TITLE: The Effect of Methadone vs. Fentanyl Administration on Postoperative Pain Control in Pediatric Patients Undergoing Cardiac Surgery: A Randomized, Double-Blinded Controlled Trial

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RESEARCH PROTOCOL
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TITLE: The Effect of Methadone vs. Fentanyl Administration on Postoperative Pain Control in Pediatric Patients Undergoing Cardiac Surgery: A Randomized, Double-Blinded Controlled Trial

ABSTRACT
The main objective of this study is to determine if administration of methadone in pediatric patients undergoing cardiac surgery improves postoperative pain control and potential opioid side effects. Large opioid doses are typically administered to patients undergoing congenital cardiac surgery to blunt hemodynamic stress response. Previous studies have shown that high dose opioid strategies can result in postoperative respiratory depression, ileus, and opioid tolerance.[1-4] Furthermore, inadequate acute postoperative periods can potentially increase risk for long-term pain, decrease patient satisfaction, and potentiate hemodynamic complications.[5,6] We intend to show through a randomized, double blinded controlled trial that compared to fentanyl, methadone administered intraoperative will significantly reduce postoperative opioid requirements for pain control by 30% during the first 24 hours. Opioid-related adverse events will be monitored closely and a secondary analysis will compare the incidence of side effects between the two groups during the first 24-hour postoperative period.

RESEARCH PLAN

A. Specific Aims:
The main objective of this study is to determine if administration of methadone in pediatric patients undergoing cardiac surgery improves postoperative pain control and potential opioid side effects. Large opioid doses are typically administered to patients undergoing congenital cardiac surgery to blunt hemodynamic stress response. Previous studies have shown that high dose opioid strategies can result in postoperative respiratory depression, ileus, and opioid tolerance.[1-4] Furthermore, inadequate acute postoperative periods can potentially increase risk for long-term pain, decrease patient satisfaction, and potentiate hemodynamic complications.[5,6]

The **Primary Aim** of this study is to compare the effect of intraoperative administered methadone vs. fentanyl on postoperative opioid requirements during the first 24 hours, in pediatric patients undergoing cardiac surgery.

Hypothesis: Compared to fentanyl, methadone administered intraoperative will significantly reduce postoperative opioid requirements for pain control during the first 24 hours.

The **Secondary Aim** of this study is to complete a secondary analysis of the incidence of opioid-related adverse events between the two groups during the first 24-hour postoperative period.

B. Background and Significance:

Pain control and hemodynamic stability are crucial for postoperative pediatric cardiac surgery patients. Anesthetic goals during pediatric cardiac surgery aim to blunt neurohormonal stress responses to surgical stimulation and cardiopulmonary bypass as well as maintain normal hemodynamic parameters. To achieve these goals, a mainstay of care includes administration of high dose synthetic opioids and inhalational anesthetics. Recent studies have also shown the benefit of multimodal drug therapy and adjuncts including alpha-agonists, such as dexmedetomidine.[7]

Currently, fentanyl is the primary analgesic used during pediatric cardiac surgery for its beneficial pharmacokinetic characteristics of rapid onset and high potency. The mechanism of action of fentanyl is through stimulation of the mu-opioid receptor, which provides not only analgesia at the mu-1-receptor, but also the undesirable side effects of respiratory depression, bradycardia, and physical dependence from stimulation at the mu-2-receptor. Postoperatively, morphine is typically administered for postoperative analgesia in the intensive care unit because of its pharmacokinetic profile of rapid onset and moderate duration of action.

Methadone is an ideal opioid analgesic for cardiac surgery because it is a strong mu-opioid analgesic with a long duration of action, prevents hyperalgesia through NMDA desensitization, and prevents morphine-induced tolerance. Furthermore, it meets the analgesic goals in the perioperative setting by limiting the neurohormonal stress response, controlling fluctuations in pain control, and decreasing unwanted respiratory and cardiovascular side effects.

Both methadone and fentanyl, when administered during major surgery, show hemodynamic and pharmacodynamic stability. In one study done by Bowdle et al, no significant differences in mean heart rate were found between 20 patients who received fentanyl compared to 33 patients who received methadone for induction of anesthesia.[8] Additionally, the same study showed that, the mean systolic and diastolic blood pressures were significantly lower in patients to whom only fentanyl was administered versus those patients who received methadone during the intubation period.[8] Other studies have demonstrated that methadone does not have decreased clearance for immature cytochrome p450 enzymes that would be found in infants less than 1 year old. In a study done by Ward et al, no differences were found for methadone clearance when comparing methadone between different age groups, including newborns, teenagers, and adults.[9]

Standard fentanyl doses used in cardiac surgery can potentiate side effects of postoperative nausea and vomiting, receptor sensitization, and opioid tolerance. Studies have shown that high dose opioid (fentanyl 30-50 mcg/kg) administration in pediatric cardiac patients is associated

