Original Article

The role of ketamine in opioid-free spinal deformity surgery: is it possible and beneficial?

Paul J. Park[1], Melvin C. Makhni[2], Meghan Cerpa[1], Eduardo C. Beauchamp[3], Nathan J. Lee[1], Ronald A. Lehman[1], Lawrence G. Lenke[1]

[1]The Och Spine Hospital, NewYork-Presbyterian/Columbia University Medical Center, New York, NY, USA; [2]Department of Orthopaedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Twin Cities Spine Center, Minneapolis, MN, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: M Cerpa; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: PJ Park, MC Makhni, NJ Lee, M Cerpa, EC Beauchamp; (V) Data analysis and interpretation: PJ Park, MC Makhni, NJ Lee, M Cerpa, EC Beauchamp; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Meghan Cerpa, MPH. The Och Spine Hospital, NewYork-Presbyterian/Columbia University Medical Center, 5141 Broadway, 3 Field West-022, New York, NY 10034, USA. Email: mc4338@cumc.columbia.edu.

Background: As the opioid epidemic in the United States has continued to gain momentum in recent years, the current study aims to explore the efficacy of ketamine in a traditionally challenging setting regarding pain control, and contribute toward developing an opioid-free intraoperative pain protocol in spinal deformity surgery.

Methods: Fifty-four patients who underwent spinal deformity surgery between January 1, 2017 and December 31, 2017 by one senior surgeon were included. Demographic data and preoperative opioid use was collected. Surgical details including number of levels fused, estimated blood loss, and operative time was also collected. All patients received a hydromorphone patient-controlled anesthesia (PCA) device postoperatively. 36/54 patients received perioperative ketamine during their procedure, both intraoperatively and postoperatively. The consumption of postoperative hydromorphone and the ratio of doses given by doses attempted postoperatively were recorded. Patient charts were also reviewed for documented ileus during their inpatient stay.

Results: Mean age was 49 years, and 31% were male. Average BMI was 24.3 kg/m^2. The average number of levels fused was 11.6. Mean operative time was 10.7 hrs, and average EBL was 1,522 mL. The mean length of stay was 8 days. Average postoperative PCA use of hydromorphone in the no ketamine group (NK) (n=18) was 5.99 mg compared to 6.91 mg for those who received perioperative ketamine (K) (n=36); there was no significant difference between populations (P=0.57), although the variances was significant (P=0.044). There was no correlation between intraoperative ketamine and postoperative PCA use (r=–0.05; P=0.72). Additionally, there was no correlation between postoperative PCA use and dose of postoperative ketamine received (r=–0.15; P=0.27). The ratio of doses given: attempted was 0.61 in the NK group and 0.59 in those in the K group (P=0.79). Average postoperative hydromorphone use was 5.48 mg in patients that did not use opioids preoperatively (n=39) compared to 12.77 mg in those who used opioids preoperatively (n=9; P=0.0003). 9/54 patients had a documented ileus during their admission, while 4/9 (11%) had received ketamine (P=0.095)

Conclusions: Though our study showed no significant change in postoperative opioid requirement in our population, our results show that integration of ketamine in these extensive operations fare similarly to traditional opioid-based regimens. There was also no significant association seen between ketamine use and adverse side effects such as ileus. At our institution we are currently establishing opioid-free intraoperative pain protocols that use ketamine as an adjunct, and further study will explore the effect this may have on postoperative opioid consumption for spinal surgery patients as well as postoperative patients in general.

Keywords: Spine surgery; opioid; spinal deformity; Ketamine; Analgesia

Submitted Dec 31, 2019. Accepted for publication Oct 27, 2020.
doi: 10.21037/jss-19-475
View this article at: http://dx.doi.org/10.21037/jss-19-475

Introduction

The opioid epidemic in the United States has continued to gain momentum in recent years. Deaths linked with prescription opioid overdose have almost quadrupled in number from 1999 to 2010 (1). In particular, attention has been turned to physicians and their contribution to these trends—as such, the onus has fallen on physicians and surgeons to reduce prescriptions of these medications. The US consumes 80% worldwide of the global opioid supply (2); acknowledging this, the government attempted to curb opioid use by switching hydrocodone to a schedule II substance from schedule III in 2014 (3).

