Perioperative Methadone Use to Decrease Opioid Requirement in Pediatric Spinal Fusion Patients

NCT02558010

Date of document: October 12, 2021

DESIGN AND METHODS

Study design

This study utilized a double-blind, randomized placebo-controlled trial design. Adolescents (10-18 years) who underwent a posterior spinal fusion planned for ≥10 levels were recruited to participate. The study ran from

February 2016 – October 2021. Participants were randomized to one of two groups after study enrollment: a Methadone group or a Placebo group (described below). The Investigational Drug Service at Children's Wisconsin maintained the randomization log (developed by a biostatistician), and prepared the methadone or placebo for surgery. This study was conducted in accordance with the CONSORT standards of reporting trials

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Age 10-18 years
- Idiopathic scoliosis
- Fusion levels planned for 10 or greater
- English speaking
- ASA class 1, 2 and 3

Exclusion Criteria:

- Current narcotic use / History of substance abuse
- Morphine, hydromorphone or methadone allergies
- Pregnancy
- Seizure Disorders
- Bleeding disorders
- Non-English speaking
- Renal or hepatic disease
- Neuromuscular scoliosis, muscular dystrophy related scoliosis, and significant pulmonary or cardiac disease.
- Long QT syndrome
- Obesity BMI > 40 or OSA
- Inability to use standard analgesic medications (gabapentin, ketoralac, acetaminophen)

Participant Recruitment and Enrollment Procedures:

All children who are scheduled for Spinal Fusion (SF) at CHW who meet the inclusion criteria will be invited to participate. Potential patients will be identified either by the anesthesia preoperative clinic (APNs), the orthopedic surgeon or physician assistant, the pain clinic research coordinator, or the anesthesiologist assigned to the spinal fusion case. Children/parents will be approached at a pre-surgical appointment or day of surgery (prior to surgery). Children and parents will be given verbal and written descriptions of the research procedure, risks, benefits, nonparticipation or withdrawal rights,

assurance of confidentiality, anonymity, protection of privacy in order to protect or minimize the risk of uninformed consent. They will be informed that the child's care will not be affected by their decision to participate and that they can withdraw at any point in the study without an impact in their care. They will be given opportunity to ask questions and be provided with answers. If both parent and child agree to participate, written informed consent from the parent, and child assent, will be obtained by a member of the research team. If the parent and / or child decline to participate, they will not be enrolled. Reasons for decline will be annotated for CONSORT data.

Subjects who turn 18 after completion of active study requirements (but before study is closed): As the surgical team/anesthesia has no contact with these patients after they leave the hospital, a Waiver of Consent and a Partial HIPAA Waiver will be submitted to the IRB.

Study Procedure

Once consent and assent are obtained, participants will be randomized to either the experimental or the control group prior to premedication for surgery. At the time of consent, the patient will complete a self-report of pain catastrophizing and on the day of surgery, patients will self-report anxiety and stress. The child, parent, anesthesiologist, surgeon, and researcher will be blinded to the group assignment. All participants will have an ECG evaluated in the operating room before anesthetic injection and throughout the surgery. . If the QTc is greater than 425msec, the patient will not receive study medication, will be excluded from the study and considered a screen failure. Anesthetic technique will be standardized as follows: Both groups will receive oral premedication of midazolam 0.5mg /kg (up to 10 mg), and oral gabapentin 15 mg / kg (up to 900 mg), which is the standard at Children's Wisconsin.

Anesthesia induction will be by inhaled Sevoflurane, followed by PIV placement. Alternatively, PIV placement will occur with lidocaine J-tip and oxygen with nitrous oxide. Once an IV is present, intubation will occur with propofol 1-3 mg /kg, rocuronium 0.6 mg /kg, and sufentanil 0.5mcg/kg. Maintenance anesthetic will include low dose isoflurane 0.3% end-tidal concentration (for amnesia) in air/oxygen, sufentanil infusion 0.25 mcg/kg/hour, propofol 100 mcg/kg/minute, and controlled ventilation. Prophylactic tranexemic acid 30 mg/kg loading dose (max 2000 mg) with a continuous infusion of 10mg / kg / hour will be used for surgical hemostasis.

Both motor and sensory evoked potentials will be monitored by the neurology service. An arterial line will be placed for invasive blood pressure monitoring and obtaining blood for intraoperative laboratory analysis.

Mean arterial blood (MAP) pressure control will be accomplished by adjustment of propofol. If blood pressures are less than 60 mmHg consistently, despite adjustment of anesthetic, the addition of phenylepherine may be added at the discretion of the anesthesiologist to keep the MAP greater than 60.

If the MAP is consistently greater than 75 mmHg, despite the adjustment of anesthetic, the anesthesiologist will be allowed to administer additional sufentanil 0.1mcg /kg every 10 minutes.

The study drug will be administered prior to incision and just prior to wound closure. The methadone group will receive 0.1 mg/kg (not to exceed 10mg) while the placebo group will receive an equivalent

volume of normal saline. At the start of wound closure, the methadone group will receive an additional 0.1 mg / kg of methadone (not to exceed 10mg) and the placebo group will receive morphine 0.1 mg / kg (not to exceed 10mg).

At the start of wound closure, the sufentanil infusion will be discontinued, all patients will receive intravenous acetaminophen 15 mg /kg (up to 1000mg). Also intravenous ketorolac (0.5mg / kg, up to 30 mg) will be given approximately 30 minutes prior to emergence. Tranexemic acid will also be discontinued at the start of wound closure.

