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Research Article

Low-Dose Ketamine Infusion in Pediatric Spinal Fusion Surgery Promotes Faster Emergence

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Abstract

Background: For patients undergoing spinal fusion, anesthesiologists are required to provide adequate intraoperative anesthesia that is conducive to swift emergence, patient comfort and reproducible participation in the neurological examination. The use of intraoperative low-dose ketamine infusion as part of the anesthetic regimen for spinal fusion surgery has waxed and waned in popularity. We analyzed a study to compare the effectiveness of low-dose ketamine in spinal fusion surgery in patients with idiopathic scoliosis.

Methods: A retrospective study was conducted to analyze 49 patients who underwent spinal fusion using one of the two TIVA protocols: propofol with Remifentanil (Protocol A), and propofol with Remifentanil in addition to low-dose ketamine infusion (Protocol B).

Results: Low-dose ketamine infusion did not improve post-operative pain scores, but patients were less sedated, and more neurologically intact when they arrived in the PACU.

Conclusion: We adapted our practice to include intraoperative infusion of low-dose of ketamine attempting to reduce intraoperative anesthetic requirements and to improve the recovery state. Our results demonstrate the benefit of low-dose intraoperative ketamine in prompt postoperative recovery in pediatric spinal fusion surgery.

Introduction

Spinal fusion surgery is becoming a common major orthopedic operation performed in children and adolescents for the treatment of congenital, neuromuscular and idiopathic scoliosis. The anesthetic plan and postoperative pain management for patients undergoing spinal fusion must address several challenges [1,2] which include blood loss, infection and possible neurological impairment. Additionally, inadequate pain control results in ileus, nausea, poor oral intake, inadequate mobilization, delayed hospital discharge, and unanticipated hospital readmission [3].

Pediatric spinal surgery carries significant risk of intraoperative neurological damage. While neural monitoring of evoked potentials is helpful, the patient's ability to participate in the neurological examination remains the best technique in preventing permanent deficit, and thus requires intact cognition and rapid emergence after many hours of anesthetic exposure. Anesthesiologists are required to provide adequate intraoperative anesthesia that is conducive to swift emergence, patient comfort and reproducible participation in the neurological examination.

Total Intravenous Anesthesia (TIVA) has become a commonly used technique for spinal fusion because it allows for readily titrated emergence from anesthesia. Despite the use of rapid onset, short acting opioids such as Remifentanil and fentanyl, the problem of prolonged emergence persists because the opioids must be combined with other agents to produce an effective anesthetic. This addition of anxiolytics and hypnotics further prolong the context sensitive half times of the continuous infusion of opioids, thus delaying emergence [1,3-5]. Various multi-modal approaches for intra-operative and postoperative anesthetic management have been reported and results are equivocal [1]. The use of intraoperative low-dose ketamine infusion as part of the anesthetic regimen for spinal fusion surgery has waxed and waned in popularity. We designed a study to compare three TIVA protocols for spinal fusion surgery in patients with idiopathic scoliosis.

Methods

Study population

After obtaining IRB approval, we retrospectively reviewed posterior spinal fusions performed at our institution from 2010 to 2014 with intraoperative and postoperative records available in the EPIC electronic charting system (Epic Systems Corporation, Verona, WI). We only included patients with idiopathic scoliosis who received SSEP and MEP monitoring. Sixty-eight patients, ages 12-16 yrs

Table 1: Demographic characteristics of study groups.

	Protocol A (Remifentanil)	Protocol B (Remifentanil with Ketamine)	P-value
Gender (F/M)[a]	12 (11/1)	16 (10/6)	0.165[b]
Age (yrs)	14.2 (2.0)	14.3 (2.2)	0.9903
Weight (kg)	50.0 (6.3)	61.9 (18.6)	0.059
Levels of spinal fusion	9.4 (2.4)	9.8 (2.2)	0.953
Surgical Length (min)	288.7 (69.8)	289.3 (67.1)	0.975

Note: [a]Gender is expressed as total individuals (female/male); [b]P-value of gender difference was calculated from Chi-square test. Rest of p-value was calculated from t-test. Data was expressed as mean (Standard deviation)

were identified and 32 patients were excluded due to a diagnosis of neuromuscular scoliosis, lack of SSEP or MEP monitoring, or trauma as the surgical indication for spinal fusion. One subject was removed due to an incomplete anesthetic record. Seven subjects were excluded from analyses due to failed epidural catheter which was placed by the surgical team at the end of the procedure. A total of 28 records were analyzed in this study.