Surgery has played a significant role in introducing patients to opioids. Opioids are necessary in the immediate postoperative period for pain control and often patients will be prescribed a short course of opioids, which may be the patient's first experience with narcotics. Although all surgical specialties face this dilemma, orthopaedic surgery in particular must address this issue. One study looked at urology, general surgery, obstetrics/gynecology, and otolaryngology procedures and found that orthopaedic patients were at relatively higher risk to develop chronic opioid use following surgery (4). They found that among postoperative patients undergoing various surgeries (appendectomy, cholecystectomy, cesarean delivery, sinus surgery, cataract surgery, prostate surgery, mastectomy, total hip arthroplasty and total knee arthroplasty), patients undergoing total knee arthroplasty were 5.1 times more likely to develop chronic opioid use, the highest in the study (4). 7.7% of all opioid prescriptions in the US in 2009 were written by orthopaedic surgeons (5). Given the nature of the field, this outcome is to be expected for orthopaedic surgery, and spine surgery in particular. Often patients are referred to a spine surgeon due to long-standing pain interfering with activities of daily living. Those that eventually undergo spine surgery are those that have already trialed and failed conservative measures such as medications, physical therapy and/or injections. The surgery itself, especially large deformity corrections, often require longer operative times and necessitate substantial pain control regimens in the perioperative period.

By reducing the opioid burden in the perioperative period surgeons can make a critical contribution in abating the opioid epidemic. This can be done by finding alternatives and adjuncts to opioids in pain control. After falling out of favor given concerns of side effects seen in its recreational use (6), ketamine use has been increasing recently. With the development of S(+)-ketamine, it's use in subanesthetic doses has been found to have strong analgesic effects via the NMDA pathway (7,8). By focusing specifically on spinal deformity surgery, the current study aims to explore the efficacy of ketamine in a traditionally challenging setting regarding pain control, and contribute toward developing an opioid-free intraoperative pain protocol. We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/jss-19-475).

Methods

Following Columbia University Institutional Review Board approval (#AAAR7003), we reviewed medical records and included 54 patients who underwent spinal deformity surgery between January 1, 2017 and December 31, 2017 by one senior surgeon. A HIPAA form B waiver was acquired in lieu of written consent. Demographic data was collected on all patients including preoperative opioid use. The extent (number of levels) of spinal deformity surgery, estimated blood loss, and operative time was also collected. All patients received a hydromorphone patient-controlled anesthesia (PCA) device postoperatively. A total 36 patients received perioperative ketamine during their procedure, both intraoperatively and postoperatively, and 18 patients did not receive any ketamine throughout their hospital stay. The consumption of postoperative hydromorphone and the ratio of doses given by doses attempted postoperatively were recorded. Patient charts were also reviewed for documented ileus during their inpatient stay. Independent *t*-tests and chi-square tests were performed on continuous and categorical variables, respectively. $P<0.05$ was considered statistically significant.

Results

The mean patient age was 49 years old, and 31% were male.

Table 1 Demographic data

Variable	No ketamine used	Ketamine used	P value
Total (#)	18	36	
Male (%)	33%	31%	0.836
Age, mean years (SD)	52 (15)	48 (17)	0.393
BMI, mean kg/m^2 (SD)	25 (3.4)	24 (5.5)	0.662
LOS, mean days (SD)	7 (2.8)	8 (6.8)	0.304
Operative duration, mean minutes (SD)	532 (98.3)	698 (848.1)	0.254
EBL, mean mL (SD)	1,544 (587.1)	1,510 (803.9)	0.874

Table 2 Postoperative opioid use following spinal surgery

Postoperative PCA data	No ketamine used	Ketamine used	P value
Postoperative PCA use, mean (mg/kg)	0.09 (0.058)	0.12 (0.079)	0.227
Postoperative PCA duration, mean (hours)	12.5 (4.0)	12.8 (3.3)	0.726
Postoperative PCA doses (given/attempted)	0.61 (0.464)	0.59 (0.485)	0.785

The average BMI was 24.3 kg/m^2. The average number of levels fused was 11.6. The mean operative time was 10.7 hours, and average EBL was 1,522 mL. The mean length of stay was 8 days postoperatively (*Table 1*).

The average postoperative PCA use of hydromorphone in patients that did not receive perioperative ketamine (n=18) was 5.99 mg compared to 6.91 mg for those who received perioperative ketamine (n=36); there was no significant difference between populations (P=0.571), although the variances between populations was found to be significant (P=0.044). There was no correlation between intraoperative ketamine and postoperative PCA use (r =–0.05, P=0.7161). Additionally, there was no correlation between postoperative PCA use and dose of postoperative ketamine received (r =–0.15; P=0.274). The ratio of doses given:attempted was 0.61 in the control group and 0.59 in those in the ketamine group (P=0.79) (*Table 2*). Preoperative opioid use was found to have a statistically significant association with postoperative PCA use. The average postoperative hydromorphone use was 5.48 mg in patients that did not use opioids preoperatively (n=39) compared to 12.77 mg in those who used opioids preoperatively (n=9; P=0.0003). However, there was no significant difference in those without or with preoperative opioid use on the doses given:attempted ratio (0.61 *vs.* 0.46, respectively) (*Table 3*). 9/54 patients had a documented ileus during their admission, while 4/9 (11%) had received ketamine (P=0.095) (*Table 4*).

