A Prospective Randomized Double Blind Controlled Trial Evaluating the Efficacy of Ketamine for Improvement in Postoperative Pain Control after Spinal Fusion for Idiopathic Scoliosis

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A. STUDY BACKGROUND AND PURPOSE

Hypothesis: The addition of a low-dose ketamine infusion to usual post-operative pain management will improve pain control as evidenced by an improvement in post-operative pain scores for patients undergoing spinal fusion for idiopathic scoliosis.

Adolescent idiopathic scoliosis is the most common form of scoliosis and occurs most commonly in girls. In 0.2-0.5% of cases, the curve in idiopathic scoliosis increases despite conservative, non-operative management and surgical intervention is required. Patients present for spinal fusion for correction of scoliosis in their adolescent years. Spinal fusion for idiopathic scoliosis is associated with significant postoperative pain which at this time is primarily managed with opiate pain medications. We aim to show an improvement in post-operative pain scores by adding a low dose infusion of ketamine intra- and post- operatively.

Ketamine antagonizes the N-methyl-D-aspartate (NMDA) receptor. Its action is related to central dissociation of the cerebral cortex and is thus referred to as a "dissociative anesthetic". Depending on the situation and dose, ketamine can be used for many different purposes ranging from pre-operative sedation and pain control to general anesthesia. For the purposes of this study, ketamine will be used as an adjunctive treatment for postoperative pain control. The dose appropriate for this purpose is a 0.5 mg/kg slow bolus prior to incision followed by an infusion of 0.2 mg/kg/hr (Cote). For comparison purposes, an induction dose of ketamine is 1-2 mg/kg with onset of action less than 60 seconds and duration of action of 10-20 minutes (Barash). Repeated bolus doses and prolonged infusion times will prolong the duration of action. According to Dr. Cote, ketamine has "one of the best safety profiles of any anesthetic agent," and he refers to a study by Green et. al which reviewed inadvertent overdoses of ketamine of 5-100x the intended dose (in the emergency room setting) and identified no long term complications despite short term respiratory depression and prolonged sedation.

The safety of ketamine as an adjunct for acute postoperative pain control has been well established in the literature. A review article published in 2004 concluded that adverse effects were not increased with small dose ketamine after review of 37 trials involving 2385 patients, of whom 232 were children (Subramaniam 2004).

Ketamine has been used safely in clinical trials in the pediatric population. Da Conceicao and colleagues used ketamine after tonsillectomy in patients 5-7 years old. They demonstrated that the use of a single, small dose of ketamine could reduce the frequency of rescue analgesia post-tonsillectomy without unwanted side effects (Da Conceicao 2006).

Ketamine has been extensively studied as an analgesic in the postoperative setting. Many articles have been published with conflicting results. In 2010, Carstensen and Moller reviewed 11 randomized, double-blinded clinical trials of ketamine added to opioid in IV PCA for postoperative pain. They found that 6 studies showed significantly improved postoperative analgesia and 5 studies showed no significant clinical improvement (Carstensen 2010).

Several studies indicate that ketamine can decrease opioid usage and improve pain control postoperatively with minimal side effects. In 2008, Yamauchi et al. showed that a ketamine bolus of 1 mg/kg followed by an infusion of .042 mg/kg/hr or .083 mg/kg/hr lowered the pain scores after cervical spine surgery in patients 20-70 years of age (Yamauchi 2008). A prospective, randomized double-blinded study in 2007 demonstrated a significant reduction in cumulative morphine consumption after thoracic surgery (Michelet 2007). Another prospective, double-blind, randomized study published in 2012 demonstrated that low-dose ketamine added to IV-PCA fentanyl after the Nuss procedure in pediatric patients reduced pain scores, consumption of fentanyl and incidence of nausea and vomiting without increasing side effects (Cha 2012). In this study, a ketamine bolus of 0.3 mg/kg was given 10 minutes prior to the end of the operation followed by an infusion of 0.15 mg/kg/hr. A review article published in 2011 concluded that not only was postoperative ketamine administration safe, but it was also effective in reducing morphine requirements after thoracic surgery and in some cases increased patient satisfaction (Mathews 2011). A randomized, double-blind control trial from 2008 concluded that low-dose ketamine after major abdominal surgery improved postoperative analgesia with a significant decrease of morphine consumption when its administration was continued for 48 hours postoperatively, with a lower incidence of nausea and with no side effects of ketamine (Zakine 2008).

