Pectoralis and Serratus Muscle Blocks for Analgesia After Minimally Invasive Cardiac Procedures:

A randomized clinical trial

Version 6.0

July 6, 2022

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Version 2: January. 2nd, 2019

Summary of Changes:

1- Change in the contributors: We added Dr. Louis Lam instead of Dr. Humberto Choi
2- Change in secondary hypotheses: quality of recovery questionnaire (QoR15) moved from secondary to exploratory hypothesis
3- Change QoR15 follow up days to be day 1 and day 3
4- Adding exploratory hypothesis
5- Change inclusion criteria to Mitral valve surgery only (no Aortic valve surgery)
6- Change the block given to treatment group to PEC 2 and Serratus plane block only (no PECS 1)
7- In the exclusion criteria: clarifying item # 12 and adding item # 16
8- In page 7: remove any description related to PECS 1 block (as it will not be given in the study)
9- In page 8: change volume injected in PEC 2 block to 20-30 ml and SAP block to 40-50 ml
10- In page 8: add that SAP block might be given deep between Serratus muscle and ribs if it is difficult to be given superficial to Serratus ant muscle.
11- In page 10: Change QoR15 follow up days to be day 1 and day 3
12- In page 11 : correct the control group description (to standard routine parental and enteral analgesia)
13- In page 11: Add Primary and Secondary analysis
14- In page 15 : change score range for OBAS score to be from 0 to 4

Version 3: October 31, 2019

Summary of Changes:

1- Page10: Blood Sample Collection added to the study measurements that will be obtained.

Version 4: May 10, 2021

Corrections to protocol amendment

1- Previous amendment about additional collection for surgical data on data collection sheet: Ultrasound record and image of fascial plain blocks (SAP and PECS) was tracked on an older version of protocol in error and submitted on 10/23/2020. This amendment is to correct this error.

Additional amendment to this protocol

1- Twelve patients' surgery type was planned to be a minimally invasive surgery, however after the randomization, their surgery type has been converted to a sternotomy during their surgery. Because of this, these patients were not qualified for the study and their follow-ups couldn't be completed. To be able to keep the power of the study, we would like to add 12 more patients to our total enrollment number which was 196 before. Adding 12 more patients, 208 is proposed to be the total number.

Version 5: November 3, 2021

- We would like to add more patients per our statistical team suggestion to increase the power. Our total number approximately will be 214. (page 13)

Version 6: July 6, 2022

- The primary analysis method was revised due to non-normality of primary outcome from "We will report model based P-value and the difference in mean OBAS scores along with confidence intervals." as "Due to non-normality of OBAS score, it will be log-transformed for analysis. We will report model based P-value and the geometric mean ratio for OBAS scores along with confidence intervals. "
- The smallest clinically important difference of 2 point reduction in OBAS score was corrected as 20% reduction in geometric means.
- One inclusion criteria was more clearly stated as "Elective MICS for isolated robotically-assisted mitral valve repair via anterolateral thoracotomy approach. "
- Sample size was more clearly stated for consistency.

Introduction

Over the past several decades the popularity of minimally invasive cardiac surgery (MICS) increased consequent to advances in imaging, instrumentation, and surgical skills.[1,2] An increase in the age-related prevalence of the valvular heart disease[3] also prompted novel surgical approaches.[4] In addition to non-inferior operative mortality, the intermediate and long-term survival results are comparable to the traditional median sternotomy approach for both mitral[5-10] and aortic valve[11-14] procedures. The reported advantages are also seen in terms of decreased infection rate, shorter time to extubation and hospital length of stay, decreased postoperative bleeding and transfusion rate, improved cosmesis, better postoperative respiratory dynamics and patient's satisfaction.[5-7,15,16]

Both mitral and aortic valve repairs or replacements can be performed using right thoracotomies.[2,4] A medial (anterior, parasternal; 3rd intercostal space) incision including rib disarticulation is often needed for the aortic valves (AV), whereas a more lateral (inframammary, mid-axillary line; 4th intercostal space) incision is needed for mitral valves (MV). Robotically assisted MV repair is performed via slightly smaller thoracotomy and 3 additional stab incisions

for the robotic instruments. Port-accessed robotically assisted surgery avoids thoracotomy incision and totally depends on the percutaneous approach.[1,4]