Discussion

The importance of finding alternatives to opioid for pain control in the postoperative setting continues to increase as the opioid epidemic rages on in the United States. Recently, there has been an increase in the use of ketamine as an adjunct to opioids and a variety of surgical subspecialties have researched the utility of ketamine. A large meta-analysis looking at several different types of surgery found that ketamine was effective in decreasing opioid burden in procedures with relatively higher postoperative pain such as upper abdominal and thoracic procedures (9). Smaller procedures such as dental or head and neck surgery did not show as robust of a response to ketamine (6). The same trend has been observed within orthopedic surgery specifically; there is a greater benefit from ketamine for more invasive/involved surgeries, such as spine surgery, as compared to smaller surgical procedures, such as arthroscopy. For this reason, this study aimed to examine the impact of ketamine on opioid use in one of the most challenging and extensive surgeries within the field of orthopedic surgery, spinal deformity surgery.

Currently, there are several large studies on the use of

Table 3 Postoperative opioid use in patients receiving either intraoperative or postoperative ketamine infusion

Postoperative PCA data	No ketamine used	Ketamine used	P value
Intraoperative ketamine (dose ≥2.4 mg/kg)			
Postoperative PCA use, mean mg/kg	0.13 (0.11)	0.11 (0.12)	0.608
Postoperative PCA duration, mean hours	12.3 (2.4)	13.3 (4.0)	0.373
Postoperative PCA given/attempts	0.60 (0.31)	0.58 (0.31)	0.852
Postoperative ketamine (duration ≥48 hours)			
Postoperative PCA use, mean mg/kg	0.12 (0.118)	0.12 (0.124)	0.919
Postoperative PCA duration, mean hours	12.5 (3.4)	12.4 (3.6)	0.938
Postoperative PCA given/attempts	0.62 (0.324)	0.56 (0.318)	0.585

Table 4 Ileus in the setting of ketamine administration

Ketamine used	No ileus present	Ileus present	P value
No ketamine used (n=18)	13 (72%)	5 (28%)	
Ketamine used (n=36)	32 (89%)	4 (11%)	0.095
Total	45	9	

ketamine in spine surgery in various settings, including intraoperatively, postoperatively, or a combination of both. An earlier study explored ketamine use in patients undergoing elective surgical lumbar discectomy with partial laminectomy and nucleotomy (10). 69 patients received either morphine only (control), ketamine only, or a combination as an IV bolus just after induction of anesthesia. Aveline *et al*. found that the combined ketamine/morphine (KM) group consumed significantly less IV morphine in the PACU than the morphine only (M) group (P=0.009), however no significant difference was seen between the KM group and the ketamine only (K) group (10), along with significantly lowered VAS scores in the KM group. Side effects such as postoperative nausea and vomiting were also significantly lower in the KM group versus the M group. While this surgical cohort is generally considered one of the less invasive procedures compared to large spine deformity reconstructions, the use of a single dose of ketamine had a significant reduction in opioid use postoperatively.

A similar prospective randomized control trial was conducted by Loftus *et al*. in 2010. There were 101 patients undergoing elective spine surgery who were randomized to receive an IV ketamine infusion from induction to wound closure, versus a control group receiving only normal saline intraoperatively. All patients received a morphine PCA postoperatively. Those in the ketamine group showed significantly less morphine consumption relative to the control group at 24 hours (30% reduction, P=0.032) and 48 hours (48% reduction, P=0.029) (11). Significant decreases in pain scores were found in the PACU as well as at the 6-week post-discharge period, where a 71% reduction in opioid use was observed (P=0.033, P=0.026 respectively) (11). These findings suggest that ketamine may provide a benefit in the short and long-term postoperative setting. Of note, this population specifically included patients with an active history of opioid use for pain management, those with a high opioid tolerance. This study demonstrated that patients who have preoperative opioid use have significantly higher use of opioids postoperatively. Our study similarly found that opioid consumption was significantly higher in those opioid tolerant patients throughout their hospital stay. Ketamine may have a stronger effect on those most vulnerable to increased consumption following surgery. Additionally, no significant differences were seen in side effects including nausea, constipation, or hallucinations (11). This finding is in contrast to common belief that ketamine may be associated with various side effects seen initially in recreational users. In our study, we found no significant correlation with ketamine use and incidence of ileus.

