1. Protocol Title

A comparison of the analgesic effects of pectointercostal fascial plane block (PIFB) alone versus PIFB with rectus sheath block (RSB) in cardiac surgery: a prospective, randomized controlled trial.

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PRO00040365: A comparison of the analgesic effects of pectointercostal fascial plane block (PIFB) alone versus PIFB with rectus sheath block (RSB) in cardiac surgery: a prospective, randomized controlled trial.

2. Purpose of the study

To determine if ultrasound-guided bilateral pectointercostal fascial plane blocks with bilateral rectus sheath blocks decrease pain scores, decrease opioid consumption, improve respiratory function, and improve quality of recovery in patients recovering from patients undergoing cardiac surgery in comparison to pectointercostal fascial plane blocks alone.

4. Design and Procedures

This is a single center, prospective, randomized, controlled, double-blinded study. We anticipate recruitment of 50-60 subjects (see #6 Recruitment and Compensation below), with 25-30 in each group. The definitive number will be determined by our final power analysis (see #12 Data analysis and statistical considerations below).

Primary Outcome:

Pain scores on a 0-10 numeric rating scale (NRS) at rest and with deep breathing at 1, 3, 6, 12, 18, and 24 hours post-extubation between subjects receiving PIFB + RSB versus subjects receiving only PIFB.

Secondary Outcomes:

- Total cumulative opioid consumption at 24 and 48 hours post-operatively.
- Change from baseline on incentive spirometry at 1, 3, 12, and 24 hours post-extubation
- Time from ICU arrival to liberation from mechanical ventilation
- ICU and hospital length of stay
- QoR-15 (Quality of Recovery) score[23] 24 hours after extubation

Preoperative Management

Subjects will be randomized on the morning of surgery to receive bilateral PIFB and bilateral RSB with local anesthetic versus bilateral PIFB with local anesthetic and bilateral RSB with saline (placebo).

Following the informed consent process, a member of the study team will instruct the patient on the appropriate use of incentive spirometry at the bedside and correct performance will be assessed. Three measurements will then be recorded to provide a baseline of incentive spirometry function.

Intraoperative Management

All subjects will receive the standard of care anesthetic regimen for their cardiac surgery, with specific medications at the discretion of their attending anesthesiologist, with the following exceptions:

- Fentanyl and sufentanil will be the only narcotics used intraoperatively.
- Fentanyl administration will be limited to bolus dosing, rather than infusions.
- Any sufentanil infusions must be stopped prior to or upon arrival in the intensive care unit.
- Sufentanil dosing range will be within 0.2-0.5 mcg/kg/hr. Extubation in the operating room is at the discretion of the attending anesthesiologist.
- Furthermore, neuromuscular blockade will be reversed prior to handoff in the ICU.

Postoperative Management

Each PIFB will be performed with 15 mL of 0.25% bupivacaine with 5 mcg/ml of epinephrine, and bilateral RSB will be performed with an additional 20 mL of 0.25% bupivacaine with 5 mcg/ml of epinephrine (10mL on each side).

Single injection pectointercostal fascial plane blocks

The ultrasound-guided pectointercostal fascial plane blocks will be performed as follows:[20] a linear high frequency ultrasound probe will be placed in a parasagittal orientation between the third and fourth ribs, approximately one centimeter lateral to the sternal border, and all relevant structures will be identified, including the pectoralis major muscle, ribs, intercostal muscles, pleura, and any vasculature, including the internal mammary artery and vein. Color doppler will be used confirm the location of vasculature.

After skin cleaning with sterile chlorhexidine solution, a 9 cm 21 gauge insulated block needle (Sonoplex, Pajunk Medical Systems, Norcross, GA) will be inserted in an in-plane approach. In this way, both the needle shaft and tip can be visualized as the needle approaches the plane between the internal intercostal and pectoralis major muscles. The needle will be redirected as needed. Once satisfactory position of the needle tip is confirmed and after frequent negative aspiration, 20 mL of a solution containing 0.25% bupivacaine with epinephrine 5 mcg/ml will be slowly injected with intermittent aspiration. Spread of local anesthetic will be documented in the appropriate plane in real time. This procedure will be performed bilaterally.