Pain following thoracotomy is a serious complication which may delay patients' recovery, prolong hospitalization, and increase morbidity and mortality,[17] — all of which impair recovery through the post-operative day 3.[18] Although long-term pain is usually reduced with MICS[19], the short term benefits of the MICS approach are inconsistent and vary based on the surgical approach and analgesia techniques used.[20] Indeed, the thoracotomy approach may be a more painful procedure than sternotomy due to the need for rib spreading or disarticulation as well as chest tube placement.[1,4,21] Compared to the standard sternotomy, patients with "J" hemisternotomy for both MV and AV procedures had better postoperative pain control, but only 30% (compared to 20% in the sternotomy group) were pain-free in the first 24 hours.[6,15] Furthermore, the reports of the MICS for MV using right thoracotomy approach showed no difference in visual analog scale (VAS) pain scores and similar amount of additional analgesics used compared to the standard approach.[20,22]

Parenteral opioids remain the most common analgesic approach. To decrease use of opioids, a supplemental regional technique may be used. However, neuroaxial analgesia is rarely used due to the concern for developing epidural hematoma as well as perioperative hemodynamic instability related to bilateral sympathectomy.[23,24] Paravertebral blocks provide pain relief that is comparable to epidural blockade, with an improved hemodynamic profile, but without incremental benefit in VAS scores compared to the intravenous analgesia in patients undergoing robotic MV procedure.[25,26] An infusion of longer-acting local anesthetic via the subcutaneous tissue catheters facilitates early extubation but has questionable overall efficacy.[27,28] Further, extrapleural intercostal catheters improved pain control, but inability to strip the pleura posteriorly from the incision may lead to inadequate positioning and added safety concerns due to systemic toxicity limit its application.[29]

An evolving technique of truncal blocks for perioperative pain management has recently been reported.[30] Blanco et al. first developed and described a novel ultrasound guided pectoral fascial plane blocks (PECS I and II blocks) as an analgesia technique for surgeries of the anterior and anterolateral chest wall.[31,32] The blocks showed a reliable but limited sensory coverage to the antero-lateral T2-T4 (with variable spread to T6) with interfascial plane injection of the local anesthetic. In order to achieve more caudad and postero-lateral sensory coverage, a serratus anterior plane (SAP) block was introduced showing dermatomal coverage in T2-T7 with a variable spread to T9.[33]

Cadaver studies show spread of dye into the tissue plane adjacent to the long thoracic as well as lateral cutaneous braches of the intercostal nerves.[34] Indeed, inadequate nociceptive block of those nerves may be why analgesia control after thoracic surgery is often unsatisfactory with traditional regional analgesia techniques.[34,35] The posterior cutaneous branches may not be directly blocked, but the clinical efficacy of the PECS and SAP blocks is not diminished, probably because the local anesthetic spreads retrogradely.[34,36] Because of the unique anatomical

communication between the muscular planes, wide LA spread is possible into the large thoracic area.[33] Thus combing both PECS and serratus blocks at the same instance provides analgesia for the large thoracic area.

The PECS and SAP blocks are easy to perform, and have a high success rate with few complications, particularly when performed with ultrasound guidance. Unlike epidural and paravertebral blocks, PECS and serratus blocks do not cause a sympathectomy which facilitates their use in the hemodynamically compromised patients.[37] Because of the *superficial* nature of the blocks, the risk of pneumothorax is minimal, particularly with the in-plane ultrasound needle guidance.[37] The local anesthetic toxicity syndrome is not been reported and could easily be avoided with a dilution of the local anesthetic and standard precautions.[38] Indeed, compared to the intercostal, interpleural, or paravertebral techniques, pain control was achieved with much smaller LA doses which suggests that there was less intravascular absorption. Under the ultrasound guidance, the blocks can be easily to perform with the patients asleep, thus avoiding discomfort and multiple injections.

