Parasternal Intercostal Nerve Block in Post-Cardiac Surgery Patients: A randomized, controlled trial of extended-release liposomal bupivacaine (Exparel®) versus placebo

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I. PURPOSE OF THE STUDY AND BACKGROUND

Purpose of the study.

The aim of this study is to examine the effect of parasternal intercostal nerve blocks with extended-release liposome bupivacaine (Exparel®) on pain control in patients undergoing non-emergent cardiac surgery in a prospective randomized controlled trial.

Background.

Inadequate post-operative pain control is a significant problem faced by many patients undergoing cardiac, thoracic and abdominal surgery. Barriers to adequate pain control include unwillingness or inability of the patient to request for pain medication, inability of nursing to reach the patient in a timely manner and hesitance of health care providers to prescribe and reluctance of nurses to administer pain medication[1]. Poorly controlled pain has been shown to lead to various physiologic changes including tachycardia and hypertension, which causes increased myocardial oxygen demand. In addition, inadequate pain control results in splinting and decreased mobilization, increased morbidity and longer lengths of stay[1,2].

Opioids along with non-opioid and nonsteroidal anti-inflammatory agents are the mainstays of treatment for post-operative pain in adult cardiac patients. However, the doses of opioid often required can result in respiratory depression, delay of extubation, nausea, vomiting, delirium, slowing of gastrointestinal motility and hypotension from peripheral vasodilatation[2,3]. For these reasons, a better method of pain management would be valuable. Neuraxial anesthesia (e.g. thoracic epidural anesthesia, spinal anesthesia and paravertebral blocks) has shown benefits, yet remains controversial and not widely accepted in cardiac surgery due to concerns regarding associated hypotension and paresthesias, as well as potential development of epidural abscess or epidural hematoma following anticoagulation[3,4].

Parasternal intercostal blocks using local anesthetics have been shown to provide improved post-operative pain control and decreased opiate requirements with less potential complications[5-8]. The sensory innervation of the thorax is provided by the 2nd through 6th intercostal nerves. The intercostal nerves terminate in anterior cutaneous branches, which divide into medial and lateral branches, providing innervation to the anterior chest wall (Fig.1). A parasternal intercostal nerve block targets the anterior intercostal nerves just lateral to the sternum (Fig. 2a). Local anesthetic is injected along the undersurface of each rib, infiltrating the space where the intercostal nerve travels (Fig. 2b). By doing this prior to sternal closure, the surgeon is able to perform the block under direct visualization of the nerves and rib interspaces.

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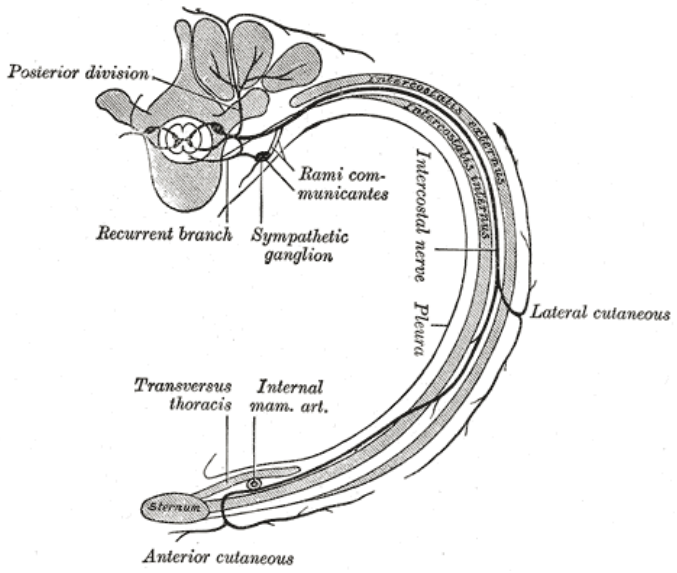
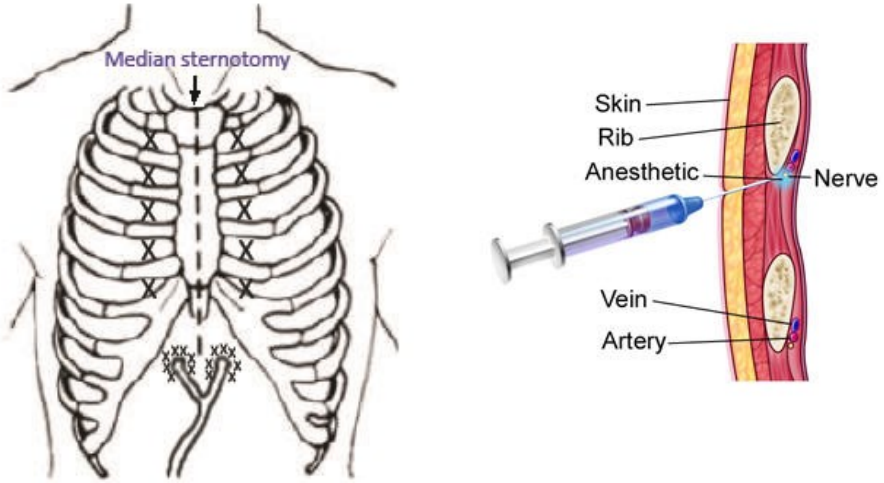


Reproduced from. Gray, Henry. *Diagram of the course and branches of a typical intercostal nerve*. 1918. Illustration. Anatomy of the Human Body, 20th ed. By Henry Gray. Philadelphia, PA : Lea & Fbiger, 1918.

Figure 1. Saggital view of intercostal space. The intercostal nerve gives off the lateral and anterior cutaneous nerves. The anterior cutaneous nerve penetrates through the intercostal muscles just lateral to the sternum before dividing into medial and lateral branches. These branches supply the anterior chest wall.

Images adapted from: (a) Singer, Raymond L. "Median sternotomy." Illustration. 12 Sept. 2012.



http://www.heartlungdoc.com/heart/bypass/coronary_images/Sternotomy%20Diagram.jpg. Accessed 12 Sept. 2012. (b) "Intercostal nerve block." Illustration. http://www.advancedorthopain.com/pain-procedures/images/interc1.jpg. Accessed 21 Sept. 2012.

Figure 2. Parasternal intercostal nerve block. **(a)** Target injection sites are marked (X). Each intercostal space was infiltrated, 2 cm lateral to the sternal border, as well as the deep subcutaneous space around the mediastinal tubes. **(b)** Local anesthetic is injected along the undersurface of each rib, where the neurovascular bundle travels.

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In a randomized-controlled trial (RCT) comparing parasternal nerve blocks using ropivacaine vs. placebo, Barr et al.[5] showed a 30-50% reduction in pain scores and total opiate use. The differences between placebo and ropivacaine group were greatest over the first 12 hours post-op and subsequently diminished over the next 12 hours of observation[5]. These benefits were extended over 72 hours with the addition of continuous local infusion of ropivacaine[6]. Thus demonstrating that the efficacy of a parasternal nerve block is limited by the duration of action of the local anesthetic used. Bupivacaine is another long-acting local anesthetic (amide-type local anesthetic) that is routinely used for postsurgical anesthesia, yet the maximum duration of this drug is only 6-12 hours. We hypothesize that use of a longer-acting local anesthetic will potentiate the benefits of improved pain control and reduced opioid requirements.