Study protocols

All patients received intra-venous midazolam premedication and the following induction and monitoring regimen. IV induction included fentanyl (1-2 mcg/kg), lidocaine (1 mg/kg), propofol (2-3 mg/kg), followed by an infusion of propofol. Intubation was accomplished by direct laryngoscopy. An arterial catheter and additional venous catheters were subsequently inserted. The maintenance anesthetic was Total Intravenous Anesthesia (TIVA) via one of two identified protocols as follows.

All protocols included infusions of Remifentanil plus propofol initiated at 150 mcg/kg/min and tapered to 50 mcg/kg/min, as tolerated. Protocol A (12 patients) included Remifentanil (0.25 ± 0.16 mcg/kg/min) and Protocol B (16 patients) used Remifentanil (0.27 ± 0.14 mcg/kg/min) plus ketamine 0.5 mg/kg load followed by ketamine infusion of 10 mcg/kg/min. Propofol infusions were stopped approximately 30 min before surgery ended in each protocol, and Remifentanil was stopped during dressing application just prior to turning the patient supine. In protocol B, ketamine infusion was stopped at the same time when Remifentanil was discontinued. The emergence phase is defined as from the time of completion of dressing application to the time of extubation in the supine position.

All patients received epidural catheters inserted by the surgeon at the time of wound closure. An epidural loading dose was given in 3-5 ml aliquots followed by a continuous infusion of 0.1% to 0.125% bupivacaine with fentanyl 2 mcg/ml at 0.2-0.3 ml/kg/hr. A Patient-Controlled Epidural Analgesia (PCEA) dose ranging from 2-3 ml Q 15-20 minutes was initiated based on weight and height not to exceed an hourly cumulative volume of 0.4 ml/kg. Q 2 hr PRN intravenous morphine (50-75 mcg/kg/dose) or hydromorphone (10-15 mcg/kg/dose) was made available for moderate to severe pain unrelieved by the epidural. The total dose of intravenous opioid administered for the first 24 hrs was converted to Morphine Equivalents (ME) using the equianalgesic conversion cited by Shaheen et al. [6].

Upon arrival in PACU, the patient's responsiveness to stimuli was assessed by the nursing staff using the University of Michigan Sedation Scale (UMSS) [7]. Data was retrieved from the EPIC system for each patient. Other data collected in addition to the UMSS score included vital signs; parenteral opioid consumption and Q 15 minutes pain scores using the visual analogue scale (VAS 0–10).

Data analysis

All analyses were conducted using the SAS 9.4 package on a PC platform (SAS Institute, Cary, NC). Gender differences between groups were analyzed using Chi-square test. Other measurements were analyzed using either t-test if normal distribution assumption was met, or Wilcoxon-Mann-Whitney test with an overall significance level of 0.05.

Results

More females than males underwent spinal fusion in each group with an average F: M ratio of 5.6:1. No differences between the groups were noted with regard to age and weight. The average number of fused levels among the three groups was approximately 9 vertebrae ranging from T3-S1, and the duration of surgery was of similar length in each group (Table 1).

Table 2: Intra- and postoperative assessment of emergence/pain management between two groups.

	Group A (Remifentanil)	Group B (Remifentanil with Ketamine)	P-value[a]
Total intraoperative Remifentanil consumption (mg)	4.0 (3.5)[b]	4.9 (2.8)	0.529
Total Intraoperative propofol infusion (mg)	1980 (1166)	1821 (719)	0.477
Emergence time (min)	26 (14)	14 (12)	0.022
PACU Stay (min)	83 (28)	74 (19)	0.217
UMSS	1.8 (1.3)	0.7 (0.9)	0.019
1st PACU Pain Score	3.5 (3.7)	0.6 (1.4)	0.006
2nd PACU Pain Score	3.2 (2.3)	1.4 (2.3)	0.039
24-hr Max Pain Score	6.8 (2.8)	5.5 (2.4)	0.161
Total PACU morphine consumption (mg)	4.6 (3.2)	6.8 (2.4)	0.173
24-hr postoperative Morphine Eq (mg)	6.5 (8.5)	1.6 (3.1)	0.183
Total Epidural fentanyl usage (mg)	638 (120)	627 (234)	0.584

Note: [a]The p-values were calculated by either two samples t-test or Wilcoxon–Mann–Whitney test.

[b]Data was expressed as mean (SD).