Liposomal bupivacaine (Exparel; bupivacaine liposome injectable suspension, Pacira Pharmaceuticals, Inc., Parsippany, NJ USA) is a prolonged-release formulation of the bupivacaine used for a single-shot infiltration of the surgical site. The advantage of the prolonged-release formulation is analgesia lasting up to 72 h which should improve analgesia after MICS. In a small retrospective study of robotically assisted cardiac endoscopic procedures, comparing incisional infiltration with bupivacaine vs liposomal bupivacaine, Balkhy et al. demonstrated lower pain scores, reduced opioid consumption, and less postoperative nausea and vomiting — although none of the differences were statistically significant.[18] The Exparel formulation containing a mixture of bupivacaine HCL and liposomal bupivacaine has demonstrated acceptable tolerability and incidence of adverse events relative to its non-liposomal counterpart, mainly in infiltration during hemorrhoid surgery, bunionectomy, breast augmentation, knee arthroplasty, and inguinal hernia repair.[39] Liposomal bupivacaine is FDA approved for infiltrative field blocks, such as the transversus abdominis plane (TAP) block which is similar to PECS and SAP blocks.[40]

A decrease in pulmonary mechanics associated with respiratory complications is one of the leading causes of postcardiac surgical morbidity.[41] Less invasive surgical approaches may decrease respiratory morbidity, particularly in already compromised patients.[42] However, the benefits of MICS in terms of pulmonary morbidity remain unclear.[20,22] Indeed, respiratory complications are directly related to the incisional pain consequent to thoracotomy, rib disarticulation, and muscle distortion. Epidural and paravertebral analgesia reduce pulmonary complications and infections, and improve respiratory mechanics in patients having thoracic surgery[43,44] but are rarely used. Other analgesia modalities including intercostal blocks did not comparably preserve pulmonary mechanics or reduce respiratory complications compared to neuroaxial techniques.[44,45]

A combination of the PECS and SAP blocks provide good analgesia for mastectomy,[46-48] thoracotomy[35,36,49-51] and multiple rib fractures.[38,52] However, their use in cardiac surgery and their effects on postoperative pain control or pulmonary mechanics have yet to be reported.

PECS and SAP blocks seem likely to enhance postoperative recovery after minimally invasive cardiac surgery. Pain after minimally invasive cardiac surgery is worst over the initial few postoperative days and compromises respiratory function. PECS and SAP blocks with liposomal bupivacaine thus seems likely to promote good analgesia and improved respiratory function.

Aims of the study

Our primary aim is to determine whether a PECS/SAP block, using a mixture of bupivacaine and liposomal bupivacaine, provides superior recovery compared to routine parenteral and enteral analgesia in patients recovering from MICS. Our primary outcome will be the simple multi-dimensional quality assessment, Overall Benefit Analgesia Score (OBAS score).[53]

Our secondary aims are to: 1) compare cumulative postoperative opioid consumption (pain medications administered over one-day periods quantified as morphine equivalents and provided by the EMR for the day of surgery and postoperative days 1, 2, and 3; 2) evaluate respiratory mechanics (forced expiratory volume in first minute (FEV_1), forced vital capacity (FVC) and peak flow) after extubation on the postoperative days 1, 2 and 3 while patients remain hospitalized

***Primary hypothesis*:**

PECS/SAP blocks with liposomal bupivacaine improve the Overall Benefit Analgesia Score averaged over the postoperative days 1, 2, and 3. A 20% reduction in OBAS geometric mean, a-priori, was defined as minimal clinically important difference.

Secondary hypotheses:

(1) PECS/SAP blocks decrease postoperative cumulative opioid consumption over the initial three postoperative days.
(2) PECS/SAP blocks improve pulmonary mechanics, on each of the postoperative days 1, 2 and 3, from the baseline.

Exploratory Hypothesis:

(1) PECS/SAP blocks improve the Quality-of-Recovery score averaged over the postoperative days 1 and 3, with a difference of 8 points being considered the minimum clinically important difference.[54]
(2) PECSII and SAP blocks reduce persistent postoperative surgical pain

Methods

The study will be conducted at the Cleveland Clinic Main Campus with IRB approval and written informed consent from participating patients.

Inclusion Criteria

1. 18-85 years old;
2. Elective MICS for isolated robotically-assisted mitral valve repair via anterolateral thoracotomy approach.