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with a higher incidence of postoperative nausea and vomiting. [4] Chia et al. demonstrated an increased incidence of emesis postoperatively after administering high doses of fentanyl intraoperatively compared to low doses of fentanyl (52% vs. 12%, respectively).[4] In contrast, a double-blinded, randomized, controlled trial of 55 participants, showed that methadone decreased the incidence of nausea and/or vomiting when compared to morphine.[10]

Sensitization of pain pathways to opioids has potential to cause opioid-induced hyperalgesia. The mechanism of opioid-induced hyperalgesia is not well understood, but has been established in several common opioids, such as morphine and fentanyl, but not methadone.[11] Cardiac surgery patients are routinely exposed to opioids during and after congenital repairs in the newborn period, intensive care sedation protocols, and subsequent reoperation later in life. Based on exposure rates, this patient population is at risk for opioid-induced hyperalgesia. The treatment of opioid-induced hyperalgesia follows closely the multimodal balanced analgesia pathway: supplementing opioids with N-methyl-D-aspartate (NMDA) receptor modulators such as ketamine, tapering opioid doses. Methadone has been shown to be effective in reducing high dose opioid-induced hyperalgesia by NMDA antagonism.[11,12]

Tolerance to opioids leads to escalation in dosing of these medications and increases risk of potential side effects. Furthermore, postoperatively and during subsequent cardiac procedures, these patients may develop a limited therapeutic window for pain control from the use of similar opioids. In one study high dose fentanyl administered intraoperative was associated with an 18-50% increase in fentanyl requirements in the immediate postoperative period.[4] Methadone prevents this buildup of opioid tolerance by antagonizing sensitization of morphine-induced receptors.[12,13]

Potential side effects of drug accumulation exist for fentanyl and morphine due to the pharmacokinetic profiles. When administered as boluses, fentanyl has a high risk of drug accumulation that increases the risk for respiratory failure, postoperative nausea and vomiting, and ileus. Similarly morphine, typically utilized for its longer half-life, can have the same trajectory of unanticipated accumulation, variable clearance, or periods of inadequate pain control. This occurs because morphine's pharmacokinetic half-life is 2-4 hours, however its desired analgesic effect may not correlate with blood plasma levels. To combat these issues, administration of opioids as an infusion has been tried in order to reach a steady state quickly. However, this can rapidly cause accumulation, and they are not easily titrated.[14] To decrease this opioid accumulation from serial boluses and infusions, medications with longer half-lives, such as methadone, may be utilized. It has a short equilibrium half-life and its effect correlates well with blood levels.[15]

Methadone has proven to significantly decrease pain scores and improve quality of pain management when compared to other opioids in adult cardiac surgery patients. A randomized, double-blinded, clinical trial in 156 patients following cardiopulmonary bypass surgery demonstrated a longer time to postoperative administration of opioid rescue medication in patients receiving methadone as compared to fentanyl during anesthesia induction.[16] Also, the total opioid dose required to alleviate pain within the first postoperative day was significantly

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less in the group receiving methadone when compared to fentanyl. Postextubation levels of pain were lower at rest and with coughing, and overall satisfaction scores with pain management were better in those patients receiving methadone versus fentanyl. This study also showed no increased incidence of opioid-induced side effects including nausea, vomiting, respiratory dysfunction, or sedation.[16] In a randomized control trial of teenage and adult cardiac patients who received methadone, morphine or placebo for induction of anesthesia, the methadone group had a lower number of patients requiring additional analgesics within the first 24 hours post procedure compared to controls.[10] In addition, time to first analgesic dose was longer in those patients who received methadone at induction. Quality measurements of pain control following methadone administration were significantly better as compared to morphine and control. [10] The prolonged analgesic effect of methadone can potentially improve acute postoperative pain control and in turn benefit hemodynamic and respiratory function.

Methadone has been widely used in the intraoperative period to attenuate need for subsequent bolus administration of opioids in the postoperative period. A prospective randomized study by Gottschalk et. al, showed a reduction by half in pain scores and a reduction in overall opioid requirements at two days when methadone, as compared to a sufentanil infusion, was administered prior to incision for patients undergoing complex spine surgery. This study also showed lasting analgesia through the third postoperative day and no difference in time to extubation, blood product utilization or length of surgery.[17] Furthermore, methadone has been shown to effectively prolong the postoperative analgesia as compared to morphine, and subsequent doses of methadone provide a substantially longer period of pain relief.[18,19] A randomized, double-blinded, prospective study on analgesic requirements showed that methadone decreased the amount of postoperative opioids as compared to morphine in pediatric patients undergoing major surgeries. These surgeries include: limb osteotomies, ureteral reimplantation, and major general surgical procedures (i.e. pectus excavatum repair). Mean pain scores were lower in the methadone group as compared to the control group. No opioid related complications occurred in either study group.[20] Superior postoperative analgesic profiles for methadone makes it an ideal choice for controlling pain in the postoperative period for major cardiac surgical cases.