There are not yet any studies evaluating the efficacy of an intra-operative and post-operative ketamine infusion for improvement in pain control in patients undergoing surgical correction of idiopathic scoliosis. We aim to show an improvement in patient pain scores and patient satisfaction in this specific population by adding a small bolus of ketamine pre-incision and a low dose ketamine infusion to the intra- and post-operative pain control regimen.

We will use the visual analog scale (VAS) for scoring postoperative pain. The VAS has been shown to have validity and reliability for measuring acute pain (Libman 2000 and Bijur 2001).

B. STUDY DESIGN

Surgical repair of idiopathic scoliosis is performed electively. In our hospital, this operation is performed by Dr. Allen Carl, a co-investigator on this study. We aim to enroll approximately 50 of his patients. Upon scheduling the operation, Dr. Carl will inform the patients and families that we are running a research study which will give them ample time to consider participation. They will have the opportunity in the clinic to ask questions of Dr. Carl regarding the protocol. They will also be contacted by the anesthesia team in the days prior to surgery for usual preoperative care. At that time, they will be asked if they would like to talk with an anesthesiologist about the study and if so, they will be contacted by one of the anesthesia investigators.

Actual enrollment will be done upon arrival to the hospital on the morning of surgery. After enrollment, patients will be randomized to either the treatment group (to receive

ketamine) or the control group (to receive saline). Randomization will be simple and will be performed by the pharmacy. Investigators and patients will be blinded to treatment group. Based on the patient's weight in the pre-operative care unit on the morning of surgery, the pharmacy will mix and provide standardized solutions for bolus and infusion in the operating room. Once the weight has been obtained, the anesthesia team will contact the pharmacy and once the medication (or saline) is ready, it will be delivered to the operating room. Surgery will not be delayed for the medication and there is ample time during induction of anesthesia for the medication to be prepared.

Patients will be unblinded by request at the completion of the study or in the event of a serious, unanticipated side effect for which we need the information to ensure patient safety.

We estimate that the average pain score of the control group will be 4-8. This is based on current average pain scores in the posterior spinal fusion population where ketamine infusions are not currently used but the patients otherwise follow the same protocol as listed below.

Patients generally stay in the Pediatric Intensive Care Unit (PICU) postoperatively for approximately 5-7 days. We don't anticipate that our study will increase or decrease the length of stay in the PICU. The full time commitment for each subject will not exceed the length of hospital stay. If serious side effects were to occur, the treatment would be unblinded and immediate care would be given to address the problem. If necessary, hospitalization or PICU time would be lengthened to adequately treat any problems and this would be reported in the study.

Inclusion criteria are ASA I, II, III patients presenting for spinal fusion for idiopathic scoliosis. Patients will be English-speaking and able to give assent to the study. Parents will need to give consent for minors and the vast majority of these patients are minors. Therefore we will obtain consent from guardians and assent from patients. Exclusion criteria include any contraindication to ketamine, previous spinal surgery, opioid dependence or chronic pain condition, significant developmental delay and pregnancy. A urine pregnancy test is not a specific component of our data as it is already part of the preoperative process and surgery would be canceled in the event of a positive pregnancy test.

As mentioned above, the study will be presented to patients in the preoperative visit by Dr. Carl. Patients will then be contacted by the anesthesia team by phone in the days preceding scheduled surgery. Consent and assent will be obtained in the preoperative care unit, in person, prior to initiation of sedation.

The location of the research is Albany Medical Center, Main Campus and the duration is the length of hospital stay: 5-7 days.

Methods:

Anesthesia induction will be at the discretion of the anesthesia attending. Maintenance of anesthesia includes approximately 0.5 MAC of volatile anesthetic and a remifentanil infusion, supplemented by a propofol infusion as necessary. A ketamine bolus of 0.5 mg/kg or saline bolus will be given and then the ketamine or saline infusion of 0.2 mg/kg/hr will be initiated prior to incision. Intra-operative opioids will be at the discretion of the attending anesthesiologist. Postoperative management will include continuation of the study drug as well as a standardized morphine patient-controlled analgesia (PCA) and acetaminophen 15 mg/kg (up to 1 gram) IV every 6 hours for 8 doses which will be initiated in the PACU. Starting at midnight going into postoperative day 1, patients are started on ketorolac 0.5 mg/kg up to 15 mg IV q8h for 24 hours. At that time they are transitioned to ibuprofen 10 mg/kg po (up to 600 mg) with meals. The ketamine or saline infusion will continue for ~ 48 hours post operatively at which point the PCA is discontinued (typically around noon) and patients are transitioned to oral pain medications (Roxicet or Lortab and Flexeril) as per the current protocol. All medications listed above with the exception of IV acetaminophen and ketamine are part of the current "Spinal Fusion Pediatric Critical Care" physician order set.