Exparel® is a long-acting, extended-release liposome injection of bupivacaine that has been FDA-approved for "single-dose infiltration into the surgical site to produce postsurgical anesthesia". Exparel® is a liquid suspension of spherical, microsomal liposomes (DepoFoam® drug delivery system) containing multiple aqueous chambers of encapsulated bupivacaine[8-10] (Fig. 3). Bupivacaine is gradually released from the liposomes by diffusion as the unprotonated (uncharged) form of bupivacaine. This formulation allows for sustained release of bupivacaine at the site of injection without exposing patients to toxic plasma concentrations[10-11]. In clinical trials, Depofoam® bupivacaine has shown duration of action up to 72 to 96 hours, while peak plasma bupivacaine concentration (0.4 to 1.4 µg/ml) remained well below the reported toxic plasma concentration (2-4 µg/ml)[11-14]. Randomized clinical trials (RCT) comparing Exparel to bupivacaine and placebo in various surgeries (e.g. hemorrhoidectomy, bunionectomy, inguinal hernia repair, total knee replacement) have shown improved outcomes of pain control and decreased narcotic requirements. In RCTs with patients undergoing hemorrhoidectomies, benefits from Exparel® were more substantial from 12-72 hours with a 47% reduction in cumulative pain score and 66% relative reduction in opioid consumption compared to bupivacaine[12-13].

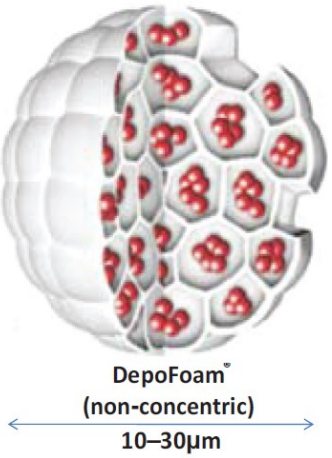

Figure 3. Cross-sectional diagram of DepoFoam® drug delivery system containing aqueous chambers filled with Bupivacaine.

Reproduced from Chahar P, Cummings KC. *Liposomal bupivacaine: a review of a new bupivacaine formulation.* J Pain Research. 2012.

To compare differences in pain control, we will use a number of validated pain assessment tools. These include the adult nonverbal pain scale (NVPS), numerical rating scale (NRS) and brief pain inventory (BPI) (see Appendix II and III). The NVPS has been adopted by the cardiovascular ICU (CVICU) for assessing pain in critically-ill, intubated patients. It includes assessments of the patient's face, body movements, muscle tension and vital signs to determine a total score ranging from 0 to 10. It has been shown to exhibit high reliability and inter-rater agreement, as well as increase patient and staff satisfaction[15-16]. The NRS is an 11-point scale ranging from 0, "no pain", to 10, "the worst possible pain", that is used by nursing staff for

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assessing and documenting pain in extubated, alert patients. The scale has shown high sensitivity and simplicity[17]. Moreover it is interval and allows for parametric analysis. The BPI consists of four questions rating pain severity and seven questions regarding impact of pain on daily function, allowing calculation of pain severity and interference indices for comparison. Studies have shown that BPI scores correlate with the number of days from surgery and decreasing analgesic requirements[18-20].

Exparel® is not currently FDA-approved for peripheral nerve blocks. There are two ongoing clinical trials studying the use of Exparel® for femoral nerve blocks[21-22]. However, Exparel® has not previously been studied for our specific application. Thus, we are conducting this study to evaluate the efficacy and safety of Exparel® in parasternal nerve blocks in cardiac surgery patients. Successful use of Exparel® for parasternal intercostal nerve blocks may revolutionize the management of post-cardiac surgery pain. Optimal pain control and reduced opioid doses would enable earlier extubation and mobilization, less opioid-associated morbidity and shorter ICU and total hospital lengths of stay.

Hypothesis: We hypothesize that administration of Exparel® in parasternal nerve blocks will provide improved pain control and decreased narcotic use in the adult post-operative cardiac surgery patient.

Primary aim: To determine if there is a statistically significant improvement in analgesia and decreased opioid requirements in the post-operative period.

Secondary aim: To look at differences in LOS (ICU and hospital), time to return of bowel function, and time to return to work or daily activities. We will also look at incidence of complications related to inadequate pain control and the incidence of adverse events.

II. CHARACTERISTICS OF THE RESEARCH POPULATION

Number of subjects.

The study will include 78 patients, 39 patients in the study drug arm and 39 patients in the control arm. Since there are two primary outcomes, we set the type I error at 0.025 for the power analysis. Based on results from a prior study by Barr et al.[5], we assumed a baseline Numerical Rating Scale (NRS) score for pain of 53.2 with standard deviation of 24.1 and a baseline cumulative morphine requirement over 24 hours of 23.2 mg with standard deviation of 8.3 mg. The proposed sample size was calculated to achieve 86% power to detect a 30% decrease in mean NRS scores at the 2.5% level of type I error (two-sided). This sample size also provides for a 98% power to detect a 30% decrease in total opioid consumption over the first 24 hours post-operatively. Note that we assumed the standard deviation decreases accordingly. A 5% drop out rate was included into the sample size calculation.

Gender of Subjects.

The study will include male subjects and non-pregnant female subjects.

Age of Subjects.

Adults (age ≥ 18 years old) will be included. Exparel® is currently only approved in patients ≥ 18 years old.

Racial and Ethnic Origin.

Subjects of all racial and ethnic origins will be included in the study.

Inclusion Criteria.

We will include adult patients (≥ 18 year old) undergoing non-emergent coronary artery bypass grafting surgery (on and off pump) requiring a median sternotomy.

Exclusion Criteria.

- Concomitant cardiac procedures (e.g. aortic valve repair/replacement, mitral valve repair/replacement, aortic root replacements)
- Redo sternotomy.
- < 50 kg (Exparel® is currently only approved in patients > 50 kg).
- Pregnant or nursing
- History of alcohol, narcotic or illicit drug abuse
- Participation in another study evaluating investigational medications within the past 30 days
- Taking narcotic analgesics within 3 days pre-operatively or perioperative stress-dose steroids.
- Chronic non-cardiac pain (e.g. lower back pain, fibromyalgia) requiring narcotic analgesics.
- Pre-operative mild liver insufficiency as defined by LFTs (i.e. ALT, AST) ≥ 1.5 times the upper limit of normal (ULN: ALT: 0-35 U/L, AST: 0-35 U/L, Alk Phos 35-105 U/L, Total bilirubin: 0-1.2 mg/dL)
- Pre-operative mild renal insufficiency (Cr ≥ 1.5 mg/dL)
- Allergy to amide-type anesthetics
- Recurrent ventricular arrhythmias, low cardiac output requiring inotrope and/or intra-aortic balloon pump support, LVEF < 30% at time of pre-operative screening/evaluation.
- Unable to provide informed consent or unable to understand how to use pain rating scales.
- Inability to understand or operate the patient-controlled analgesia (PCA) machine.