In a recent study by Perelló *et al*. on adolescent idiopathic scoliosis patients undergoing surgery, ages 10–18 years old, the authors examined morphine consumption, pain at rest and movement, side effects, onset of oral intake, onset of ambulation, and length of stay for scoliosis surgery. Patients were randomized into a control group and a ketamine group: one group received an IV bolus of ketamine at induction as well as continuous IV infusion until 72 hours postoperatively; the control group received the equivalent in normal saline. No significant differences were seen in this population with total cumulative morphine consumption. Secondary outcomes, such as pain at rest or during movement, nausea, vomiting, itching, or dysphoria, hallucinations, nightmares, diplopia, or respiratory depression had no significant difference compared to those seen in the control group. This again addresses concerns regarding the safety of ketamine and its possible side effects in analgesia (12).

The most well studied combination of pain control has been ketamine with a morphine PCA, of which positive results were seen (10,11,13,14). A study in 2008 similarly looked at ketamine combined with a hydromorphone PCA where 26 narcotic-tolerant patients undergoing a 1–2 level lumbar fusion were given either ketamine at induction and for the following 24 hours versus a control group. This study found that those who had received ketamine had significantly less pain in the first postoperative hour and at on POD1. These results were found to be both at rest and while working with physical therapy (15). Though the ketamine group did require less hydromorphone overall however, the differences were not statistically significant in this smaller study (15). Another study in 2011 of patients undergoing lumbar or thoracolumbar laminectomy, looking at hydromorphone PCAs combined with ketamine infusion intraoperatively and for the first 24 hours, similarly found no significant difference in pain scores, at rest or movement, or in hydromorphone consumption between the control and ketamine groups (16).

Several prospective studies have looked at ketamine in perioperative pain control for spine surgery with generally positive results showing decreased opioid requirements following surgery. Of note, however, the vast majority of these studies were performed in smaller spine surgeries such as 1- to 2-level decompressions or fusions. As seen previously, the effect of ketamine appears to be in procedures that often require higher pain control measures following surgery (9). The current study aimed to explore the role of ketamine in one of the most demanding spine surgeries regarding pain control, large degenerative or idiopathic spinal deformity surgery in an adult population. Limitations of this study include its retrospective nature. Though it is a smaller cohort of 54 patients, the collection of data by a single surgeon in a short period enabled a more consistent study population concerning a specific pain regimen protocol and complexity of surgery. The scale of these procedures can be seen in the average number of levels fused (11.6), the average anesthesia time of 10 hours, and the average estimated blood loss of 1,522 cc; previous research using ketamine in spine surgery has only been in much shorter and less extensive procedures. There are inherent challenges in assessing ketamine's role in pain control such as the use of multimodal pain regimens, each of the aforementioned studies had a slightly different protocol, and the specific combination of medications used. Additionally, the use of ketamine itself in sub-anesthetic doses for analgesia is still in the process of being optimized - in some studies, it was given as a single dose at the beginning of surgery, as continuous infusions throughout the procedure, or sometimes as a continuous infusion up to several days postoperatively as well.

Conclusions

The scale of the current opioid epidemic in the United States requires a culture shift on multiple levels to address. For surgeons, the main contribution can be through reducing opioid exposure and use for patients in the postoperative period by looking for effective alternatives. Ketamine has shown potential throughout multiple surgical subspecialties in this role, and several recent studies have attempted to characterize its efficacy. Spine surgery inherently requires significant postoperative pain control given both the patient's preoperative pain requirements and the procedure itself. We have the unique opportunity to collect data on a population undergoing large spinal deformity surgery, among the most demanding for postoperative pain control. Though our study showed no significant change in postoperative opioid requirement in our population, our results show that integration of ketamine in these extensive operations fare similarly to traditional opioid-based regimens. There was also no significant association seen between ketamine use and adverse side effects such as ileus. At our institution we are currently establishing opioid-free intraoperative pain

protocols that use ketamine as an adjunct, and further study will explore the effect this may have on postoperative opioid consumption for spinal surgery patients as well as postoperative patients in general.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at http://dx.doi.org/10.21037/jss-19-475