Children's National Health System (CNHS) routinely employs administration of methadone for major surgery, including posterior spinal fusion, at doses of 0.3 mg/kg. This practice is supported by work that showed methadone at doses of 0.2-0.25 mg/kg can be used for pain control in children undergoing major surgery, including pediatric posterior spinal fusion.[20,21] Additional data shows that methadone at doses of 0.2 mg/kg prior to incision improved postoperative pain control in complex spine surgery.[17] Furthermore, methadone dosing of 0.2-0.3 mg/kg showed no changes to postoperative complication rate.[16,18,20] The CNHS Cardiac Intensive Care Unit (CICU) routinely administers methadone in doses ranging from 0.1-0.3mg/kg for treatment of withdrawal syndrome and assisting with weaning opioid infusions.

C. Preliminary Studies:
Methadone is currently administered during cardiac surgery at the discretion of the cardiac anesthesia team. In a retrospective review of the cases in which methadone has been used at

Children's National during the last two years, there has been less opioid requirement in the first 24 hours. Our proposal would be the first to study methadone in a randomized controlled setting in pediatric subjects undergoing cardiac surgery.

D. Research Design and Methods:

The proposed study will be conducted in a single tertiary medical center (Children's National Health System). Pediatric subjects undergoing cardiac surgery requiring cardiopulmonary bypass will be recruited over a period of 24 months. The investigator will identify potential subjects from the operative schedule and will make initial contact during the preoperative anesthetic evaluation on the day prior to surgery. Eligible and consenting participants will be assigned a unique identification number and will be randomly assigned to receive either methadone or fentanyl using a computer-generated randomization scheme. A total of 76 participants will be enrolled to each arm of the study, providing 80% power to detect a 30% difference between groups. The proposed total number of subjects to enroll in the study that includes conservative estimates of 10% dropout rate is 168 subjects, with 84 subjects for each arm of the study.

Screening and Randomization Phase

Once eligibility is confirmed and informed consent is obtained, the investigator or his/her designee will conduct a detailed medical history, review of medications taken in the past 24 hours, and a physical examination including baseline vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature), physical measurements (height and weight), and an initial pain score using the Face, Legs, Activity, Cry, Consolability (FLACC scale) (Appendix II). The FLACC scale is a validated behavioral pain scale utilized in young children between the ages of 1 and 7 years.[22]

Eligibility Criteria

Each of the following criteria must be met for the potential subject to be eligible for study participation:
1. Age greater than or equal to 2 years and less than 8 years at the time of randomization.
2. American Society of Anesthesiologists (ASA) physical status of ASA II, III, or IV (Appendix I).
3. Informed consent to participate from the parent or legally authorized guardian.
4. Scheduled for cardiac surgery requiring cardiopulmonary bypass (Appendix V).

Exclusion Criteria

Subjects will not be eligible to participate in the study if any of the following exclusion criteria apply:
1. History of allergic reaction to methadone or fentanyl.
2. Emergency Cardiac Surgery.
3. Currently receiving inotropic agents or using a pacemaker.
4. Prexisting long QTc interval of greater than 460ms determined by medical history, medical record documentation, or electrocardiogram obtained during the routine preoperative cardiac surgery evaluation.
5. History of chronic nausea and/or vomiting.

6. History of opioid abuse, addiction, or tolerance.
7. Known significant hepatic disorders determined by medical history, medical record documentation, physical examination, or laboratory tests obtained during the routine preoperative cardiac surgery evaluation or cardiology visit (International Normalized Ratio (INR)>1.5).
8. Known significant renal disorders determined by medical history, medical record documentation, physical examination, or laboratory tests obtained during the routine preoperative cardiac surgery evaluation or cardiology visit (Creatinine (Cr) >1.5).
9. History of documented current pulmonary hypertension on medication.
10. Obesity defined as a body weight greater than 130% of the ideal weight.
11. Participation in another clinical trial or any study that may interfere with participation in this trial.

The inpatient pharmacist at CNHS will randomly assign eligible participants to receive methadone or fentanyl. The randomized groups will be assigned in a 1:1 ratio determined by a computer-generated random sequence with an equal number of male and female participants.[23] All investigators, research personnel, staff, and study participants will be blinded to group assignment.

The pharmacist will prepare 0.3 mg/kg of methadone and 20 mcg/kg of fentanyl for loading dose administration, diluted to 20 mL.