Withdrawal Criteria.

Patients meeting these intra-operative and post-operative criteria will be withdrawn from the study because of the likelihood that these characteristics will independently affect primary and secondary study outcomes. However, primary and secondary outcomes will still be collected for these patients and results included in an "intention-to-treat" analysis.

- Post-operative intubation longer than 16 hours.
- Cardiopulmonary bypass time > 3 hours or aortic cross-clamp time > 120 minutes.
- Return to OR during hospital admission.

Vulnerable Subjects.

No vulnerable subjects will be included in this study. Only patients deemed competent to voluntarily consent to participation in this study will be included.

III. METHODS AND PROCEDURES

Methods and Procedures.

Refer to Appendix I for overview of Study Schedule.

Patient enrollment

Screening procedures will be performed in the outpatient clinic, inpatient floor or cardiac cath lab. During the screening visit, medical/surgical history, vital sign measurements, and routine clinical laboratory tests, which are normally obtained in all cardiac surgery patients (complete metabolic panel, CBC, INR/PTT). If the patient meets eligibility criteria and is willing to participate, then informed consent will be obtained. Consenting patients will also undergo drug/alcohol screening and forced vital capacity (FVC) measurement prior to surgery. The patients will be trained on the pain assessment tools used during the study, including the adult NVPS and NRS (see Appendix II).

Prior to the planned operation, patients will be administered the Brief Pain Inventory to establish baseline pain scores (see Appendix III). The patient will also receive a sheet reviewing the NVPS and NRS pain assessment scales and be asked to rate their pain on the NRS scale. They will also be instructed on how to use the PCA pump prior to surgery.

On the day of surgery, the subjects' history, physical and labs will be reviewed by research staff to confirm study eligibility. They will also be instructed on how to use the incentive spirometer and their peak inspiratory capacity (IC) will be measured.

Randomization and Blinding

Patients will be randomized on the day of surgery to either placebo or treatment group. The subjects will be randomized in blocks of 4 to ensure a 1:1 ratio of placebo to treatment groups.

- Placebo: 0.9% normal saline
- Treatment group: 0.53% Exparel®

A randomization sheet will be generated by the study pharmacist, listing the randomization schedule in sequence for each block. The study pharmacist will have control of the randomization sheet. At the time of randomization, he will go to the next available row to determine which medication to disperse. The randomization sheet will document each subject's number, initials, date of surgery and study arm (active or placebo).

The study pharmacist will hold the key identifying which study group corresponds with which letter. In order to maintain blinding of the study investigators, the pharmacist will not reveal the subject's group assignment and data collection will be done according to the subject number. At quarterly intervals during the trial, the study pharmacist will reveal the blinding to the Independent Data/Safety Monitor (DSM) only. This will enable the Independent DSM to capture for any alarming trends in adverse events or serious adverse events as they are occurring. At completion of data collection and analysis for the entire study, the pharmacist will provide the study investigators with a copy of the report revealing which subject belonged to which study group.

The subjects will be blinded to their study arm and remain blinded for the entire duration of this study. Subjects who wish to know which drug they received (Exparel® or placebo), may contact the PI or co-PI and they will be informed of their study group following completion the study.

The study investigators, surgeon administering the medications, operating room staff and ICU/floor staff will all remain blinded. Only the pharmacist who will prepare and dispense the medication will be unblinded.

Anesthetic Regimen

A standard anesthetic regimen to promote early extubation will be used, per our institutions protocols. The regimen will include:

- Pre-induction with midazolam.
- Induction with midazolam, fentanyl/sufentanyl, vecuronium/rocuronium, and isoflurane.
- Maintenance of intra-operative anesthesia with isoflurance and vecuronium/rocuronium.

Intraoperative monitoring will include standard ASA monitor, an arterial catheter and a central venous catheter. Pulmonary arterial catheters and transesophageal echocardiography will be used per institutional standards.

Parasternal intercostal nerve block

The parasternal blocks will be performed by a blinded surgeon at the end of surgery, just prior to sternal closure.

The medication will be prepared and dispersed by the study pharmacist in a concealed vial. The contents of the vial will be drawn up into two sheathed sterile 30 cc syringes by the operating room staff. Due to the distinct visual characteristics of normal saline (transparent) compared to Exparel® (translucent), sheathed syringes will be used to maintain blinding of the surgeon and operating room staff.

The components of a parasternal nerve block include anesthetizing the anterior cutaneous branches of intercostal nerves two through six and the deep subcutaneous layers around the mediastinal drain sites (Fig. 2). First, sequential intercostal blocks will be performed with 4 mL per intercostal space across 5 intercostal spaces bilaterally. Then 10 mL will be injected in the superficial to deep subcutaneous tissue surrounding mediastinal drains. A total of 50 mL of either 0.9% normal saline or 50 mL of 0.53% Exparel® will be used for the parasternal block.

Cardiac and Neurologic Monitoring

Continuous electrocardiogram (ECG) and vital sign (heart rate, blood pressure, respiratory rate) monitoring will be performed following administration of Exparel®, per standard protocol. Electrocardiogram tracing and vital signs will be documented pre-injection, during injection, post-injection, and at 1 hour and 2 hour post injection. Continuous ECG monitoring will be maintained for at least 48 hours post dose. Vital signs will be measured and recorded at time 0, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours post dose.

Neurologic assessments will include evaluation for signs of lethargy, restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors and convulsions. Patients will be assessed to the extent possible while still intubated and recovering from anesthesia. The assessments will be performed upon the patient's initial arrival to the ICU (prior to initiation of continuous sedation) and at 2, 4, 8, 12, 24, 36 and 48 hours post dose.

If a subject exhibits signs of suspected bupivacaine toxicity (e.g. cardiotoxic and/or neurotoxic signs or symptoms), then a blood sample will be drawn as soon as possible to determine plasma bupivacaine levels. Cardiovascular system reactions may include atrioventricular block , ventricular arrhythmias and/or cardiac arrest. Central nervous system reactions may include lethargy, restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors and/or convulsions.

Post-operative pain control

Patients will be treated with fentanyl boluses during the immediate post-operative period and while intubated

in the ICU, until they are able to use the PCA. Pain will be evaluated using the adult NVPS (see Appendix II) and medication will be administered for NVPS score ≥ 4. Per routine cardiovascular ICU protocol, patients will receive Indomethacin 25 mg every 8 hours for three doses if they meet the following criteria: (1) Cr < 1.5 and (2) age < 75.

The patients will be extubated per the standard cardiovascular ICU protocol (see Appendix IV). Following extubation, pain will be assessed using the NRS (see Appendix II) and pain regimen will be adjusted for NRS score ≥ 4. All patients will receive either fentanyl IV or hydromorphone IV (if fentanyl is poorly tolerated or patient is allergic to fentanyl) via PCA device following extubation. The PCA will be continued for the first 48 hrs postoperatively.

