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Protocol

1. **Project Title**: Dosing of methadone for spine surgery

2. **Investigators**:
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3. **Abstract**:
   Patients undergoing complex spine surgery experience considerable amount of pain. Uncontrolled post-operative pain contributes to decrease ambulation, bowel dysfunction and other complications. With our diverse spine population in terms of age, weight and chronic use of narcotics, methadone dosing is difficult and there is no clear dosing protocol. In this study we want to compare two protocols for administration of methadone. We will randomize patients to receive either 1) 0.2 mg/kg based on ideal body weight after induction of anesthesia or 2) incremental aliquots of methadone up to 0.5mg/kg based on ideal body weight titrated to respiratory depression. We will compare post-operative opioid requirement at 24 and 48 hours. All subjects will be maintained on a remifentanil or sufentanil infusion for the entire case per standard of care.

4. **Background**:
   Patients with spine surgery experience a significant amount of pain that can interfere with healing, rehabilitation and contribute to morbidity in the post-operative period. Articles in the literature have established the use of methadone as a single dose from 0.2 mg/kg up to 0.5 mg/kg on opioid dependent patients[1]. We want to determine if methadone given in small aliquots until respiratory depression can act as a self-control to determine the correct dose required.

5. **Specific Aims:**
   The specific aim is to assess the safety and efficacy of a patient being used as his own control to personalize dosing of methadone for complex spine surgery.

   Hypothesis: Titrating methadone to respiratory depression allows the patient to act as his own control determining the dose he will require, improving pain control and consequently decreasing side effects and complications.

6. **Research Plan:**

Up to 100 patients will be enrolled in this study. Patients will be approached about their willingness to participate in this study either in a pre-operative surgical or anesthetic clinic visit or in the pre-operative area on the day of surgery. All attempts will be made to approach subjects about the study as early as possible in order to give subjects the maximum amount of time to consider participation in the study. Consent will be obtained by a member of the research team. The patient will be given time to read the consent, have all study related questions answered, and discuss the study with their family, if desired. A copy of the signed consent will be placed in the patient's chart, and a research progress note documenting study enrollment will be made in the patient's electronic medical record.

Inclusion Criteria:

1. Patients must consent to participate and sign the IRB-approved informed consent prior to beginning any study specific procedures.
2. At or between the ages 18 to 75 years.
3. Undergoing multilevel thoracic, thoracolumbar and/or lumbar spine surgery with instrumentation and fusion.

Exclusion Criteria:

1. Methadone or buprenorphine use.
2. Morbid obesity with BMI>40 Kg/m^2.
3. Chronic renal failure with creatinine>2.0 mg/dL.
4. Liver failure as determined by cirrhosis or history of fulminant hepatic failure.
5. Current or historical alcohol abuse.
6. Current or historical drug abuse.
7. Patients with history of a prolonged QTc, defined as a QTc value >450 ms in males and >460 ms in females.
8. Patients with ASA status IV or V.
9. Surgical diagnosis including spine tumor, infection, or trauma.
10. In the Principal Investigator's opinion is not a candidate for the study.
11. Unwilling to sign the informed consent form.

Preoperative Period:

Standard of care: Before surgery, the pre-op nurse will ask the subject to rate the pain scale from 0-10, obtain history of opioid use and vital signs. This data will later be collected by the study team from the medical record.

Research related procedures: Consented subjects will be randomly assigned to one of two different protocols by a designated study team member based on a computer generated randomization table. Randomization will occur on the day of surgery. Randomization will be 1:1. The two groups consist of:

1. Group 1 will receive 0.2 mg/kg based on ideal body weight of methadone after the intubation and before positioning.

2. Group 2 will receive incremental aliquots of methadone up to 0.5 mg/Kg based on ideal body weight titrated to apnea. Each subject will receive a 5-10 mg loading dose then aliquots of 5mg each, given at 3 to 5 minute time intervals. The practitioner will continue to coach patient to take deep breaths. After reaching the apnea threshold as determined by respiratory rate less than 8 breaths/min, induction of general anesthesia and intubation will proceed.