In the event of side effects from the ketamine as described in Section E, the anesthesia pain service will be contacted and changes to the pain regimen will be made. If side effects are noted but not bothersome to the patient, then a 10% decrease in the infusion rate will be made. If the side effects are concerning to the patient, such as dysphoria or hallucinations, then the infusion will be decreased by 50% and an anesthesia attending will be contacted. If side effects are severe then the infusion will be discontinued and an anesthesia attending will be contacted.

Pain scores will be solicited hourly from patients by the bedside nurse. We will record the highest (or worst) pain rating from each 4 hour time period for data analysis up until the end of postoperative day 2.

C. SUBJECT POPULATION (WHO, WHAT, WHERE)

Patients will be recruited from Dr. Allen Carl's clinical practice. Approximately 50 patients will be enrolled. The population of patients is adolescents and young adults who present for repair of idiopathic scoliosis. The majority of these patients are pediatric and this is justified for the research as we aim to improve the pain control specifically for this group of patients.

D. DATA ANALYSIS

Please refer to attached data collection sheets for details on data collection. Our primary endpoint is patient satisfaction. Our secondary endpoints are pain scores, opioid usage (including total morphine consumption) and length of hospital stay. Identifiers on the data collection sheets will include a subject number and a medical record number. These data sheets will be kept strictly confidential and data will be analyzed only by subject number.

Data analysis will be performed by the investigators with the help of our statistician. Data analysis will be performed on campus of the Albany Medical Center and identifying

information will not be removed from the site. Only members of the investigation team and individuals who are helping with data analysis will have access to the data and data will thereafter be contained in the Anesthesia Research Office.

Under the guidance of our statistician, we estimate that we need up to 50 patients enrolled to demonstrate the desired effect. (Based on a two-proportion sample size, assuming 70% of patients currently report "unsatisfactory" pain control, and assuming a 25% improvement in pain score, with an alpha of 0.05 and power of 0.8). The assumption that 70% of patients currently report unsatisfactory pain control is an estimate based on the fact that we know most patients are significantly uncomfortable after this operative for a period of several days.

Our primary responsibility is optimal care of our patients throughout the study period. If at any time a patient needs to be removed from the study then we will do so. Inadequate pain control is unlikely to be a cause for removal from the study but if a patient or family is unhappy with care, they can certainly be removed at any time and the data would reflect this.

e. RISKS

The risks of the study include the risks of adding ketamine to the post-operative management. As previously demonstrated, low-dose infusions of ketamine have been shown in the anesthesia literature to be safe with a low incidence of side effects. However, patients will be informed that possible side effects of ketamine include dysphoria, hallucinations (pleasant or otherwise), vivid dreams, sialorrhea, and increased blood pressure and heart rate. There are not described long term side effects from a low dose ketamine infusion administered perioperatively. Side-effects that have been noticed in other studies resolve with a decrease in the infusion rate of the ketamine. We will have a step-wise protocol in place to decrease the ketamine (or saline) infusion if side-effects are noted. Patients will have access to the Anesthesia Pain Service (APS) 24 hours a day, 7 days a week as well as access to the investigators. The APS currently manages many patients throughout the hospital who are receiving ketamine infusions for postoperative pain control.

F. BENEFITS

The major benefit for patients is the potential for improved pain control after a major operation that is associated with significant post-operative pain. Control patients will also have ready access to clinicians who can help to control postoperative pain. Intraoperatively, ketamine improves the evoked potentials which are monitored to minimize the risk of postoperative disability. Additionally, they will be contributing to improvement in postoperative pain management for future patients. Overall, we feel that the risks posed by the study are small and the potential benefits are quite large. There are minors involved in the study and they will have the same benefits described above.

G. CONFIDENTIALITY

Data will be maintained with the strictest confidentiality. Initial forms will be handwritten and data will be entered into a password protected computer file. A

randomized master key linking subjects to their study number will be used and destroyed at the completion of the study and data analysis.

H. OPTIONS

At any point in the study, the subject may choose to discontinue participation and opt for standard treatment.

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