The initial PCA orders will be written by a study team member. If the PCA requires dose adjustment or medication change, then the cardiovascular ICU or floor providers will modify the order per the protocol below. This is a safety mechanism, in case a study team member is unavailable at the time.

The PCA will be set accordingly (see Appendix V):

- A fentanyl PCA will be set up with the following specifications:
  - Loading dose: 1 mcg/kg IV bolus fentanyl divided into 2 doses given 10 minutes apart
  - Bolus dose: 10 mcg IV bolus fentanyl with a lockout interval of 15 minutes and maximum 1 hr limit of 80 mcg. The incremental bolus dose of fentanyl will be increased by 25-50% if analgesia is inadequate (NRS ≥ 4).
  - If the patient experiences undue side effects from fentanyl PCA (see below) and pain is still inadequately controlled at current dosage, then the patient will be switched over to a dilaudid PCA. However, if pain is controlled with the fentanyl PCA bolus, but the patient is experiencing undue side effects, then the following steps will be taken:
    1. Decrease the PCA bolus dose to 7.5 mcg IV bolus with a lockout interval of 15 minutes.
    2. If the patient still does not tolerate the fentanyl PCA well, then decrease the PCA bolus dose to 5.5 mcg IV bolus with a lockout interval of 15 minutes.
    3. If the patient still does not tolerate the fentanyl PCA well, then decrease the PCA bolus dose to 4.0 mcg IV bolus with a lockout interval of 15 minutes.
    4. If patient continues to not tolerate the fentanyl PCA well, then switch over to a dilaudid PCA.

- If the patient is allergic to fentanyl or continues to poorly tolerate fentanyl (despite dose adjustments), then the patient will be switched over to a dilaudid PCA:
  - Loading dose = 0.02 mg/kg IV bolus hydromorphone divided into 2 doses given 10 minutes apart,
  - Bolus dose = 0.2 mg IV bolus hydromorphone with a lockout interval of 15 minutes and maximum 1 hr limit of 1.6 mg. The incremental bolus dose of hydromorphone will be increased by 25-50% if analgesia is inadequate (NRS ≥ 4).

- "Poor tolerance" and/or undue side effects of the narcotic may include:
  - Excessive nausea/vomiting refractory to antiemetics.
  - Itching/rash deemed related to narcotic and refractory to Benadryl.
  - Altered mental status or feeling "high" from narcotic bolus.

- The PCA dose may be titrated up or down to attain adequate anesthesia and minimize side effects from the narcotics.
- Naloxone may be used for respiratory depression (respiratory rate < 8 breaths per minute), over-sedation or muscle rigidity secondary to opioid overdose. The PCA bolus dose will be decreased by 25-50% if this occurs.

Following discontinuation of the PCA, patients will be transitioned to Percocet 5/325 mg 1-2 tabs PO every 4 hours as needed or Hydrocodone-Acetaminophen 5/325 mg 1-2 tabs PO every 6 hours as needed.

Rescue pain medication:

- A dose of Toradol 15 mg IV or Tramadol 50-100 mg PO will be administered as rescue medication if patient is still reporting inadequate analgesia (NRS ≥ 4), but has already met the 1 hour maximum dose of fentanyl or dilaudid.
- Once the patient has been transitioned to PO pain medications, a dose of dilaudid 0.5 mg IV or morphine 2 mg IV may be administered as rescue medication if the patient is still reporting inadequate analgesia (NRS ≥ 4), but cannot receive additional narcotics (i.e. Percocet or Hydrocodone-Acetaminophen) for that time period.

Standardized bowel regimen

Bowel regimens will be standardized to control for differences in prescribed stool softeners and laxatives.

All patients will receive Colace 1 tab twice daily, Dulcolax 1 tab oral every morning and Senna 1 tab nightly once they are able to tolerate PO medications. If patients do not have a bowel movement by post-operative day 2 (POD #2), the bowel regiment will be increased until the patient has a bowel movement. The order of escalation of prescribed medications will be as follows:

- POD #2 AM: Dulcolax suppository + Milk of Magnesia
- POD #2 PM: Lactulose oral or Miralax
- POD #3 AM: Lactulose oral or Miralax (whichever he/she did not receive on POD #2)
- POD #3 PM: Enema (soapsuds, fleets, mineral oil, etc.)

Follow-up

The subjects will be seen by their primary care physician within 7-10 days per standard URMC protocol. They will return to clinic for a post-operative visit approximately 30 days from discharge. During this visit, they will be administered a brief questionnaire regarding presence/quality of continued pain following discharge (BPI-SF, see Appendix III). They will also be asked to rate the quality of their pain control during their hospitalization and recall their time to return to work or daily activities. During this visit, they will also be debriefed about the study.

In addition, in order to assess the success of maintenance of the blind, we will ask the subjects to: (1) guess which treatment (Exparel® or placebo) they think they received in the study, (2) express their degree of certainty regarding their guess, and (3) explain their reasons for their guess.

Measurements/Data collection.

Pain assessment:

The adult NVPS will be used to assess pain while patient is intubated in the ICU. This scale is used routinely in intubated and nonverbal critically ill patients in the Cardiovascular ICU (CVICU). The NVPS will be performed by a blinded care provider (e.g. nurse or nurse manager) who is trained on how to use the scale. Time 0 will be designated as the time the patient leaves the OR. The NVPS will be performed every 2 hrs for the first 4 hrs and then every 4 hrs following until the patient is extubated.

The numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain ever) will be used to assess pain

once the patient is extubated and alert. The scale will be administered every 4 hrs for the first 72 hrs post-op.

Cumulate pain scores at time points at 2, 4, 8, 12, 24, 36, 48, 60 and 72 hrs will be compared.

Opioid requirements:

All narcotics will be converted to fentanyl equivalents (see Appendix VI) in order to calculate total morphine requirements for each interval. Cumulate morphine equivalents used at time intervals 2, 4, 8, 12, 24, 36, 48, 60 and 72 hours will be calculated.

Secondary outcomes:

"ICU length of stay" will be calculated as the time the patient leaves the OR to the time that the patient is deemed appropriate for transfer out of the ICU by the treating physician and nursing staff, in hours.

"Hospital length of stay" will be calculated as the time the patient leaves the OR to the time of discharge, in days.

"Time to extubation" will be calculated as time the patient leaves the OR to the time of extubation, in hours.

"Time to return of bowel function" will be calculated as the time the patient leaves the OR to the time of first recorded bowel movement, in days.

Other variables:

Splinting can occur from inadequately controlled pain, resulting in the subject avoiding deep inspiration. The degree of splinting will be measured by a change in bedside inspiratory capacity (IC) at post-operative day 1-2 from preoperative IC.