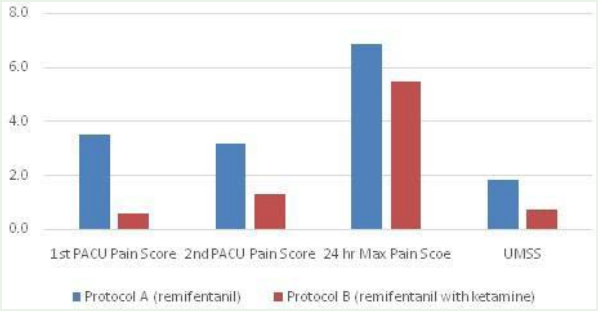

Figure 1: Patients receiving low-dose ketamine infusion in Protocol B had faster lower pain scores on arrival to PACU and lower UMSS scores, suggesting that patients in Protocol B were more comfortable, less sedated, and more neurologically intact when they arrived in the PACU than the group without ketamine. However, the 24-hour maximum pain scores were similar among the three groups. Intraoperative low-dose ketamine infusion did not decrease postoperative PCEA demands and epidural fentanyl consumption.

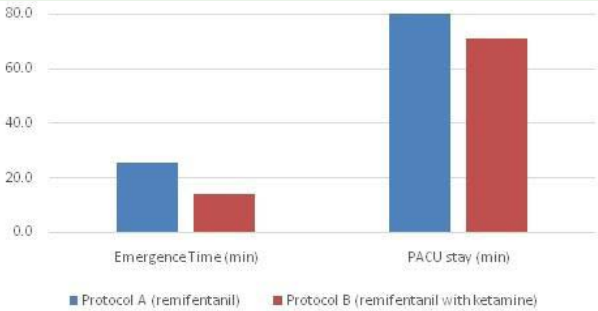

Figure 2: The addition of a low-dose intraoperative ketamine infusion (in Protocol B) showed a significantly shorter time to emergence, but did not reduce PACU stay time.

The average total propofol consumption was similar in both groups. The average total Remifentanil consumption was (4.0 ± 3.5 mg) in Protocol A and (4.9 ± 2.8 mg) in Protocol B which was not a significant difference. The length of PACU stay was similar for all groups (Table 2).

The addition of low-dose intraoperative ketamine infusion in Protocol B, showed a significantly shorter time to emergence (14 min vs. 26 min, p=0.022) (Table 2 and Figure 1). The protocol B group also had significantly lower UMSS scores (0.7 vs. 1.8, p=0.019), suggesting that patients receiving intraoperative low-dose ketamine infusion were less sedated, and more neurologically intact when they arrived in the PACU (Table 2, Figure 2). Patients in Protocol B had lower pain scores on arrival to PACU than in Protocol A (1st Pain Score 0.6 vs. 3.5, p=0.006, 2nd PACU pain score 1.3 vs. 3.2, p=0.039, Table 2, Figure 1). However, the 24-hour maximum pain scores were similar between groups. Intraoperative low-dose ketamine infusion did not decrease postoperative PCEA demands and epidural fentanyl consumption (Table 2).

Discussion

Ketamine is an *N*-Methyl-D-Aspartate (NMDA) receptor antagonist which was first approved for use as a general anesthetic agent in 1962. Studies demonstrate that ketamine can decrease central excitability, decrease acute postoperative opioid tolerance, and serve as a potential modulator of opioid receptors [8,9]. Furthermore, ketamine has been shown to be an effective intrinsic analgesic and adjuvant in balanced analgesia techniques when combined with opioids, nonsteroidal anti-inflammatory medications, or acetaminophen [1,10-12]. However, the clinical benefit of intraoperative ketamine for spinal fusion in the pediatric population remains unclear. Studies by Guignard et al. used a loading dose of 0.5 mg/kg of ketamine followed by a continuous infusion of 5 mcg/kg/min and showed a reduction in postoperative opioid demand with no adverse effects [8,13]. Loftus et al. and others used a similar loading dose but twice the intraoperative infusion rate yet, showed no improvement in postoperative analgesia when compared to placebo [8,11]. However, the patient populations and procedures were dissimilar in the Guignard and Loftus studies. Selective application of intraoperative ketamine must be examined.

We adapted our practice to include intraoperative infusion of low-dose ketamine attempting to reduce intraoperative anesthetic requirements and to improve the recovery state. Our results demonstrate a benefit of low-dose, intraoperative ketamine infusion for prompt postoperative recovery. Ketamine infusion can decrease immediate postoperative pain score in recovery, but no postoperative opioid sparing effect could be detected at the ketamine dose employed.