Exclusion Criteria

1. Weight less than 50 kg;
2. Pregnancy or lactation;
3. Emergency surgery and patients transferred from the ICU to the operating room;
4. Redo cardiothoracic surgery or post-operative reoperation within 72 hours of index procedure (including minor chest wall procedures including tube thoracostomy, thoracentesis or percutaneous drain placement);
5. Anticipated endotracheal intubation > 24 hours;
6. Anticipated non-study nerve block that provides analgesia to the intercostal nerves;
7. Active systemic or cardiopulmonary infection;
8. Mechanical circulatory support;
9. Allergy or contraindication to study local anesthetics;
10. Current chronic pain or routine opioid use (patients on chronic enteral opioids like Percocet or Vicodin) in a dose of > 30 mg of morphine-milligram-equivalents for at least 10 days in last 30 days;
11. Poorly controlled psychiatric disorders;
12. Clinically important current neurologic deficit; e.g. spinal cord injury, paralysis of extremity, any neurologic deficit in the region of the block
13. Active liver disease or cirrhosis;
14. Pacemaker generator or breast implants ipsilateral to surgery;
15. Previous participation in this study.
16. eGFR <30 or chronic kidney disease

Study protocol

Consent will be obtained at least a day before surgery. Patients will be randomized the day of surgery upon presentation to the operating room to either a *treatment group* (PECS/SAP blocks) or a *control group* (standard parenteral analgesia technique with or without incisional LA infiltration) using secure web-based randomization**.** Randomization will be stratified by aortic or mitral valve surgery, with random blocking in each case. The system will be accessed shortly

before surgery to conceal allocation as long as possible. Clinicians will not be blinded to the intervention, but all outcomes will be assessed by research personnel who are blinded to the group assignment.

Anesthetic and Surgical Management

Anesthetic care will be performed as usual for Cleveland Clinic cardiothoracic surgical procedures. This includes use of standard ASA monitors and may include the use of arterial or central venous pressure monitoring, trans-esophageal echocardiography, and lung isolation using a bronchial blocker or a double lumen endotracheal tube. Medication administration for induction and maintenance of anesthesia will also be consistent with usual care and will include intravenous opioids such as fentanyl and hydromorphone. Intravenous lidocaine will not be administered upon induction of anesthesia.

Pressure-control ventilation will be used with a tidal volume not exceeding 6-10 ml/kg ideal body weight during two- and one-lung ventilation. Fluids will be managed conservatively per routine. Patients not extubated at the end of the procedure will be sedated with propofol. Surgical procedures with the assistance of the cardio-pulmonary bypass will be performed in their usual manner. The general approach for the AV replacement will be via the right anterior thoracotomy in the 3rd intercostal space.[4] The MV repair/replacement procedures will be approached via the right lateral thoracotomy inframammary incision in the 4th intercostal space in the mid-axillary line and augmented, as needed, with the stab incisions for the robotic ports.[4]

Chest Wall Analgesia

The anatomic basis for chest wall analgesia has been described in detail previously.[31-33,49] We describe the conduct of the blocks as used for MICS procedures at our institution. The patients randomized to the "blocks" will receive PECS II and serratus anterior for the MVR requiring antero-lateral thoracotomy and port incisions. The PECS/serratus blocks will be performed with the patient under the general anesthesia before incision. If proves impossible to perform blocks preoperatively because of surgical urgency, they will be done at end of surgery.

PECS II blocks:

Patients will be positioned supine, and prepped and draped in a sterile fashion. An ultrasound probe will be placed just below the clavicle in the mid-clavicular line.

For the PECS II block, the probe will be scanned inferiorly and laterally until the plane between the pectoralis minor and serratus muscle is identified. The serratus muscle can be clearly seen coursing over the ribs, while the intercostal muscles are seen in the interspaces between the ribs. Once the plane is identified the needle is again advanced in an "in-plane" fashion. Once the needle location is confirmed by normal saline hydro-dissection, a 20-30 ml of local anesthetic solution is administered into the space.

Serratus plane block:

With the patient in a supine position, a will be placed under the operative side to achieve a slightly lateral tilt. The arm is abducted to expose the costal margin. The patient is prepped and draped in a sterile fashion. The positioning and prepping can be done prior to the PECS block to avoid repositioning if both blocks are being performed. The ultrasound probe is scanned laterally from the pectoralis to the axillary region at approximately the level of the 4th rib. The plane between the serratus muscle and the latissimus dorsi muscle is identified and the needle advanced in an "in-plane" fashion until the tip is between the muscles (superficial SAP block). A small bolus of 0.5 ml of normal saline is used for hydro-dissection of the tissue planes to confirm that the needle is not intramuscular. The needle is then aspirated every 5 ml as 40-50 ml of local anesthetic solution is deposited into the plane. As these are field blocks, adequate volume of infiltration is important in achieving optimal analgesia. If proves impossible to perform as superficial SAP block, it will be given between the posterior border of the Serratus anterior muscle and the corresponding surface of the rib (deep SAP block).

