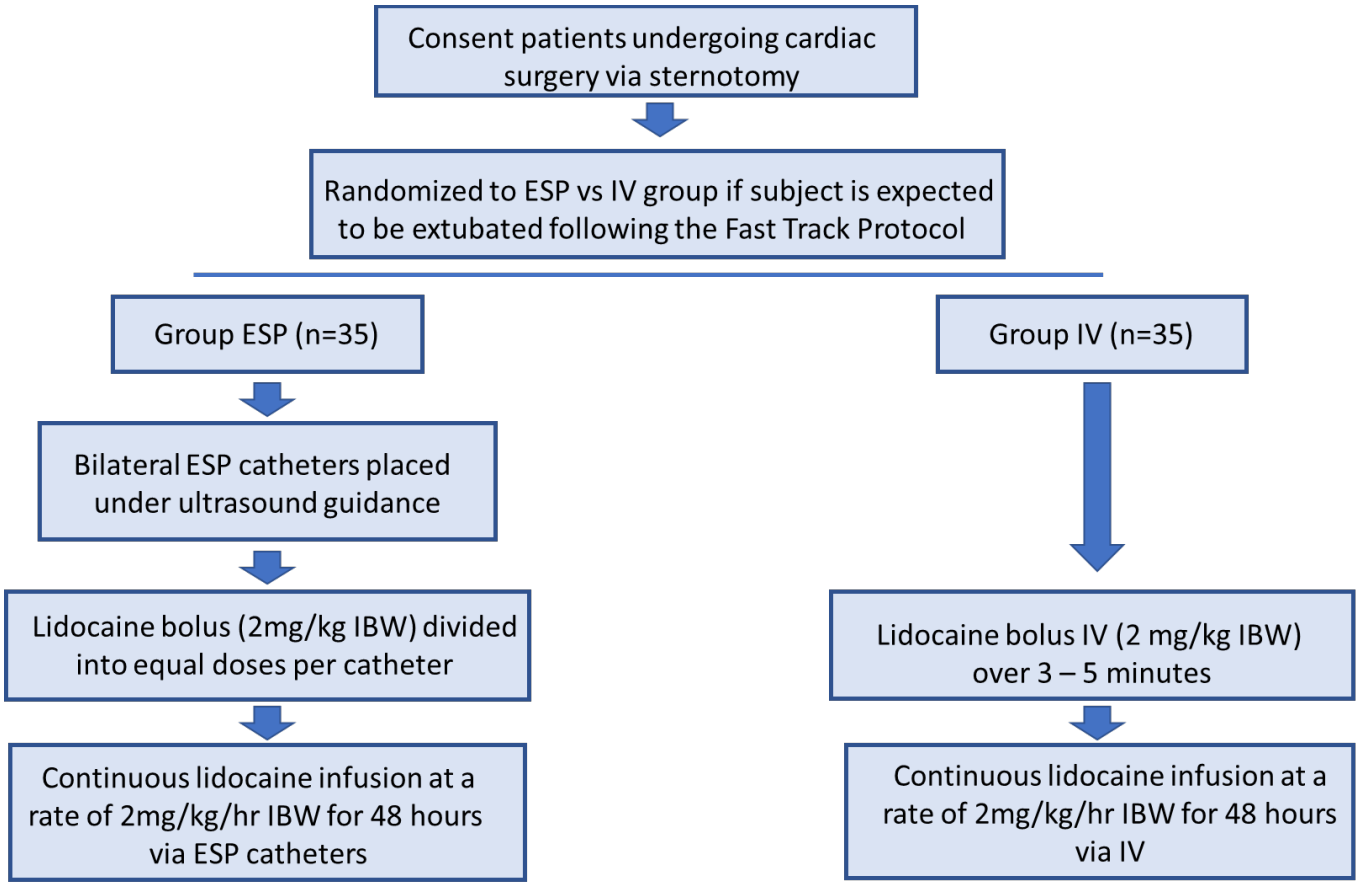
E. Group IV (Study Procedures)

• Patients will receive lidocaine at a dose of 2 mg/kg ideal body weight (IBW) through IV route.
• Subjects will then lie in a supine position.

• Lidocaine infusion via IV route at a rate of 2 mg/kg/hour for approximately 48 hours.
• Blood samples will be drawn at 5, 30, 60, 120 minutes, 6 and 24 hours and assessed for lidocaine concentration.
• Pain scores (resting and with movement/cough) will be collected from bedside record and EPIC medical record. Standard assessment protocol already in place has this charted every 2 - 4 hours by ICU nursing staff
• All patients will receive continued oral multimodal analgesia
• When not eligible to receive oral medications (e.g. NPO), pain analgesia will be provided through an IV route. This can include an IV PCA pump using hydromorphone 0.2 mg with a lockout of 10 minutes and a maximum dose of 6 mg in 4 hours continued postoperatively.
• If oral medications are insufficient to provide pain relief, and the subjects are not receiving medications via PCA, pain medications will be provided IV.

• Opioid doses (both oral and IV) will be assessed and reported in morphine equivalents.

ii. Provide a schedule of all study assessments and subject activities, including a tabular representation or timeline as applicable



VII. Safety Monitoring Plan

i. **Definition of adverse events, serious adverse events**:

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality or relationship to the drug.

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Any adverse experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, or it is suspected that the use or continued use of the product would result in the patient's death.

ii. What procedures will be used to monitor subject safety?

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be accomplished. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

For the purpose of being prepared to deal with the side effects of lidocaine (Bradyarrhythmia, hypotension, infusion site reactions), the blocks will only be performed in the Cardiac ICU, where pharmacological and non-pharmacological measures are available to treat these side effects. The foundation of local anesthetic toxicity is outlined in seizure management with pharmacological seizure management, advanced cardiac life support (ACLS) to support the heart and use of 20% lipid emulsion to reverse local anesthetic toxicity. Oxygen can be provided for patients needing improved oxygenation and all the emergency medications, pharmacists and intensivists are readily available in the ICU.

iii. **Who (list names) will identify, document, and report adverse events?**
Nursing staff in the CVICU should report adverse events to Dr. Archit Sharma or Dr. Rakesh Sondekoppam within 12 hours of the event. After the subject is stabilized this information will be reported to a member of Anesthesia Innovative Research Core who will report the event to the IRB.

iv. **What is the frequency for review of summarized safety information and who will perform the review (e.g., safety monitoring board)?**

No committee is currently in place for this pilot study.

v. **What are the stopping rules with regard to efficacy and safety?**

If an adverse/serious adverse event occurs, the study will be paused until careful evaluations is performed.

VIII. Analysis Plan

Study variables will be collected and tabulated. The continuous and discrete variables will be presented as mean and standard deviation after calculation and the categorical variables will be presented as frequencies. Normality of distribution will be assessed using Q-Q plots followed by Shapiro-Wilk test. Normally distributed data will be assessed using independent sample t-test and non-normally distributed data will be assessed using Mann-Whitney U-test. Categorical variables will be tested using chi-square tests or Fisher's exact test. Tests for equivalence will be applied for the primary outcome measures

failing which, tests of superiority will be applied. P values <0.05 will be considered statistically significant.

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