Adverse events will be recorded:
- Adverse cardiac events: angina, myocardial infarction, new cardiac arrhythmia
- Neurologic: transient ischemic attack (TIA), stroke (CVA)
- Gastrointestinal: constipation, ileus, bowel obstruction
- Pulmonary: Pneumonia
- Renal: renal insufficiency
- Wound infection, wound dehiscence

Assessment of the blind

Subject responses at follow-up regarding speculation about the treatments received will be compared to each subjects actual group assignment in order to determine adequacy of the blind.

Data Analysis.

Data Analysis
- Patient demographics/Pre-op characteristics:
    - Age, sex, race, Body surface area (BSA)/BMI
    - Co-morbid diseases: Diabetes mellitus, COPD, smoking, hypertension, coronary artery disease
    - Left ventricular ejection fraction (%)

  - Creatinine (Cr), Cr clearance
  - Functional status: New York Heart Association (NYHA) class, American Society of Anesthesiologists (ASA) classification
- Intra-operative characteristics:
  - Operation type: CABG (on/off bypass), AVR, MV repair/replacement, Maze, Other (i.e. TV repair/replacement, ASD closure)
  - Internal mammary artery (IMA) harvested (one or two)
  - Cardiopulmonary bypass time (min)
  - Aortic cross-clamp time (min)
  - Intraoperative fentanyl (μg), intraoperative versed (mg)
- Pain assessment:
  - Calculate mean area under the curve (AUC) for adult NVPS scores over the time intervals "0-2", "0-4", "0-8" and "0-12" hours.
  - Calculate mean AUC for NRS scores over the time intervals "0-12", "0-24", "0-36", "0-48", "0-60" and "0-72" hours.
- Opioid requirement:
  - Calculate mean cumulative fentanyl equivalent use for time intervals "0-2", "0-4", "0-8", "0-12", "0-24", "0-36", "0-48", "0-60" and "0-72" hours.
  - Use of breakthrough pain medication (e.g. Toradol or Tramadol)
- ICU length of stay:
  - Calculate mean lengths of stay (hours) for placebo and Exparel® groups.
- Hospital length of stay:
  - Calculate mean lengths of stay (days) for placebo and Exparel® groups.
- Time to extubation:
  - Calculate mean time to extubation (hours) for placebo and Exparel® groups.
- Time to return of bowel function:
  - Calculate mean time to return of bowel function for placebo and Exparel® groups.
- Splinting
  - Mean change in IC from pre-operative to POD #1-2 in both treatment arms.
- Assessment of blind
  - Calculate the percentage of correctly guessed treatment assignments.

Statistical analysis

Descriptive statistics will be reported for each group. Means with standard deviation and 95% confidence intervals of the means will be reported for continuous variables and frequency and proportion distribution will be reported for categorical outcomes.

Student t-test (for normally distributed continuous variables) and Wilcoxon rank sum tests (for non-normally distributed variables) will be used to compare continuous outcomes such as AUC for adult NVPS/ NRS and opioid requirements between the two groups. For categorical outcomes, chi-square tests will be used to compare differences between the two groups. If some cell counts are small and the asymptotic tests are not reliable, then exact methods will be used. A general linear regression model for NRS scores will be applied to show the main effect for the treatment group, adjusting for covariates. Regression analysis will also be applied to opioid requirements. For the binary outcome of whether a patient has reached his/her maximum allowed dose of opioid, logistic regression models will be applied. For the opioid requirement outcome, patients who have reached their maximum allowed dose of opioid will be treated as censored and a Tobit regression model will be applied. Since there are two primary outcomes, a type I error of 2.5% will be used. All the tests will be two-sided.

Survival analyses will be applied for time to event data, such as the lengths of stay and mean time to return of bowel function. Logrank tests will be applied for simple comparisons between the two groups. Cox proportional hazards models will be used to facilitate the inclusion of covariates in the regression analysis. Note that although no censoring of subjects are expected in the study (i.e. the lengths of stay and mean time to return of bowel function will be observed for each patient) and a general linear regression analysis may be applicable, our survival analysis approach enables us to estimate the survival curves and read the different rates at different time points from the curves.

Since variables such as NRS are measured repeatedly over the 72-hr time period, we may refine our analysis by using all of the measures instead of using the simple summarizing index, AUC. Methods for longitudinal data will be applied to deal with the correlation among repeated measures in the same patient. The two most popular approaches for longitudinal data modeling are the generalized estimating equations (GEE) approach and the mixed-effects model (MM) approach. MM explicitly models between- and within-subject variation using random effects, and thus has the advantage of being able to separate between-subject variability from the total variability of responses. However, it requires parametric assumptions on observed and latent variables, which render inference vulnerable to departures from a normal distribution. An alternative approach to these models is the GEE approach. GEE ignores between-subject variability in model specification, but accounts for such variability during model estimation in order to ensure inference validity; therefore, GEE can provide robust estimates for between-group differences, as it does not require any assumption of the distribution. However, GEE is limited in that it requires the missing completely at random (MCAR) assumption, which may be violated. We will examine the nature of the missing data and use a weighted GEE (WGEE) approach as needed to address potential informative dropout. Our hypotheses concern between-group differences, so both parametric and semi-parametric approaches will be used. Both approaches will be used in the analysis and if discrepancies in MM and GEE (or WGEE) analyses occur, GEE (or WGEE) will be recommended, as the latter semi-parametric approach generally provides more robust inference.

All analyses will be performed using the latest version of SAS, which includes procedures for all of the analyses proposed, including Tobit regression, survival analysis, linear mixed model, and GEE (or WGEE) models. A statistician will be involved in reviewing the final analyses and confirming statistical soundness.

Data Safety Monitoring.

Data Safety Monitoring Plan

Dr. Stephen Breneman will serve as our independent DSM. He is not directly involved in data collection or patient interaction and will be used to avoid conflict of interest. The DSM will be unblinded, so that he can identify any alarming trends in adverse events or serious adverse events that may warrant modification or stopping of the study. The independent DSM will conduct periodic unblinded assessments of the aggregate data at 25% (20 patients), 50% (39 patients), 75% (59 patients) and 100% (78 patients) study enrollment. If enrollment is slow, then the independent DSM will review all aggregate adverse events at least yearly and review completed electronic adverse event case report forms (stored in RedCAP) at least quarterly during throughout the year.

Dr. Candice Lee will serve as the Clinical Monitor. The Clinical Monitor will review all adverse events as they occur to make sure that they fall within reason of the study (expected possible adverse events). The Clinical Monitor will contact the DSM if there are concerns regarding a greater than expected number of adverse events or serious adverse events. All serious adverse events will be reported to the DSM within 24 hours of identification of the event's occurrence. The DSM will review these events in an unblinded fashion. If there is an alarming trend with multiple occurrences of serious adverse events that are determined to be significant enough to warrant modification or stopping of the trial, then the DSM will notify the PI.

The study investigator-sponsor is responsible for ensuring that all adverse and unexpected events related to study participation are reported in a timely fashion to the FDA and institution IRB.