Local anesthetic:

The local anesthetic used for the blocks will be a 0.5% bupivacaine HCL in a dose not to exceed 2.5 mg/kg. The local anesthetic solution can be diluted for smaller patients to allow for appropriate volume of injection. Typically the block has duration of action of less than 12 hours after infiltration.[55] Patients will therefore also be given liposomal bupivacaine (Exparel, Pacira Pharmaceuticals, Inc. San Diego, CA) in a dose of 266 mg in 20 ml can be safely combined with bupivacaine HCL at a ratio not exceeding 2:1, but cannot be combined with other local anesthetics due to the concern of rapid release of encapsulated bupivacaine and subsequent local anesthetic toxicity.[56]

Liposomal bupivacaine dosing is not weight-based and the full 266-mg bottle can be administered to adult thoracic patients. A maximum of 150 mg bupivacaine HCl can be mixed with Exparel. This equates to one 30-mL bottle of 0.5% bupivacaine HCl or two (2) bottles of 0.25% bupivacaine HCl. If a higher volume of the local anesthetic is needed a 10 ml of normal saline can be added to the mixture of bupivacaine HCL and liposomal bupivacaine. Thus patients ≥60 kg will receive 150 mg of bupivacaine HCL, while patients weighing <60 kg need to have the bupivacaine dose calculated but can still receive full 20 ml of Exparel.

Patients randomized to standard analgesia technique will be given parenteral opioids (such as fentanyl or hydromorphone) until they are converted to the enteral medications such as Percocet.

Study Measurements

Patent demographics will be collected from preoperative interviews and chart review (Table 1). Cumulative opioid consumption, non-opioid analgesics, and length of stay will be

captured electronically using Epic and/or PHDS. Other secondary and descriptive outcome data as well as surgical and intraoperative data will be collected prospectively (Table 2).

Data will be obtained from the following sources: The Society of Thoracic Surgeons (STS) database, Cardiovascular Information Registry (CVIR) of the Heart and Vascular Center at the Cleveland Clinic, the electronic medical record (EPIC), and the electronic Anesthesia Record Keeping System (ARKS).

a) OBAS score

The OBAS score questionnaire (Table 3) will be obtained and score calculated by the research team on post-operative days 1-3. We will calculate the average of the OBAS scores obtained. The OBAS score is a validated postoperatively calculated, multi-dimensional questionnaire that consists of 7 items (Table 3) encompassing not only scale-rated pain score but different aspects of analgesia benefits, side effects and overall patient's satisfaction.[53]

The OBAS score is based on 7 questions and ranges from 0 to 28 points that will be administered on POD 1 – POD 3. Although these are longitudinal ordinal data, we will be able to treat OBAS scores as continuous data in the analyses with the lower score correlating with better resolution of the analgesia treatment. A 20% reduction in OBAS geometric mean, a-priori, was defined as minimal clinically important difference..[57,58]

b) Pain assessments

Pain scores on a 0-10 verbal response scale will be evaluated, per routine, by the nursing staff every four hours while patients remain hospitalized. Pain scores (0-10) will be recorded along with the OBAS measurements at rest and then after provocation in the form of a vigorous coughing.

Total opioid consumption as well as intraoperative and postoperative day 1, 2, and 3 totals will be collected and converted to milligram morphine equivalents (Table 4). Patients will not be given opioid patches because there is no known conversion to morphine equivalents.

c) FEV_1, FVC and peak flow

FEV_1, FVC and peak flow will be recorded preoperatively at baseline and at bedside, on the first postoperative mornings 1, 2 and 3. The FEV_1, FVC and peak flows will be measured using Easy on-PC Spirometry System (ndd Medical, Andover MA) with the patient in the sitting position. The measurements and will be obtained by the qualified research personnel and interpreted by the staff pulmonologist. The average of three tests will be considered to be the final result.