Drug Preparation
Drug Information: A specific study supply of both methadone and fentanyl will be purchased and maintained in the Investigational Drug Service (IDS) pharmacy. Methadone is supplied as a single-dose 1 mL vial containing methadone 10 mg/mL; fentanyl is supplied as a single-dose 2 mL vial containing fentanyl 50 mcg/mL. Orders provided to the IDS pharmacy will reflect the weight-based calculated dose for both drugs. The syringes will be prepared with the assigned drug and will be diluted to 20 mL, with 0.9% sodium chloride. For example, a 2-year old child weighing 12 kg is prescribed 3.6 mg (0.36 mL) of methadone and 240 mcg (4.8 mL) of fentanyl; the final syringe will be prepared as 20 mL. A 7-year old child weighing 23 kg is prescribed 6.9 mg (0.69 mL) of methadone and 460 mcg (9.2 mL) of fentanyl; the final syringe will be prepared as 20 mL.

To ensure blinding, final dose preparations will be labeled "Methadone or Fentanyl 20 mLs"; dose information will not be provided on the label. Prepared doses will be delivered to the operating room (OR) the morning of the scheduled case. Study syringes will have a beyond use expiration of 8 hours when stored at room temperature. All transfers of study syringes between the IDS and the OR/Anesthesiology will follow institutional requirements for handling of a C-II drug.

Storage and Accountability: The IDS pharmacy is a temperature controlled, limited access area restricted to pharmacy personnel only. Both methadone and fentanyl are stored at room temperature in the IDS Controlled Substance vault. Drug accountability records will be

maintained by the IDS pharmacy to reflect drug preparation, including patient initials, subject ID, individual dose, lot and expiration of both methadone and fentanyl. Any unused portion of both methadone and fentanyl will be disposed per Department of Pharmacy standard operating procedures for waste of a controlled substance (C-II) drug.

Treatment Phase
The treatment phase will begin at the induction of general anesthesia and finish at the end of the surgical procedure (Figure 1). Standard anesthetic practice for monitoring, induction, and maintenance of general anesthesia will be preserved throughout.

At the discretion of the anesthesiologist, subjects will be premedicated with midazolam 0.5 mg/kg suspension by mouth (up to 20 mg maximum) or a 0.1 mg/kg intravenous injection. Oral Midazolam has a maximum dose due to the volume of medication administered into the digestive tract, high volumes of fluid or volume in the stomach create a higher risk for aspiration during anesthetic induction. The intravenous midazolam maximum dose is 4mg and is subject to achieve anxiolytic effect. Standard monitoring procedures will be put in place during the induction of general anesthesia, including an electrocardiogram (Lead II and V), heart rate, continuous blood pressure, respiratory rate, continuous pulse oximetry, end-tidal CO_2, end-tidal sevoflourane concentrations, and temperature.

For patients without intravenous access prior to arrival to the operating room, anesthesia will be induced via mask inhalation with sevoflurane at 8% or introduced at a low concentration after nitrous oxide/oxygen (2:1). Once the participant is anesthetized and intravenous access is established, the subject will receive 1 mcg/kg of fentanyl and 1 mg/kg of rocuronium to facilitate intubation.

If the subject has intravenous access preoperatively, anesthesia will be induced with intravenous anesthetics including: fentanyl 1 mcg/kg and a short acting intravenous anesthetic (ketamine 1-2 mg/kg bolus, etomidate 0.2-0.3 mg/kg bolus, or propofol 1.5-2.5 mg/kg bolus) at the discretion of the anesthesiology team. The subject will also receive 1 mcg/kg of fentanyl and 1 mg/kg of rocuronium to facilitate intubation.

After the endotracheal tube is confirmed in situ and secured, the subject will be mechanically ventilated. A catheter for measuring arterial blood pressure will be inserted and additional intravenous catheters will be placed peripherally or centrally as per practice.

Participants will receive either 0.3 mg/kg of methadone or 20 mcg/kg of fentanyl prior to surgical incision, over 60 minutes. The medication will be prepared as described above and all research and staff personnel as well as the study participant will be blinded to treatment group assignment.

General anesthesia will be maintained with isoflurane. Rocuronium will be titrated to achieve surgical paralysis. Subjects will receive the required preoperative antibiotics prior to surgical incision. Standard documentation of vital signs will be recorded every 5 minutes in the

anesthesia record and will include: arterial blood pressures, heart rate, respiratory rate, oxygen saturation, end-tidal CO2, end-tidal sevoflurane concentrations, temperature, and mechanical ventilator settings. Use of inotropes or vasopressors to maintain hemodynamic stability will be recorded.