All nerve blocks will be performed by an anesthesiologist experienced in regional anesthesia and/or a trainee supervised by an anesthesiologist experienced in regional anesthesia.

Single injection bilateral high rectus sheath nerve blocks

The ultrasound-guided rectus sheath blocks will be performed as described by Grant and Auyong[21]. A linear high frequency ultrasound probe will be placed in a transverse position in the midline, just inferior to the edge of the sternum. The probe will be moved laterally to visualize the lateral edge of the rectus abdominis muscle. The transversalis fascia, abdominal contents, and vasculature will be visualized, with color doppler confirmation of the location of vascular structures.

After skin cleaning with sterile chlorhexidine, a 9 cm 21G insulated block needle (Sonoplex, Pajunk Medical Systems, Norcross, GA) will be inserted from the lateral aspect of the ultrasound probe in a lateral to medial direction and aligned with the ultrasound scanning plane (in-plane approach). In this way, both the needle shaft and tip can be visualized as the needle approaches the rectus sheath plane, just deep to rectus abdominis and superficial to the posterior fascia. The needle will be redirected as needed. Once satisfactory position of the needle time is confirmed and after frequent negative aspiration, 10 mL of a solution containing 0.25% bupivacaine with epinephrine 5 mcg/ml or saline will be slowly injected with intermittent aspiration into this plane. Spread of local anesthetic will be documented in the appropriate plane in real time. This procedure will be repeated on the contralateral side.

Again, all nerve blocks will be performed by an anesthesiologist experienced in regional anesthesia and/or a trainee supervised by an anesthesiologist experienced in regional anesthesia.

Postoperative Evaluation

Evaluation of acute postoperative pain intensity using a 0-10 numeric rating scale (NRS) will be undertaken at the following time points, both at rest and with deep breathing:

- 1, 3, 6, 12, 18, and 24 hours post-extubation

Incentive spirometry will be assessed at 1, 3, 12, and 24 hours post-extubation, with three measures taken at each time point in order to compare postoperative performance with baseline spirometry.
Review of the medical chart will be made post-operatively to gather other data, including total intraoperative oral morphine equivalent consumption, cumulative opioid consumption at 24 and 48 hours, time from ICU arrival to tracheal extubation, length of stay in the ICU, length of stay in the hospital, administration of other analgesic or sedating medications in the first 48 hours after extubation, and QoR-15 (Quality of Recovery) score[22] administered 24 hours after extubation (with margin of error of 18-30 hours to avoid waking patients in the middle of the night). Occurrences of any adverse events reported by the subject or medical team will also be collected.

Collect additional surgical data: intraoperative OME, total surgical time, total cardiopulmonary bypass time, and total aortic crossclamp time. It is important to collect this data in order to control for these elements, as it is known that longer cardiopulmonary bypass time and aortic crossclamp time are associated with longer time to extubation and longer ICU length of stay [23.]

5. Selection of subjects

Criteria for inclusion:

- Subjects scheduled for elective cardiac surgery involving primary median sternotomy and subxiphoid chest tube placement
- Age 18-85 years of age
- BMI 18-50 kg/m2
- Weight > 60 kg

Criteria for exclusion:

- Left ventricular ejection fraction (LVEF) < 30%
- Preoperative, intraoperative, or immediate post-operative placement of intra-aortic balloon pump or deployment of extra-corporeal membrane oxygenation (ECMO)
- Inability to understand or speak English
- Allergy to bupivacaine or other amide local anesthetic
- Contraindication to peripheral nerve block (e.g. local infection, previous trauma to the block site)
- Chronic opioid consumption (daily oral morphine equivalent of >20 mg) in the past three months
- Severe pulmonary or hepatic disease
- Neurological deficit or disorder
- Suspected or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past two years
- Uncontrolled anxiety, schizophrenia, or other severe psychiatric disorder
- Patients who remain intubated for >24 hours after the stop of anesthesia will be removed from the study

6. Subject recruitment and compensation

Participating cardiac surgeons will share a basic study information sheet with potential subjects in their pre-operative surgery clinic visit. Potential subjects (see inclusion criteria above) will be identified on the surgical schedule by a member of the study team, typically at least one day in advance of the surgical procedure. These individuals will be contacted by telephone or in-person, if they are pre-admitted, and asked for permission to discuss the study. The purpose of the study will be explained, the consent form

read out loud, and any questions answered. Potential subjects will be encouraged to take time to discuss the study with family and will be told that there will be additional time to answer any questions on the day of surgery (or date prior, if pre-admitted). Potential subjects will be told that there is no obligation to take part in the study and their decision will not affect the quality of their care.