Low-dose ketamine infusions have been reported to improve postoperative pain and to reduce opioid usage in various surgical procedures. However, the results were equivocal [14]. Some studies suggested that Perioperative ketamine in sub-anesthetic doses is effective against postoperative pain, reducing morphine consumption in the first 24 hours, postoperatively [8]. In addition, ketamine usage can also reduce postoperative nausea and vomiting without significant side effects [15]. Other studies demonstrate that sub-anesthetic doses of ketamine may not exhibit a postoperative opioid-sparing effect [16]. Loftus et al. studied a group of chronic pain opioid- tolerant patients who underwent lumbar spinal surgery. They concluded that intraoperative ketamine reduces opioid consumption in the 48-h postoperative period in opioid-dependent patients with chronic pain. Ketamine may also decrease opioid consumption and pain intensity throughout the postoperative period [8]. Subramaniam et al. conducted a double-blind, randomized prospective study that extended ketamine infusion into the postoperative recovery period. The authors concluded that the addition of low dose IV ketamine infusion does not improve postoperative analgesia in these patients [11].

Our results indicate that a Perioperative TIVA technique consisting of Remifentanil, propofol and low dose ketamine does not improve postoperative pain management in pediatric spinal fusion patients. The initial PACU pain scores were lower in patients who received ketamine yet; parenteral opioid consumption was no different among the three groups. As our data indicated, ketamine infusion did not decrease total intraoperative propofol or Remifentanil consumption. It is unclear why these discrepancies exist between our data and previously published results that used similar ketamine dosing. Loftus's study showed that patients with chronic pain and higher opioid tolerance may benefit more from low dose ketamine infusion. Our pediatric population was opioid naïve and without a history of chronic pain or chronic pain behaviors

(e.g. frequent preoperative analgesic consumption). Grathwohl has indicated, sample populations and variation of ketamine dosage may result in these discordances in different studies [17].

Unexpectedly, we found that TIVA with low-dose ketamine infusion provides significantly faster recovery from anesthesia, allowing for an expedited neurological exam. This early reanimation effect may be attributed to low-dose ketamine. The mechanism of ketamine-induced early reanimation is unknown. Also, mu receptor binding by ketamine occurs at anesthetic doses and thus, our low dose infusion does not explain the witnessed reduction in the initial postoperative pain score [9]. Ketamine is a non-competitive NMDA receptor antagonist, which has growing promise in the management of treatment-resistant depression and other behavioral disorders [18]. The same mechanism for the mood altering, antidepressant effects of ketamine may play a role in faster emergence. While anesthetic doses of ketamine cause neurocognitive impairment and loss of responsiveness, sub-anesthetic doses may have a paradoxical effect [19]. Animal studies show increased striatal activity when ketamine is administered. This may infer similar activity in humans where striatal stimulation is associated with reward and increased response to aversive, novel or intense stimuli [20]. Thus, a faster, exaggerated response to stimulation during commands upon emergence from anesthesia with low-dose ketamine may be interpreted by the patient as intense stimulation evoking a more rapid response.

A second theory regarding ketamine's effects on emergence may deal with preservation of homeostasis and, in particular, sleep homeostasis. Ketamine demonstrates beneficial properties of maintaining hemodynamic stability in patients in a wide dose range due to its α and β-adrenergic receptor agonist effects [9]. Ketamine plays a unique role as a "homeostatic regulator" in the acute inflammatory response and in stress-induced immune disturbances [21]. Other regulatory functions may be impacted by ketamine. Animal studies on sleep homeostasis have identified genes and anatomic locations that determine sleep induction and wakefulness. Studies by Joiner et al. suggest that induction and emergence are not caused by identical processes operating in reverse [22]. The inertial barrier known as "neural inertia" leads to the safeguarding of wakefulness as well as anesthesia and is maintained via a controlled hysteresis that regulates neuronal excitability. Rapid emergence may occur by narrowing of the neural inertia barrier and perturbation of hysteresis morphology. Modulation of ion channels and neuronal excitability by ketamine may play a role in emergence. The impact of ketamine on neural inertia at the genetic and molecular levels provides future areas of study.

The limitations of this study include the retrospective design and the study population size. However, our findings of rapid emergence and awareness are statistically and clinically significant. A prospective study is indicated to control bias and to support our findings. The need for further studies on the effects of low dose ketamine as a reanimation adjuvant for emergence from general anesthesia is warranted.

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