The subject will be transitioned to cardiopulmonary bypass under the direction of the cardiovascular surgeon. On bypass, subjects will receive 0.05 mg/kg of midazolam and 1 mg/kg of rocuronium, and Isoflurane. The surgeon will place the usual intracardiac lines and electrocardiac pacing. If necessary, inotropes or vasoactive agents will be initiated by the cardiovascular surgeon and anesthesiologist. The subject will be transitioned from cardiopulmonary bypass to spontaneous circulation by the cardiovascular surgeon and anesthesiologist.

Volume resuscitation, inotropes and vasopressors, and electrocardiac pacing will be administered as standard care to ensure the subject's vital signs are stable. Doses of inotropes and vasopressors, volume of blood products (i.e. packed red blood cells, platelets, and cryoprecipitate), volume of crystalloid, and volume of colloid will be recorded in the anesthesia record.

As per standard anesthetic practice, the subject will continue to be evaluated for hemodynamic stability, postoperative risk of bleeding, and respiratory effort. Morphine at 0.05 mg/kg per dose will be administered intravenously as needed for pain control. All subjects will be started on an infusion of dexmedetomidine at 0.25-1 mcg/kg/hr. In the operating room, extubation timing will be at the discretion of the anesthesiologist; time of extubation will be recorded in the anesthesia record. Subjects who are not prepared for extubation in the operating room will remain intubated, mechanically ventilated, and sedated with dexmedetomidine while in the CICU through the immediate postoperative period. The subject will be transported to the cardiac intensive care unit (CICU) for monitoring, and care will be transitioned to the cardiac intensive care team.

Surgical procedures and times will be recorded in the operative report via the electronic medical record.

Postoperative ICU Phase
The postoperative CICU phase will begin at admission to the CICU and will end on the third day of hospital admission (Figure 1). As mentioned above, subjects who are not prepared for extubation in the operating room will remain intubated, mechanically ventilated, and sedated with dexmedetomidine in the immediate postoperative period in the CICU. Postoperative care including hemodynamic stability, resuscitation, and respiratory support will be at the discretion of the CICU team.

As per CICU protocol, the nurse will monitor and record vital signs and FLACC scores beginning at handoff from the anesthesia team to the intensive care team. The nurse will continue to document vital signs including: blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, minute ventilation when mechanically ventilated, and oxygen supplementation

when appropriate, in the electronic medical record every hour. As per nursing protocol, FLACC scores will be recorded in the electronic medical record every 4 hours or when the nursing staff witnesses pain during the entirety of the subject's CICU stay.
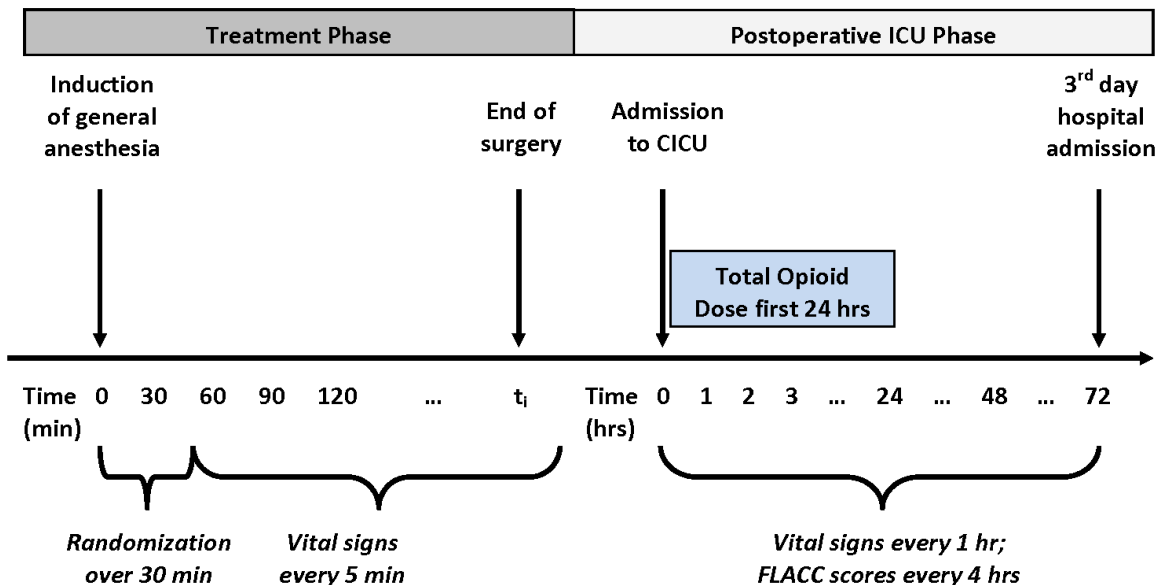
All subjects will receive analgesics and sedation medication based on CICU postoperative pain control and agitation protocol as follows:

- The nurse will document all medications administered in the electronic medical record.
- Non-pharmacologic pain treatment plans such as music therapy and parental presence will be initiated.
- Infusion of 0.25-1 mcg/kg/hr of dexmedetomidine for acute postoperative agitation or anxiety with the goal being zero to one on the Modified Motor Activity Assessment Scale (Appendix III). This will be discontinued by the intensive care team as the patient transitions from the immediate postoperative period to a lower acuity of care or in the case where anxiolysis is no longer clinically required.
- Non-opioids including acetaminophen 15 mg/kg/dose around the clock every 4 hours for 48 hours then as needed, with maximum doses of 500 mg or 2 grams/24 hours, and ketorolac 0.25-0.5 mg/kg/dose every 6 hours for 48 hours once the chest tube output is less than 5 ml/kg/hour and non-sanguineous (maximum dose 15-30 mg).
- Opioids for postoperative pain control will include oxycodone at 0.1 mg/kg enterally every 6 hours as needed for pain greater than or equal to a FLACC score of 4 (once taking enteral medication), maximum of 5-10 mg/dose. Morphine, 0.05-0.1 mg/kg will also be administered intravenously as needed for pain greater than or equal to a FLACC score of 4. The nursing staff will document opioid doses and time of administration in the electronic medical record.

Nausea and Vomiting:
- As per standard postoperative protocol, subjects will receive antiemetics (0.1 mg/kg of ondansetron IV or 0.25 mg/kg of promethazine IV) for recorded episodes of moderate or severe nausea and emesis. Adverse events including nausea, vomiting, arrhythmias, and hypoventilation as well as the total number of antiemetic doses and total doses given per kilogram will be recorded in the electronic medical record.

Figure 1. Timeline of treatment and postoperative ICU phase.

| Treatment Phase | | | | | | Postoperative ICU Phase | | | | | | | |

Induction of general anesthesia — **End of surgery** — **Admission to CICU** — **3rd day hospital admission**

Total Opioid Dose first 24 hrs

Time (min) 0 30 60 90 120 ... t_i Time (hrs) 0 1 2 3 ... 24 ... 48 ... 72

Randomization over 30 min   *Vital signs every 5 min*   *Vital signs every 1 hr; FLACC scores every 4 hrs*

Data Collection

The investigator or designee, blinded to group assignment, will collect all of the relevant data (Appendix IV) from the electronic medical record within six months of the cardiac surgery and enter it into the Medical Center's proprietary web-based data-entry and data-management system, REDcap (Research Electronic Data Capture). The source of information will be medical records at the Children's National Health System "Anesthesiology" and "Bear Tracks" information systems provided by Cerner Corporation.

Data will be obtained specifically for research purposes. Subject identifiers (e.g. name, date of birth, address) will not be entered into the REDcap system. The previously assigned unique identification numbers will be used.

Statistical Considerations

All analyses will be conducted under the intent-to-treat principle using the assigned randomization groups. The distribution of all variables will be assessed and transformations or nonparametric methods will be employed accordingly. The primary study outcome is the total postoperative opioid dose in morphine equivalents in the first 24 hours and will be analyzed quantitatively.

The distribution of the total opioid dose in the first 24 hours will be evaluated by randomization group (methadone vs. fentanyl) and differences between groups will be tested using the parametric t-test or Wilcoxon rank-sum test, if appropriate.

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Power: For the **Primary Aim**, it is hypothesized that compared to fentanyl, methadone administered intraoperative will result in a significantly lower total opioid dose (morphine or oxycodone) during the first 24 hour postoperative period. An internal case review was performed on 76 cardiac surgery patients (mean age 4.3 ± 1.7, mean weight 17.1 ± 7.45 kg) who received 10-30mcg/kg of fentanyl prior to the cessation of cardiopulmonary bypass, did not receive a patient controlled analgesic device or infusion in the postoperative period, and who met the criteria of age from 2 to 8 years old. This analysis demonstrates the mean total dose of morphine in the first 24 hour postoperative period to be 0.363 mg/kg, with a standard deviation of 0.239. Assuming no difference between the two treatment strategies in the population, a total sample size required is 76 in each group. This will provide 80% power to detect an effect size of 0.109, using a two-sample t-test at the 0.05 significance level. Significance will be measured as a 30% reduction in postoperative pain requirement.

We will consider a dropout rate of 10% and plan to enroll a total of 168 patients, 84 in each arm, in this randomized control study.

Secondary Analyses: For the **Secondary Aim** the Pearson's contingency chi-square test will be used to evaluate any differences between the randomization groups in opioid-related adverse events during the first 24-hour postoperative period.

E. Study Population
The population for this study will be both male and female pediatric subjects from all ethnic backgrounds, with an ASA physical classification of II, III, or IV who will undergo congenital cardiac bypass surgery.

F. Human Subjects
The research material obtained from human subjects will be in the form of data collection as previously described. Data will be obtained specifically for research purposes.