On the day of surgery or day prior to surgery (if pre-admitted), one of the investigators will approach the potential subject in his/her hospital room or the preoperative area, as appropriate, and answer any remaining questions. Subjects that indicate their interest in participating will then sign an informed consent and complete a HIPAA authorization form. There will be no compensation for subjects for their participation.

7. Consent process

The consent process will be conducted by one of the study team members. The consent process will take place in the patient's hospital room or the pre-operative area, depending on whether or not the patient has been pre-admitted. Throughout the consent process, measures will be taken to maintain privacy, such as conducting face-to-face conversations in private rooms. As much time as necessary will be spent with each potential subject to sufficiently explain and answer all questions and address all concerns they may have in regard to the study and/or consent process.

8. **Subject's Capacity to Give Legally Effective Consent**

Subjects who do not have the capacity to give legal consent will not be approached for participation in this study.

9. Study interventions

See #4.

10. Risk/benefit assessment

Risk to the subject

This study involves multiple injections, either with a local anesthetic solution or saline. Risks associated with the nerve block include bleeding, infection, nerve damage, and damage to surrounding structures, including blood vessels and lungs.

Benefits to the subject

The potential benefit of participating in the study is that patients receiving PIFB + RSB may require less pain medication resulting in fewer side effects, experience improved respiratory function, and achieve milestones sooner than those who do not receive PIFB + RSB blocks.

11. Costs

There will be no costs to the subject for participation in the study. Subjects will not be compensated for their participation.

12. Data analysis and statistical considerations

In order to appropriately complete our power analysis, following IRB approval and prior to patient recruitment we will review charts of 10-20 patients who have undergone CABG surgery and who have

received PIFBs within the last year at our institution in order to define baseline pain scores within the first 24 hours and opioid usage within the first 48 hours postoperatively.

Our data analysis plan is as as follows: since we had no pilot data on AUC pain outcomes, we considered a conservative scenario when the two outcomes are uncorrelated and described detectible differences between study outcomes in terms of standard deviations (SDs). To evaluate power properties of the Hotelling T2 at ALPHA = 5% test, we considered statistical power of two two-sample t-tests at ALPHA = 2.5%. At 24 patients per group, the detectible at 80% power difference between group means = 0.9 SDs (ALPHA = 2.5%). If the normality assumption is violated, Mann-Whitney test will have the same power properties at 25 patients per group. At 29 patients per group, the detectible at 80% power difference between group means = 0.8 SDs (ALPHA = 2.5%); Mann-Whitney nonparametric alternative will have the same power properties at 30 patients per group.

13. Data & Safety Monitoring

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study, all AE reports will be reported per the MCW IRB policies. PI will be monitoring all AEs and submitting reports to the IRB per MCW IRB policy.

Furthermore, an independent monitor has been chosen for the study, and this individual is a regional anesthesiologist, who will not be involved in study proceedings but who will be updated on study progress as per the DSMP.

14. Privacy, Data Storage and Confidentiality

Potential subjects and their families will be approached in private rooms or preoperative bays. Any guests not involved in the consent process will be asked to leave the room during any communications, unless the subject allows them to be present. Efforts to maintain subject confidentiality will include assignment of following Federal Privacy Regulations which provide safeguards for privacy, security, and authorized access. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Medical College of Wisconsin or Froedtert Hospital. Subjects will be not be revealed in any reports or publications resulting from this study. For records disclosed outside of MCW/Froedtert, subjects will be assigned a unique code number. The paper/electronic data will be stored as per the data safety and monitoring plan.

The only exception to the above is that the Investigational Drug Services pharmacy may unblind in cases of medical emergency with written or verbal consent from Dr. Castro (PI). Only the investigator will be unblinded to the subject's treatment group, and this will be done only in the case of a medical emergency.

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