Self-audit

An internal self-auditing of the blinded data will be conducted by the PI and co-PI. The data evaluated by the PI and co-PI during self-audits will be in the blinded form. Subject groups will only be identified by the arbitrary letter assigned to them by the study pharmacist in order to protect the true identity of their group (placebo or Exparel®). An initial self-audit will be conducted after completion of the 1st patient participation. During this audit, the PI and co-PI will review and discuss:

- abnormal laboratory data
- cumulative pain scores
- cumulative opioid use
- secondary outcomes
- adverse events
- signed informed consents
- any need for revision of study methods and procedures or data collection forms

Also reviewed during self-audits will be any feedback from involved departments (including pharmacy, anesthesia and nursing) regarding adverse events or concerns related to the subjects' participation. These departments may contact the PI or co-PI with any concerns at any time during the study via telephone or email.

A repeat self-audit will be conducted after completion of the 3rd patient participation to evaluate effectiveness of any changes made to the study protocol and/or data collection forms. Another self-audit will occur following 50% completion of subject participation (39 patients).

Indications for termination of study

The study will be terminated if an overwhelming amount of serious adverse events deemed related to therapy (e.g. significant new cardiac arrhythmias, CNS reactions, wound infection/dehiscence or severe allergic reactions) occur in either the Exparel® group or the placebo group.

Data Storage and Confidentiality.

Data collection will be entered and stored in the Research Electronic Data Capture (REDCap) system, which is a password-protected web application for building and managing online surveys and databases. REDCap allows database creation and storage of collected data in a secure manner. A comprehensive REDCap database will be created by the PI, co-PI and study coordinator. Only the PI and co-PI will have full administrative access to the database; meaning that they can add users, restrict levels of user access, export data and change data collection forms. The co-PI and trained study investigators will be in charge of entering patient data into the developed data collection forms. Each patient will be assigned a unique identification number (UID) upon initial entry into the REDCap database. Limited access to the REDCap database will be granted to the study statisticians and Medical/Safety Monitor. These persons will be allowed read-only access with all patient identifiers blocked (subjects identifiable only by their assigned UID). A printed key linking the patient medical record number (MRN) and UID, as well as any questionnaires including patient identifiers will be kept in a locked cabinet in Dr. Knight's office. Only Dr. Knight and the co-PI will have access to the file. All printed data collection sheets will contain only the subject's UID.

The database will include data collection sheets that will store demographic information and clinical outcomes for each subject, including the following information: age at time of surgery, sex, race,

comorbidities (diabetes mellitus, COPD, smoker), left ventricular ejection fraction (%), baseline pain assessment score, surgical procedure performed, intraoperative measures (aortic cross-clamp time, LIMA harvest, cardiopulmonary bypass time, amount of crystalloid/blood products/cell saver received), total intraoperative opiate and benzodiazepines administered. Subjects' NVPS and NRS pain scores, opiate requirements, length of stay, time to first bowel movement and any adverse events will also be stored on data collection sheets.

At completion of data collection and entry into the database, all identifiers linking patient to UID will be destroyed and only the key will remain. The key will be destroyed following completion of this study. Study records will be maintained in a secured location for 3 years following closing of the study. No identifiers will be released in reported results or publications.

IV. RISK/BENEFIT ASSESSMENT

Risk Category: This study constitutes a greater than minimal risk to the patient.

Potential physical harm arises from the possible side effects of Exparel®. Neurologic and cardiac adverse reactions that have been reported with Exparel® administration include dizziness (6.2%), headache (3.8%), somnolence (2.1%), hypoesthesia (1.5%), lethargy (1.3%), tachycardia (3.9%) and bradycardia (1.6%). High levels of bupivacaine in the plasma result from accidental overdose, unintended intravascular injection or accumulation of the drug in the plasma secondary to decreased hepatic metabolic degradation or decreased plasma protein binding capacity due to acidosis[5]. Clinical trials of Exparel® reveal a good safety profile[5-7]. Side effects that have been reported in clinical trials are represented in the following table.

Table 1: Adverse reactions reported with use of Exparel®

Incidence	Adverse reaction
Most common (≥ 10%)	Nausea, constipation, vomiting
Common (≥ 2 or ≤ 10%)	Pyrexia, dizziness, peripheral edema, anemia, hypotension, pruritus, tachycardia, headache, insomnia, postoperative anemia, muscle spasm, hemorrhagic anemia, back pain, somnolence, procedural pain
Less common/rare (< 2%)	Chills, erythema, bradycardia, palpitations, supraventricular/ventricular extrasystoles, ventricular tachycardia, anxiety, urinary retention, pain, edema, tremor, postural dizziness, paresthesia, syncope, incision site edema, procedural hypertension/hypotension, procedural nausea, muscular weakness, neck pain, cold sweat, urticaria, confusional state, depression, agitation, hyperhidrosis, restlessness, blurred vision, tinnitus, hypoxia, apnea, urinary incontinence, drug hypersensitivity.

Information reproduced from: *Exparel Prescribing Information.* 23 Jan. 2012. Pacira Pharms, Inc. San Diego, CA.

All parasternal intercostal nerve blocks will be performed by a cardiac surgeon familiar with the study protocol and experienced in performing the procedure. The benefit of performing parasternal blocks prior to sternal closure is the ability to directly visualize and confirm appropriate placement of the needle tip. The syringe will be aspirated prior to injection to avoid intravascular injection of the drug. Hemodynamics and electrocardiography tracings will be monitored closely for arrhythmias and hypotension following administration of the drug.

PCA's are not routinely used after cardiac surgery, but are often used after other major surgeries including abdominal and orthopedic procedures. The risks of PCA are related to the adverse effects of opioid use, which may include: constipation, nausea/vomiting, sedation, respiratory depression, pruritus,

confusion/hallucination, urinary retention, sweating, miosis and myoclonic jerks. All patients will be monitored closely while using the PCA and if they start showing signs of opioid toxicity, then PCA dosing will be decreased or changed appropriately. If patients show signs of narcotic overdose (respiratory rate < 8 breaths per minute, over-sedation, or muscle rigidity), then naloxone will be administered for opioid reversal.

This study also constitutes a potential psychological stress arising from the blinding of subjects as to which research arm (placebo vs. Exparel®) they are assigned. There is also a risk of invasion of privacy because of the storage of identifiable clinical data. All clinical data will be in de-identified form. The key containing identifiers and linking medical record number will be kept secure and be accessible only to the PI and primary study coordinator. All clinical data released will be in de-identified form.

Potential benefits to the subjects are that the parasternal intercostal nerve blocks with Exparel® may provide improved pain control. This would benefit the patients by leading to less discomfort post-operatively, less narcotic requirements, lower morbidity and quicker time to recovery. Patients randomized to the placebo group would receive no direct benefit from participating in this study.

V. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

Assessment for patient eligibility for the study will be performed by a qualified physician participating in the care of the patient who is familiar with the study and its objectives. Patients meeting eligibility criteria and none of the exclusion criteria will be recruited during their initial outpatient clinic visit prior to surgery.