The investigator will identify subjects who are eligible for this study after review of the surgical schedule. Subjects and their parents will be approached about participation in the study after the preoperative anesthetic evaluation has been completed. The investigator or his designee will describe the study protocol and procedures and answer any questions pertaining to the study. Written informed consent will be obtained from the subject's parent or legal guardian in accordance with all applicable regulatory requirements. Informed consent will be obtained prior to conducting any study related tests or procedures. Subjects will be approached during the preoperative anesthetic evaluation in a private closed-door forum in the preoperative surgical waiting area. The subject's parent or legal guardian will be given time to deliberate and a copy of the signed consent can be taken home. No other opportunity will be allowed for consenting.

Interpreters will be present for the informed consent for non-English speaking subject. A short form of the consent in Spanish or Arabic will be made available.

The participant's involvement in the study will begin at the time informed consent is obtained and end after three days of follow-up in the CICU.

G. Risks and Side Effects
The potential risks realted to the use of methadone include respiratory depression and arrhythmias associated with prolongation of the QTc interval on ECG.

The risk of respiratory depression exists with all administered opioid medications including methadone and fentanyl. As per the standard of care, subjects will remain mechanically ventilated throughout the duration of the surgical procedure, from induction to emergence. Adequacy of ventilation and oxygenation will be required for discontinuation of mechanical ventilation and emergence from anesthesia during the treatment phase. Subjects who do not meet extubation criteria will remain intubated, mechanically ventilated, and sedated with dexmedetomidine while in the intensive care unit until the subject has adequate ventilation and oxygenation. The intensive care team will manage postoperative respiratory support as standard of care. If prolonged intubation and mechanical ventilation is secondary to intraoperative opioid administration at three days this will be grounds for disclosure of opioid medication administered in the intraoperative period. These adverse events will be reported to the regulatory committee for review.

Normal QTc values adjusted for age and gender for diagnosing QT prolongation for children between the ages of 1 and 15 years old is less than 440ms, borderline QT prolongation is considered 440ms-460ms, and prolonged is greater than 460ms.[24] Furthermore, in data pooled from 4 studies the QTc for newborns receiving methadone remained in the normal range of 400ms with a standard deviation of 20ms.[9] Prolongation of the QT interval and cardiac conduction abnormality is more closely related to chronic adult dosing of methadone, large multiple daily doses, or treatment of addiction.[25] Subjects will not be eligible if their preoperative QTc interval is greater than 460ms or documentation of acquired or congenital long QT-syndrome. Advanced age and methadone doses greater than 100 mg/day were independently associated with having a cardiac event.[26] In this pediatric study no subject will receive doses of 100 mg/day. Licensed physicians and nurses will monitor patients in the perioperative setting. As per standard of care licenses physicians and nurses will take electrocardiograms in the postoperative period for abnormal telemetry tracings. Arrhythmias interpreted by the intensive care staff during the first 24-hour period to be medication induced will require standard practice intervention and care. Within the first 24 hour period recurrent arrhythmias arising from the prolongation of the correct QT interval that cause hemodynamic instability refractory to therapy will be grounds for disclosure of opioid medication administered in the intraoperative period. These adverse events will be reported to the regulatory committee for review.

No other risks related to study participation are anticipated.

H. Benefits

The information generated by this study will provide clinically useful information regarding the effectiveness of methadone. Subjects may benefit from the direct analgesic effects of intraoperative administration of opioids. Although participation in this study may not benefit all subjects, the information obtained can be directly applied to children for future use.

I. Outside Consultants/Collaborators
No outside consultants will be used.

J. Contractual Agreements
There are no contractual agreements. There are no additional costs to subjects for participation.

L. Conflicts Of Interest
There are no conflicts of interest.

M. Confidentiality
Subject confidentiality will be maintained at all times. To protect the privacy of subjects and maintain confidentiality of medical record, each subject will be assigned a unique study identification number and all participant data will be labeled only with the study identification code. The study necessitates that a master subject enrollment log containing the subject's name and medical record number be kept in the study files, but limited access to this log (consisting of site study personnel and Federal Regulatory personnel in the event of an audit) will be implemented. All study case report forms will be stored in a locked cabinet in the Investigators office/office suite. Data entered via the web-based electronic data collection system will be securely stored on the Medical Center's server. The results of this study may be published in scientific journals or presented at medical meetings, but the subject's identity will not be disclosed. HIPAA compliance will be adhered to at all times per IRB and Institutional standards.

N. Subject Compensation
There is no subject compensation for participation in this study.

O. Facilities and Equipment
This study will be conducted in the operating rooms and CICU of Children's National Health System. All materials for this study are a part of routine care.