Postoperative Management

All patients will be admitted to the orthopedics post-surgical floor and followed by the Acute Pain Management Service. Post-operative pain management will consist of a multi-modal regimen. PCA morphine 0.02mg/kg/dose every 6 minutes with a maximum dose of 0.12 mg /kg/ hour will be initiated in the PACU. Additionally, ketorolac will be continued at 0.3 mg / kg every 6 hours for 4 doses and acetaminophen at 15 mg / kg (to 1000 mg) every 6 hours for 4 doses. As part of standard treatment at CHW, all patients will have the option to receive diazepam 0.05mg/kg IV every 4 hours as needed. If pain scores are greater than a score of 5 after 4 PCA doses the prior hour, the floor nurse will be allowed to administer additional morphine 0.04 mg / kg every 3 hours, given at the patients request. For patients with a prior history of morphine allergy or intolerance, an equivalent dose of hydromorphone will be substituted. Likewise, for patient with an adverse response to morphine, they will be converted to an equivalent dose of hydromorphone using a 5:1 conversion ratio. When the patient is ready to transition from IV to enteral pain opioid, standard conversion guidelines will be employed (5).

Data to be collected for 72 hours following surgery

- Demographics (age, ethnicity, gender, weight, coexisting morbidity-respiratory, gastrointestinal, neurological, cardiovascular, or hepatorenal disorders, and home medications)
- Vital signs, every 1-4 hours for 72 hours
- Surgical blood loss, in mls / kg
- Number of pain assessments documented / 24 hours
- Average pain scores (and range) using the Numeric Rating Scale (0-10)
- Number of times/24 hours pain scores are greater than 4/10
- Average opioid consumption (morphine equivalents, mg/kg/hour) for each postoperative day
- Average number of injections/hour
- Average number of attempts/hour
- Number of treatment changes (dose changes, frequency changes, or any PCA settings changes)
- Oxygen supplementation (L/minute and time on oxygen)
- Adverse effects
- Frequency of respiratory depression as defined as: <10 breaths/minute for age 4-9 years and <8 breaths/minute for age >9 years.
- Respiratory depression requiring naloxone bolus, intubation, or respiratory support other than oxygen.
- Pruritis
- Nausea / vomiting/ retching requiring ondansetron

- Frequency of sedation scores <4 any time during 24 hours using the modified Ramsay score (for patients recruited while modified Ramsay was still being used)
- Frequency of sedation scores <-3 or >2 any time during 24 hours using the RASS score
- Urinary retention requiring intervention
- Time to first bowel movement
- Number of days PCA used

As part of the standard of pain management at CHW, benzodiazepines will be allowed in combination with a narcotic PCA to treat muscle spasms not effectively treated with opioids. This will be administered at the discretion of the child's nurse but will be held if the Ramsey score is 4 or less.

If side effects or inadequate pain control are encountered, standard approaches are in place to best improve pain control. This will be performed by the Acute Pain Service and the anesthesiology department, available 24 hours /7 days.

Foley catheters are placed in all spine fusion patients for several days following surgery. The surgical team determines removal of the foley catheter. Once the foley is removed, standard protocols (per floor nursing personnel) will be followed if the patient is unable to void. Bladder scanning is available at the discretion of the RN; straight catheterization orders are available as needed.

Statistical Analysis

At the time of study initiation, the apriori power analysis was based on our expectation that the size of our between-group difference for total opioid consumption would be comparable to that found in a similar study involving gabapentin as an adjuvant analgesic for adolescent spinal fusion patients.

The previous study showed a Mean between-group difference of 0.02 mg/kg/hr in opioid consumption. We estimated that we would need 22 patients per group: Using a two-sided t-test at an alpha of 0.05, we will have 80% power to detect (conservatively) a 0.15 mg/kg/hr difference in total post-operative opioid consumption.

Modified intent-to-treat analyses included all randomized participants, with the exception of those who did not receive the allocated intervention, as shown in the CONSORT diagram (Figure 1). Data were assessed for normality and heteroskedasticity using kolmogorov-smirnov and Levene's tests. Data are presented as mean ±SD or median (IQR), as appropriate. Categorical data are described using frequency statistics. Between-group differences were assessed with Mann-Whitney tests. Differences in categorical variables were assessed with chi-square or Fischer's exact tests. Missing data were treated using listwise deletion, and assumed to be missing completely at random. A 2-sided P-value <0.05 was used to define what was considered significant.

Multivariable mixed effects models were used to assess the effects of the intervention group over time, on four dependent variables: 1) total opioid use via PCA (including boluses), 2) total post-operative opioid consumption (including oxycodone), 3) total intra- and post-operative opioid consumption, and 4) PCA injection:attempt ratio. All outcomes were collected over PODs 0 – 3. The opioid consumption by PCA, total post-operative opioid consumption, and total intra- and post-operative opioid consumption were transformed using square root to satisfy model assumptions. The parameters were estimated using maximum likelihood, and an unstructured covariance structure was used for repeated measurements. Analyses controlled for patient age. The mixed model with random

effects allows for missing data, under the assumption that data were missing at random. Statistical analyses were calculated using SPSS V.27 (IBM SPSS Inc, Chicago, IL).