Intraoperative Period

Standard of Care:

All patients may receive midazolam 2 mg IV before induction of general anesthesia. Anesthesia will be induced with propofol 1.0 to 2.5 mg kg adjusting for age. Endotracheal intubation aided with rocuronium 0.1-0.5 mg/kg. Maintenance of anesthesia will be accomplished with remifentanil or sufentanil and propofol infusion, addition of inhalation agent is possible if no neuro monitoring is used.

All patients will have an infusion of remifentanil or sufentanil as part of the anesthetic technique, either volatile anesthesia or total intravenous anesthesia (TIVA) technique, titrated to achieve a target bispectral index (BIS) level of 40-50.

Inadequate anesthesia at the end of the case can be treated with aliquots of fentanyl 50 mcg increments at the discretion of the anesthesiologist.

Postoperative Period:

Standard of care: Post-operative management of pain include a PCA pump of fentanyl or hydromorphone or intermittent boluses of hydromorphone, fentanyl or morphine at the discretion of the surgical team. They can be converted to PO narcotics at the discretion of the surgical team.

Patients will be prescribed only PRN pain medication for the first 12 hours post operatively and will resume previous pain medication regimen or scheduled pain medication after the first 12 post-operative hours

Research Related Procedures: We will collect the following intraoperative data: total dose of all anesthetics, length of surgery, number of levels, estimated blood loss, time to extubation, total and type of fluids and vasopressors administered, vital signs and total opioid use. We will also collect age, weight, BMI, and ASA status.

The following post-operative data will be collected: patient daily pain based on the analog scale of 0-10 by blinded staff post-operative for the first 72 hours, total opioid usage, length of stay, time to get out of bed. Out of bed is defined by sitting up, dangling legs off of bed at the least.

We will calculate the opioid requirement for each 24 hour period and the whole 72 hours.

We will monitor and record the occurrence of any of the following complications: Respiratory depression with rate < 8/min, respiratory arrest, hypoxemia, desaturations, need for oxygen supplementation to maintain saturation >95%, need for vasopressors, hypotension defined as decrease >30% from baseline, cardiac arrhythmias, myocardial infarction, nausea, vomiting and pruritus.

Statistical analysis: Differences between groups will be compared using student *t* test or Mann-Whitney *U* test. We will study side effects using χ^2 as needed.

Please note that because methadone has not been studied in a large population of patients undergoing complex spine surgery, a power or sample-size analysis is not simple. The amount of patients planned for enrollment is based on a previous similar study that first completed a retrospective review of patients undergoing spine surgery.[1]

Table of Study Events

Activity	Screen	Pre-operative Period	Day of surgery	72 hours after surgery follow-up
Informed consent	X			
Inclusion / Exclusion Criteria	X			
Randomization		X		
Methadone Dosing			X	
Record intraoperative data			X	
Record post-operative pain score and total opioid administration				X
Record post-operative data as described in protocol				X

7. **Possible Discomforts and Risks**:
   Methadone is routinely used as part of care for all patients undergoing complex spinal surgery. There will be no discomfort involved, as the medication does not burn on injections. Possible risks associated to methadone involve the same risks as any other narcotic medication including: constipation, respiratory depression, nausea, vomiting, drowsiness, dizziness, weakness, dry mouth, confusion, difficulty urinating and itching. The main risk is the risk for respiratory depression resulting from the administration of methadone. This risk will be mitigated through close observation of the patient post operatively as patients who receive this surgery require admission to an intermediate or intensive care unit. All patients that receive narcotics are routinely monitored with pulse oximetry. In patients with prolonged QT interval repeated doses of methadone may precipitate an abnormal cardiac rhythm. All patients with history of prolonged QTc interval, as defined above, are excluded, and every patient will be monitored by EKG during the administration of methadone and for as long as they are in the ICU.

8. **Possible Benefits:**
   Subjects in Group 2 have the potential of benefiting in that when the patient serves as his own control for the dose of narcotics we believe he will have fewer side effects and better pain control.

9. **Conflict of interest**:
   Everyone in the investigation team denies any conflict of interest. Everyone will independently attest of no conflict as they agree to participate in the study.

10. **References**

1. Gottschalk, A., Duriex, M. E., & Nemergut, E. C. (2011). Intraoperative Methadone Improves Postoperative Pain Control in Patients Undergoing Complex Spine Surgery. Pain Medicine, 112(1), 218-223. Retrieved from www.anesthesia-analgesia.org