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jss-19-475

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at http://dx.doi.org/10.21037/jss-19-475). Lawrence G Lenke serves as an unpaid editorial board member of *Journal of Spine Surgery* from Oct 2019 to Oct 2021. Dr. Lehman reports other from Medtronic, other from Stryker, other from Depuy Synthes Spine, outside the submitted work; Dr. Lenke reports personal fees from Medtronic, grants and personal fees from DePuy-Synthes Spine, personal fees from K2M, non-financial support from Broadwater, non-financial support from Seattle Science Foundation, grants and non-financial support from Scoliosis Research Society, non-financial support from Stryker Spine, non-financial support from The Spinal Research Foundation, grants from EOS, grants from Setting Scoliosis Straight Foundation, personal fees from Fox Rothschild, LLC, personal fees from Quality Medical Publishing, other from Evans Family Donation, other from Fox Family Foundation, grants and non-financial support from AOSpine, outside the submitted work; Dr. Lenke reports personal fees from Medtronic, grants and personal fees from DePuy-Synthes Spine, personal fees from K2M, non-financial support from Broadwater, non-financial support from Seattle Science Foundation, grants and non-financial support from Scoliosis Research Society, non-financial support from Stryker Spine, non-financial support from The Spinal Research Foundation, grants from EOS, grants from Setting Scoliosis Straight Foundation, personal fees from Fox Rothschild, LLC, personal fees from Quality Medical Publishing, other from Evans Family Donation, other from Fox Family Foundation, grants and non-financial support from AOSpine, outside the submitted work; The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was followed by Columbia University Institutional Review Board approval (#AAAR7003). A HIPAA form B waiver was acquired in lieu of written consent.

References

1. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical Overdose Deaths, United States, 2010. JAMA 2013;309:657-9.
2. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. Pain Physician 2008;11:S63-88.
3. Jones CM, Lurie PG, Throckmorton DC. Effect of US Drug Enforcement Administration's Rescheduling of Hydrocodone Combination Analgesic Products on Opioid Analgesic Prescribing. JAMA Intern Med 2016;176:399.
4. Sun EC, Darnall BD, Baker LC, et al. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Intern Med 2016;176:1286.
5. Volkow ND, McLellan TA, Cotto JH, et al. Characteristics of Opioid Prescriptions in 2009. JAMA 2011;305:1299-301.
6. Morgan CJA, Curran HV. Ketamine use: a review. Addiction 2012;107:27-38.
7. Arendt-Nielsen L, Nielsen J, Petersen-Felix S, et al. Effect of racemic mixture and the (S+)-isomer of ketamine on

temporal and spatial summation of pain. Br J Anaesth 1996;77:625-31.
8. Oye I, Paulsen O, Maurset A. Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther 1992;260:1209-13.
9. Laskowski K, Stirling A, McKay WP, et al. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anesth 2011;58:911-23.
10. Aveline C, Hetet H, Vautier P, et al. Peroperative ketamine and morphine for postoperative pain control after lumbar disk surgery. Eur J Pain 2006;10:653.
11. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative Ketamine Reduces Perioperative Opiate Consumption in Opiate-dependent Patients with Chronic Back Pain Undergoing Back Surgery. Anesthesiology 2010;113:639-46.
12. Perelló M, Artés D, Pascuets C, et al. Prolonged Perioperative Low-Dose Ketamine Does Not Improve Short and Long-term Outcomes After Pediatric Idiopathic Scoliosis Surgery. Spine (Phila Pa 1976) 2017;42:E304-12.
13. Garg N, Panda NB, Gandhi KA, et al. Comparison of Small Dose Ketamine and Dexmedetomidine Infusion for Postoperative Analgesia in Spine Surgery—A Prospective Randomized Double-blind Placebo Controlled Study. J Neurosurg Anesthesiol 2016;28:27-31.
14. Nitta R, Goyagi T, Nishikawa T. Combination of oral clonidine and intravenous low-dose ketamine reduces the consumption of postoperative patient-controlled analgesia morphine after spine surgery. Acta Anaesthesiol Taiwan 2013;51:14-7.
15. Urban MK, Deau JTY, Wukovits B, et al. Ketamine as an Adjunct to Postoperative Pain Management in Opioid Tolerant Patients After Spinal Fusions: A Prospective Randomized Trial. HSS J 2008;4:62.
16. Subramaniam K, Akhouri V, Glazer PA, et al. Intra- and Postoperative Very Low Dose Intravenous Ketamine Infusion Does Not Increase Pain Relief after Major Spine Surgery in Patients with Preoperative Narcotic Analgesic Intake. Pain Med 2011;12:1276-83.

Cite this article as: Park PJ, Makhni MC, Cerpa M, Beauchamp EC, Lee NJ, Lehman RA, Lenke LG. The role of ketamine in opioid-free spinal deformity surgery: is it possible and beneficial? J Spine Surg 2021;7(1):55-61. doi: 10.21037/jss-19-475