P. Appendix

APPENDIX I
American Society of Anesthesiologists (ASA) classification of physical status:

Class I. There is no organic, physiologic, biochemical or psychiatric disturbance. The pathologic process for which operation is to be performed is localized and is not a systemic disturbance.

Class II. Mild to moderate systemic disturbance caused either by the condition to be treated surgically or by other pathophysiologic processes.

Class III. Severe systemic disturbances or disease from whatever cause, even though it may not be possible to definite the degree of disability with finality.

Class IV. Indicative of the subject with severe systemic disorder already life threatening, not always correctable by the operative procedure.

Class V. The moribund subject who has little chance of survival but is submitted to operation in desperation.

APPENDIX II
Face, Legs, Activity, Cry, Consolability Scale (FLACC)[22]

Categories	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

Scores range from zero to ten.
0= Relaxed and comfortable
1-3=Mild discomfort
4-6= Moderate pain
7-10= Severe pain/ discomfort

APPENDIX III
Modified Motor Activity Assessment Scale (MMAAS)
The MMAAS will be scores as the subject's response to voice, then touch, and then noxious stimulation (i.e. planned ETT suctioning or <5 seconds of nailbed pressure).

(-3) Unresponsive= No spontaneous respiratory effort. Minimal or no response to noxious* stimulus. Does not communicate or follow commands.

(-2) Responsive only to noxious* stimuli: Spontaneous but ineffective respiratory effort. Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with noxious* stimulus. Some spontaneous movement. Does not communicate.

(-1) Responsive to gentle touch or name: Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with gentle touch or when name is spoken. Follows simple commands. Drifts off after stimulation

(0) Calm and cooperative: Spontaneous and effective tidal volume. No external stimulus is required to elicit movement. Calm, awakens easily, and follows commands

(+1) Restless but cooperative: No external stimulus is required to elicit movement. Increased limb movement. Picking at tubes but consolable.

(+2) Agitated: Having difficulty synchronizing with ventilator. No external stimulus is required to elicit movement. Attempting to sit or moves limbs to get up. Difficult to console despite frequent attempts. Requires physical restrain

(+3) Dangerously agitated: Unsynchronized with mechanical ventilation - desaturating. No external stimulus is required to elicit movement. Subject unsafe- attempting to pull at ETT/catheters. Biting ETT. Thrashing side to side; climbing over the rail; striking at staff.

Appendix IV
Data Collection Form

Medical Record Number
Age
Weight
Date and times of surgery
Surgery performed
Cardiopulmonary bypass times
Drugs, doses, times administered intraoperative
Time of intubation and extubation
Vasoactive and inotropic dose and time administered
Total volume of blood products administered (FFP, PLTs, Cryo)
Drugs, doses, and times administered postoperative

Appendix V - Pediatric Cardiac Surgery Requiring Cardiopulmonary Bypass
- Absent Pulmonary Valve Repair
- Anomalous Left Coronary Artery Reimplantation
- Aortic Stenosis Repair
- Aortic Regurgitation Repair
- Aortopulmonary Window Repair
- Atrial Septal Defect Repair
- Atrioventricular Septal Defect, Complete Repair
- Atrioventricular Septal Defect, Partial Repair
- Bicuspid Aortic Valve Repair

- Coarctation of the Aorta Repair
- Coronary Artery Fistula Repair
- Damus-Kaye-Stansel Procedure
- Dilated Cardiomyopathy Repair
- Double Aortic Arch Repair
- Double-Inlet Left Ventricle Repair
- Double-Outlet Right Ventricle Repair
- Ebstein's Anomaly Repair
- Eisenmenger Complex Repair
- Endocardial Cushion Defect Repair
- Fontan Operation
- Bidirectional Glenn Procedure
- Hypertension, Pulmonary Treatment
- Hypertension, Systemic Treatment
- Hypertrophic Cardiomyopathy Repair
- Hypoplastic Left Heart Syndrome Repair
- Interrupted Aortic Arch Repair
- Kawasaki Disease Treatment
- Marfan Syndrome Repair
- Mitral Stenosis Repair
- Mitral Valve Prolapse Repair
- Partial Anomalous Pulmonary Venous Repair
- Patent Ductus Arteriosus Ligation & Division
- Pulmonary Atresia Repair
- Pulmonary Stenosis Repair
- Ross Procedure
- Septal Myectomy
- Single Ventricle Repair - Tricuspid Atresia
- Single Ventricle Repair - Double Inlet Left Ventricle
- Single Ventricle Repair - Hypoplastic Left Heart Syndrome
- Tetralogy of Fallot Repair
- Total Anomalous Pulmonary Venous Repair
- Transposition of the Great Arteries, D-Type Repair
- Tricuspid Atresia Repair
- Tricuspid Valve Repair
- Truncus Arteriosus Repair
- Vascular Ring Repair
- Ventricular Septal Defect Repair

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