d) Quality-of-Recovery-15 (QoR-15) score

The QoR-15 is a quality of recovery score that provides a patient-centered global measure of overall health status after surgery and anesthesia. It comprises 15-item questionnaire with range of responses from 0-150 (http://links.lww.com/ALN/B274). The patients will be given a questionnaire on the first and the third postoperative days, the response collected and the difference from the previous days calculated. Myles et al. reported a minimal clinically important difference in the QoR-15 score of 8 which will be used in this study.[54]

e) Pharmacokinetic (PK) Sample Collection

Blood samples (4 mL each) will be collected from 16 subjects from the treatment group in order to determine pharmacokinetic parameters of liposomal bupivacaine. These samples will be collected at the following time stamps after the injection of the liposomal bupivacaine through PECS/SAP blocks: 15±5 min, 30±5 min, 1h±5 min, 4h±10 min, 24h±20 min, 32h±20 min, 40h±20 min, 48h±20 min, 72h±20 min, 84h±20. The samples will be obtained from a dedicated IV line in a separate location or from an arterial line.

The Blood samples will be collected into K2EDTA tubes and will be centrifuged at 1000 to 1200g for 10 min to obtain plasma within 1 hour of collection. After centrifugation, the plasma will be transferred into polypropylene tubes. The plasma samples will be stored frozen at -20°C or colder until shipment. All samples will be shipped frozen with dry ice to ABS Laboratories, Inc. The shipment address is as follows: Dr. Mira V. Doig ABS Laboratories, Ltd. 36 Hospital Fields Road York, YO10 4DZ, UK

Descriptive and Safety Outcomes

a) Total ICU length of stay;
b) Hospital length of stay;
c) Cumulative non-opioid analgesics included acetaminophen, ketorolac, ibuprofen, gabapentin, and pregabalin will be recorded and compared over the initial three postoperative days;
d) Anxiolytics such as alprazolam, lorazepam, and diazepam will be recorded and compared.

Statistical analysis

We will compare groups on potentially confounding demographic and preoperative risk factors listed in Table 1 using appropriate summary statistics (i.e., mean ± standard deviation, median [Q1, Q3], or N (%) as appropriate) as well as surgical and intraoperative data will be collected prospectively (Table 2). Randomized groups will be compared on balance on these characteristics using absolute standardized difference, defined as the absolute difference in means, mean ranks, or proportions divided by the pooled standard deviation.
Analyses will be modified intent-to-treat, including all randomized patients who received PECSII/serratus blocks (regardless of whether it's consistent with the randomization).

We will summarize descriptive and safety outcomes by randomized groups using appropriate summary statistics (i.e., mean ± standard deviation, median [Q1, Q3], or N (%) as appropriate). No statistical tests will be performed on these outcomes.
We will use an alpha of 0.05 for both the primary and secondary analyses, with a significance criterion of 0.05 for the primary analysis and 0.0167 for each secondary analysis (i.e., 0.05/3, Bonferroni correction). Analyses will be completed using SAS version 9.4 or newer (SAS Institute, Carey, North Carolina) or R version 3.2.4 or newer (R Project for Statistical Computing, Vienna, Austria).

Primary analysis

We will estimate the PECS/SAP blocks effect on OBAS scores using a repeated measures linear regression model with an autoregressive correlation structure, adjusting for ALL imbalanced confounders (if any). Based on these model we would be able to claim if the PECS/SAP blocks had any effect on the OBAS score compared to standard routine analgesia during any of the postoperative time up to third postoperative day. Due to non-normality of OBAS score, it will be log-transformed for analysis. We will report model based P-value and the geometric mean ratio for OBAS scores along with confidence intervals. To assess whether the PECS/SAP blocks effect is heterogeneous over three postop days, we will assess the treatment-by-time interaction using a significance criterion of 0.20. If it appears that the treatment effect is heterogeneous, we will report the treatment effect separately for each postoperative day POD 1, POD 2 and POD 3 using a Bonferroni correction as appropriate (e.g., 0.05/3; 3 postoperative days).

Secondary Analysis

Morphine equivalents will be calculated based on the conversions specified in Table 4 below. Total opioid consumption as well as intraoperative and postoperative day 1, 2, and 3 totals will be collected and converted to milligram morphine equivalents. Patients will not be provided opioid patches for pain relief because there is no known conversion to morphine equivalents.
Cumulative opioid consumption data is typically right skewed, so we will normalize it for analyses using a log transformation. Opioid consumption will be reported separately for postoperative day (POD) 0 after surgery, POD 1, POD2, and POD3. We will estimate the effect of PECS/SAP blocks to standard routine analgesia on log cumulative opioid consumption using a repeated measures linear regression model with an autoregressive correlation structure, adjusting for any imbalanced baseline or surgical characteristics between groups.
To assess whether the effect of PECS/SAP blocks is heterogeneous over time, we will assess the treatment-by-time interaction using a significance criterion of 0.20. If it appears that the treatment effect is heterogeneous, we will report the treatment effect separately for each postoperative day using a Bonferroni correction as appropriate (e.g., 0.05/3; 3 postoperative days).