Capacity of the individual will be ascertained by the research personnel obtaining consent. The study, risks and benefits of participation will be described to the subjects by the PI, co-investigators or study personnel. Determination of capacity is based upon the potential subject's ability to respond to the process appropriately. The person who obtains the consent will ensure that the subject is alert, able to communicate, able to understand information about the research, make a decision based upon the information and give informed consent. The research personnel obtaining consent will ask questions such as naming potential risks of participating in the study, summarizing the aim of the study, asking the subject to explain what he/she would do if he/she no longer wanted to participate, and asking the subject to explain what he/she would do if he/she experienced distress or discomfort during the study in order to assess the research subjects ability to comprehend and consent.

Willing participants will be presented with a detailed consent form explaining the purpose and nature of the study. The consent form will be in the appropriate language for the patient. Consents will be obtained by an authorized study investigator with the use of a language or sign language interpreter if necessary. The investigator obtaining consent will explain to the patient that participation is not required and that refusal to participate will not alter the quality of their care.

The consent form will be written in a language comprehensible by the lay public. Patients will be given adequate time to review the study with the surgeon and meet the PI if desired. All questions will be encouraged and answered. The consent form will contain contact information of the PI, participating surgeons, and primary study investigator who may be contacted if any further questions arise.

Debriefing Procedures.

In this study, it is necessary for the patients to be blinded to their treatment arm (placebo vs. Exparel®). Withholding this information is necessary in order minimize bias and control for a possible placebo effect. Following completion of the study, the subjects will be debriefed at their follow-up appointment, approximately 30 days following their surgery. During this debriefing, the patient's study arm will not be

revealed. If the patient wishes to know their study group assignment, then they may be informed of their group assignment following completion of the entire study. They will have the opportunity to ask any questions and express any concerns regarding study participation.

Documentation of Consent: Signed consent forms will be stored in the locked office of the co-PI, Candice Lee, MD.

Costs to the Subject: There is no additional cost to the subjects for participating in this study.

Payment for Participation: There are no incentives (monetary or otherwise) for participation in this research study.

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Appendix I: Study schedule and procedures

Table 2: Study schedule and procedures

Procedure					After Study Drug Administration										
						2-72 Hours									Site Visit
	Time post-drug				**0**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	
	Study Day	**Day -30 to -1**	**Day -1 to 1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**30**
	Time Window (±h)					**0.25**	**0.25**	**0.5**	**0.5**	**1**	**2**	**2**	**4**	**4**	**96**
Informed consent		X													
Drug screen		X													
Clinical labs[1]		X													
Assess/confirm eligibility		X	X												
Medical history, demographics and baseline characteristics		X	X												
Train self-assessments		X	X												
Pregnancy test (women of childbearing potential)			X												
Physical examination		X	X												
Randomize subject & prepare study drug			X												
Vital signs[2]		X	X		continuous monitoring in CVICU				X	X	X	X	X	X	X
ECG		X			Continuous monitoring										
Neurological assessment		X			X	X	X	X	X	X	X	X			
Inspiratory capacity			X[3]							X[3]	X[3]	X[3]			
Study drug administration				X											
NVPS rating[4]					1h	X	X	X[5]	X[5]						
NRS rating[4]			X					X[5]	X[5]	X	X	X	X	X	
PCA								X	X	X	X	X			

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Table 2: Study Schedule and Procedures (Cont.)

Procedure					After Study Drug Administration										
						2-72 Hours									Site Visit
	Time post-drug				0	2	4	8	12	24	36	48	60	72	
	Study Day	Day -30 to -1	Day -1 to 1	1	1	1	1	1	1	2	2	3	3	4	30
	Time Window (±h)					0.25	0.25	0.5	0.5	1	2	2	4	4	96
Oral narcotics													X	X	
Subject's satisfaction with postoperative analgesia										X				X	X
Brief Pain Inventory	X														X
Record occurrence and duration of nausea/vomiting					X	X	X	X	X	X	X	X	X	X	
Record date/time of each bowel movement					X	X	X	X	X	X	X	X	X	X	
Record date/time of each rescue pain medication dose					X	X	X	X	X	X	X	X	X	X	
Subject productivity (date subject returned to work or normal daily activities)															X
Concomitant medications[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record AEs and SAEs				X	X	X	X	X	X	X	X	X	X	X	X

[1] Clinical labs will include Complete Metabolic Panel, CBC and INR/PTT.
[2] Temperature, heart rate, blood pressure, oxygen saturation will be monitored continuously in the cardiovascular ICU (CVICU) and at the time points listed.
[3] Inspiratory capacity (IC) will be measured using the handheld spirometer at baseline (pre-op) and then once between POD #1-2.
[4] Pain will be assessed with the NVPS or NRS scores at the end of anesthetic and before the first dose of rescue pain medication.
[5] Pain will be assessed with NVPS if the patient is still intubated and/or sedated. Pain will be assessed with the NRS score if the patient is extubated and alert/responsive.
[6] All medications that the subject used within 3 days prior to surgery will be recorded; including medication name, dose and date last taken.

Appendix II: Pain assessment tools

Adult Nonverbal Pain Scale (NVPS)

Table 4: Revised Adult Nonverbal Pain Scale

	0	1	2	Score
1. Face	No particular expression or smile	Occasional grimace, tearing, frown or wrinkled forehead	Frequent grimace, tearing, frown or wrinkled forehead	
2. Activity (movement)	Lying quietly, normal position	Seeking attention through movement of slow cautious movements	Restless activity and/or withdrawal reflexes	
3. Guarding	Lying quietly, no position of hands over areas of body	Splinting areas of body, tense	Rigid, stiff	
4. Physiologic I (vital signs)	Stable vital signs, no change in past 4 hours	Change over past 4 hours in any of the following: SBP > 20 HR > 20 RR > 10	Change over the past 4 hours in any of the following: SBP > 30 HR > 25 RR > 20	
5. Respiratory	Baseline RR/SpO_2 Compliant with ventilator	RR > 10 above baseline or 5%↓ SpO_2 Mild asynchrony with ventilator	RR > 20 above baseline or 10%↓SpO_2 Severe asynchrony with ventilator	
Revised Nonverbal Pain Scale (NVPS)			**Total**	

Abbreviations: HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, oxygen saturation as measured by pulse oximetry.

Referenced with permission from Strong Memorial Hospital, University of Rochester Medical Center, Rochester, NY.

Numeric Rating Scale (NRS)

When evaluating pain, the care provider is to explain to the patient that "0" represents "no pain" and that "10" represents the "worst possible pain". Patients are to indicate the number that best reflects the intensity of pain that they are currently experiencing. Any score ≥ 4 requires a pain management plan to be implemented.