We will estimate the effect of PECS/SAP blocks on FEV_1 , FVC and peak flow rate using three separate repeated measures regression models with an autoregressive correlation structure, adjusting for baseline FEV_1 , FVC , peak flow rate and imbalanced confounders (if any).
The Wald tests for regression model coefficients will be used to test each of the secondary hypotheses; the Bonferroni correction for four outcomes will be employed to control the overall Type I error rate at 0.05 for the secondary outcomes.

Exploratory Analysis
Two separate linear regression models will be developed to assess the relationship between analgesia strategy and each of the two exploratory outcomes (quality of recovery after anesthesia survey and persistent postoperative surgical pain). To compare patients from two groups on these outcomes mean difference will be reported along with 95% confidence intervals.

Descriptive and Safety Analyses
We will summarize descriptive and safety outcomes by randomized groups using appropriate summary statistics (i.e., mean ± standard deviation, median [Q1, Q3], or N (%) as appropriate). No statistical tests will be performed on these outcomes.

Sample Size Considerations

Per Mamoun, observed a coefficient of variation (CV) of 53% in the placebo group of cardiac surgery patients.[59] We assumed a slightly more conservative CV of 50% and that the treatment effect favored PECS/SAP blocks by 20% (i.e., true ratio of geometric means of 0.80). We will need to enroll approximately 192 patients (96 per group) to have 90% power at the 0.05 significance level to detect superiority of PECS/SAP blocks to standard routine parental and enteral analgesia in patients recovering from MICS .

We also plan for two interim analyses at 1/3 and 2/3 of the planned enrollment to assess safety, feasibility and formal efficacy and futility. Therefore, interim adjusted sample size is N=98 patients per group, or N=196 total. We will use the conservative gamma spending function with parameters -5 and -5 for alpha (efficacy) and beta (futility), respectively. If the alternative hypothesis is true (the treatment effect exists) there will be a cumulative probability of 10%, 53% and 100% of crossing either an efficacy or futility boundary at the 1st, 2d and final analyses, respectively (Table A and Figure 1 below contains boundary Information). Planned first and second interim analyses will be performed upon accrual of 66 and 132 patients respectively. **Therefore, planned number of patients for the analysis is N=98 patients per group, or N=196 total.**

We will also enroll at least 5 pilot patients in the beginning of the study to test the feasibility of protocol adherence and data collection.

Table A. Boundary Information for interim analysis (3 analyses = 3 stages):

Boundary Information (Standardized Z Scale)
Null Reference = 0

Stage	Information Level	Alternative Reference		Boundary Values			
				Lower		Upper	
	Proportion	Lower	Upper	Alpha	Beta	Beta	Alpha
1	0.3333	-1.88730	1.88730	-3.18319	-0.02167	0.02167	3.18319
2	0.6667	-2.66904	2.66904	-2.64022	-0.53609	0.53609	2.64022
3	1.0000	-3.26890	3.26890	-1.97517	-1.97517	1.97517	1.97517