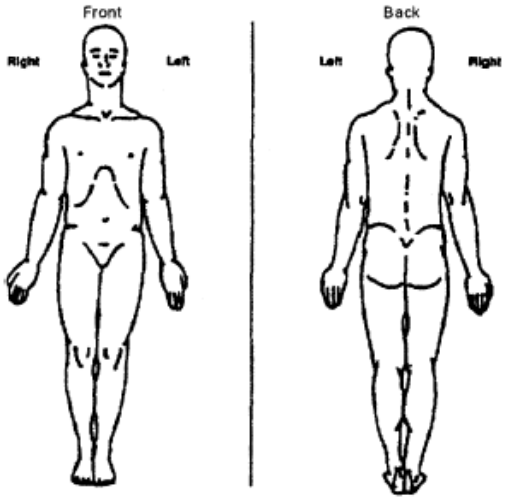
Scores: 1-3 = mild pain
4-7 = moderate pain
8-10 = severe pain

Appendix III: Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain during the last week?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its *worst* in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its *least* in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the *average.*

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have *right now.*

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

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8. In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much *relief* you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how much, during the past week, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Scoring:

Pain Severity Score = Mean of items 3–6 (pain at its worst, pain at its least, average Pain Interference Score = Mean of items 9A–9G (interference of pain with: general activity, mood, walking, normal work, relations, sleep, enjoyment of life)

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Appendix IV: Criteria for extubation

URMC, Strong Memorial Hospital, Cardiovascular Intensive Care Unit
Cardiac Surgery Practice Guideline

Postoperative Cardiac Surgery Weaning From Mechanical Ventilation Guideline

This guideline is not to be used for the post-operative Ventricular Assist Device or Heart Transplant patient.

1. **Criteria to initiate the Fast Track Protocol**
    a. Chest tube drainage <100cc/hour
    b. Core temperature >or = 36.0° C
    c. Hemodynamic stability with no escalation of care
        i. Cardiac Index > 2.2
        ii. SBP 90-140 with or without inotropes or vasoactive medications
        iii. Heart Rate <120 bpm
    d. Satisfactory arterial blood gases (ABGs) on full ventilation
        i. PO2 >70 and PCO2 <45 on 40% FIO2, peep 5-8
2. **Extubation Criteria**
    a. Awake without stimulation
    b. Adequate reversal of neuromuscular blockade (able to hold head off pillow for 3 seconds or more)
    c. Acceptable respiratory mechanics
        i. Tidal Volume >5mL/kg
        ii. Vital Capacity >10 – 15 mL/kg
        iii. Spontaneous respiratory rate <24 /min
    d. Acceptable arterial blood gases (ABGs) on 5 cm or less CPAP
        i. PO2 >70, PCO2 <50 on 40% FIO2, peep 5-8

Guidelines are intended to be flexible. They serve as reference points or recommendations, not rigid criteria. Guidelines should be followed in most cases, but there is an understanding that, depending on the patient, the setting, the circumstances, or other factors, guidelines can and should be tailored to fit individual needs.

Referenced from Strong Memorial Hospital, University of Rochester Medical Center, Rochester, NY.

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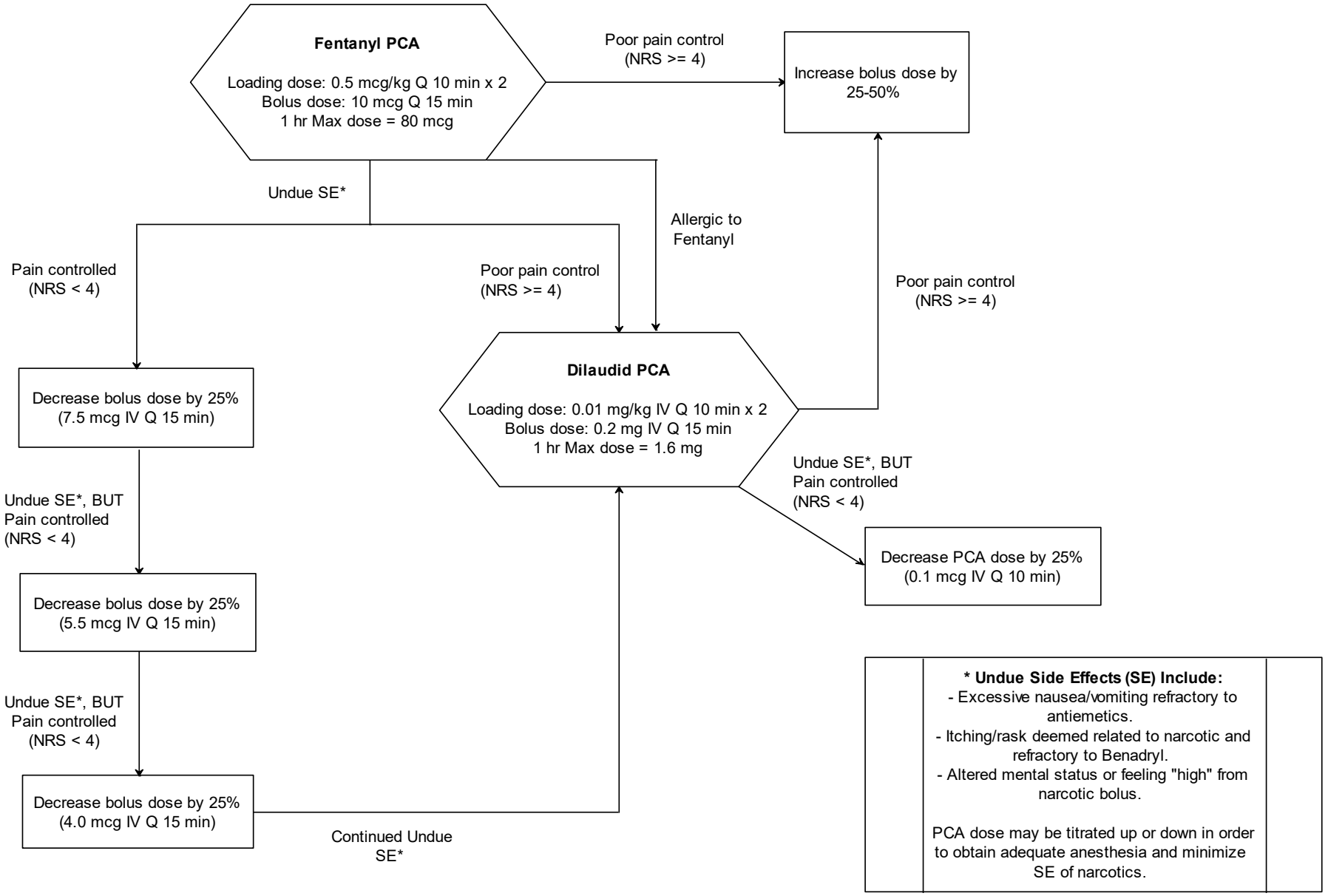
Appendix V: PCA Set-up Flow Chart



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Appendix VI: Equianalgesic Table

Table 5: Equianalgesic Table

MEDICATION	EQUIANALGESIC DOSE	
	IM/IV	PO
Morphine	10 mg	30 mg
Fentanyl	100 mcg	N/A
Hydromorphone	1.5 mg	7.5 mg
Oxycodone	N/A	20 mg
Hydrocodone	N/A	30 mg
Codeine	130 mg	200 mg

Information adapted from: ViaHealth Pain Initiative 2010. *Equianalgesic Table for Adults*, pamphlet, ViaHealth, Rochester, NY.

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