Figure 1. Boundary plot

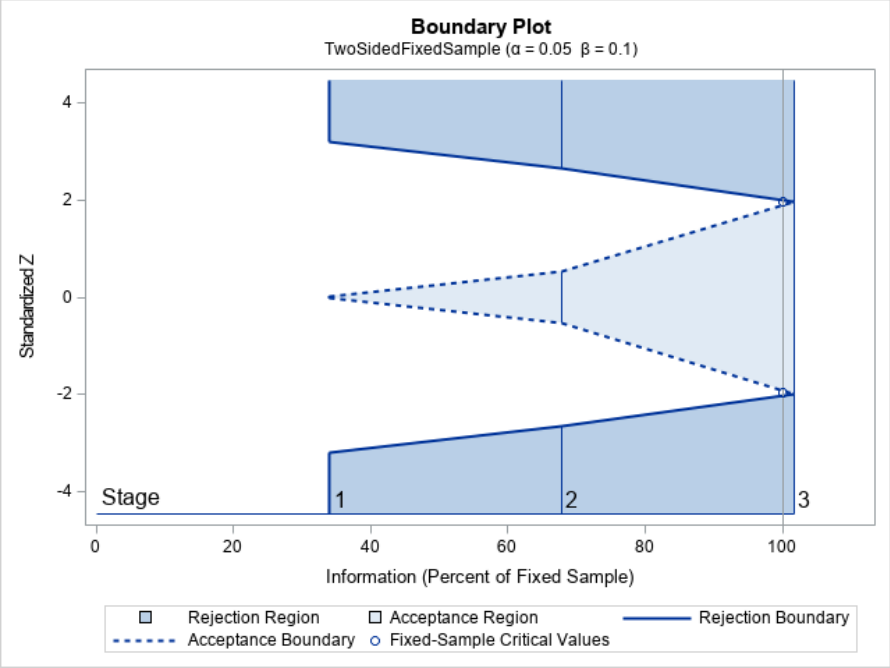

Table 1: Patient demographic and preoperative risk factors

Sex
Age (years)
Surgery Type (Robot MVR, thoracotomy MVR, AVR through RAT)
Coronary Artery Disease
Hypertension
Pervious Myocardial infarction
Peripheral Arterial Disease
Previous vascular surgery
Smoker (current or former)
Cerebrovascular disease
Diabetes mellitus

Renal failure: Indicate whether the patient has 1) a documented history of renal failure and/or 2) a history of creatinine > 2.0. Prior renal transplant patients are not included as pre-op renal failure unless since transplantation their creatinine has been or currently is > 2.0.
Left ventricular EF

Table 2: Surgical, intraoperative and postoperative data

Time on CPB
X-clamp time
RBCs
Plt
FFP
Cryo
Inotropes in the OR
Time to extubation
Length of ICU stay
Length of hospital stay
Comps-Pulm-Pneumonia Indicate whether the patient had Pneumonia diagnosed by any of the following: positive cultures of sputum, transtracheal fluid, bronchial washings, and/or clinical findings consistent with the diagnosis of pneumonia. May include chest X-ray diagnostic of pulmonary infiltrates
Comps-Pulm-Vent Prol Indicate whether the patient had Pulmonary Insufficiency requiring ventilator. Include (but not limited to) causes such as ARDS and pulmonary edema and/or any patient requiring mechanical

ventilation > 24 hours postoperatively
Comps-Other-GI Comps Indicate whether the patient had a postoperative occurrence of any GI complication including: a. GI bleeding requiring transfusion b. pancreatitis with abnormal amylase/lipase requiring nasogastric (NG) suction therapy c. cholecystitis requiring cholecystectomy or drainage d. mesenteric ischemia requiring exploration e. other GI complication

Table 3: OBAS score – To calculate the OBAS score, obtain sum of scores in questions 1–6 and add '4 minus score in question 7'.

1	Please rate your current pain at rest	0 minimal pain, 1 mild pain, 2 moderate pain, 3 severe pain, and 4 maximum imaginable pain
2	Please grade any distress and bother from vomiting in the past 24 h	0 = not at all to 4 = very much
3	Please grade any distress and bother from itching in the past 24 h	0 = not at all to 4 = very much
4	Please grade any distress and bother from sweating in the past 24 h	0 = not at all to 4 = very much
5	Please grade any distress and bother from freezing in the past 24 h	0 = not at all to 4 = very much
6	Please grade any distress and bother from dizziness in the past 24 h	0 = not at all to 4 = very much
7	How satisfied are you with your pain treatment during the past 24 h	0 = not at all to 4 = very much

Table 4: Morphine Equivalent Conversion Table

Agent	PO (mg)	IV (mg)

Morphine	**30**	**10**
Hydromorphone	**7.5**	**1.5**
Fentanyl	**-**	**0.1**
Oxycodone	**20**	**-**
Hydrocodone	**30**	**-**

Table 4: Surgical, intraoperative and postoperative data

Time on CPB
X-clamp time
RBCs
Plt
FFP
Cryo
Inotropes in the OR
Time to extubation
Length of ICU stay
Length of hospital stay **Intraoperative ultrasound record and image of fascial plain blocks (SAP and PECS)**

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