



The role of perioperative ketamine in postoperative pain control following spinal surgery

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Abstract: Opioid abuse has rapidly developed into an epidemic across the United States. Patients are often introduced to opioids following surgical procedures—this is particularly relevant following spinal surgery. Surgeons can help reduce this opioid burden by finding alternatives to narcotic analgesia in the postoperative period. One such medication that has shown potential in this role is ketamine, which has been studied in various surgical specialties. A review was performed of current literature regarding ketamine use in the perioperative period specific to spinal surgery. This review focused on prospective randomized control trials; the primary endpoint was opioid consumption in the postoperative period, monitored through patient-controlled analgesia (PCA) use. Both pediatric and adult spinal surgery patients were included; cervical, thoracic, and lumbar procedures were also all included. 10 studies were selected for this reviewed based on inclusion criteria, published between 2004 and 2017. 7 of these studies demonstrated a significant decrease in postoperative opioid use with the integration of ketamine in the perioperative period, while 3 trials showed no significant difference in opioid consumption. There is inherent difficulty in standardizing studies of this nature—dosing protocols, medication timing, and supplemental analgesia were variable throughout the included studies. However, this review of the most up-to-date prospective studies indicate ketamine has potential to play a significant role in reducing opioid requirements following spinal surgery, and further study is warranted in this field.

Keywords: Ketamine; pain control; spinal surgery; opioid

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Introduction

The current opioid epidemic

In recent years opioid misuse and abuse have become an epidemic in the United States. 80% of the world's opioid supply is now consumed by the US alone (1). In 2015, it was reported that 2 million people were addicted to prescription opioids, and a staggering 12 million reported opioid misuse (2). Deaths caused by prescription opioid overdose annually have nearly quadrupled from 1999–2010 (3) with

a 124% increase in unintentional prescription opioid deaths seen from 2004 to 2008 (4). A significant relationship was seen with overdose deaths and maximum prescribed daily dose of opioid medication (4), and those with a history of substance abuse were at almost 14 times greater risk (5). In addition to the cost of life, several studies have also looked at the growing economic burden—one study estimated that opioid misuse costs the US \$50 billion annually, a large majority in lost productiveness followed by criminal justice costs (6).

Narcotics in postoperative pain control

A major gateway through which people are introduced to opioids is through postoperative care as patients. As a result of these trends, the United States surgeon general issued a recent call to action. This call to action aims to focus on prescription monitoring programs, responsible prescribing, recognition of addiction in patients, and the de-stigmatization of those battling opioid addiction. In 2014, the FDA also reclassified hydrocodone to a schedule II substance from a schedule III substance to help curb overprescribing (7).

Although this trend affects patients undergoing all different types of procedures, orthopaedic surgery is one of the largest impacted. A recent study 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), patient undergoing total knee arthroplasty were 5.1 times more likely to develop chronic opioid use, the highest in the study (8). 7.7% of all opioid prescriptions in the US in 2009 were written by orthopaedic surgeons (9). Opioid overprescribing disproportionately affects orthopedic surgery, and spine surgery in particular, given the nature of the field. Generally, longstanding pain and difficulty with activities of daily living lead to orthopedic spine referrals. Patients that eventually undergo surgery are often those that have failed conservative management with medications, physical therapy and/or injections. The procedure itself, especially in large deformity corrections, also necessitates substantial pain control regimens in the perioperative period. Though medications exist to help patients in the treatment of opioid addiction such as buprenorphine and naltrexone (9), as orthopedic surgeons we can aid in fighting this epidemic and preventing addiction by setting patient expectations, identifying at-risk patients, and finding alternatives to opioids for postoperative pain control (10).

Ketamine in postoperative pain control

Finding alternatives to opioids in postoperative pain control is critical in reducing opioid dependence following discharge; one such alternative that has been gaining popularity recently has been ketamine. Ketamine is an NMDA receptor antagonist, a glutamate receptor in the nociceptive pathway (11). With the advent of S(+)-ketamine form, ketamine in sub-anesthetic doses for pain control

has been increasing in use (11). This form of ketamine has been shown to have a 4 times stronger affinity for NMDA, with increased clinical analgesic effects (12,13). Pain stimuli peripherally lead to NMDA receptor activation—this may lead to windup phenomenon, in which repetitive stimulation can cause prolonged increase in neuron excitability, increasing subjective pain (14). This may then lead to central sensitization and pain memory; interrupting this pathway is the principle by which ketamine plays a role in pain control (14).

A common concern with the use of ketamine has been its side effects seen in drug abuse including agitation, hallucinations, and confusion (15). In a large meta-analysis of ketamine adjuncts to opioid for pain control which included 37 randomized double-blind clinical trials of 2,385 patients overall, various central nervous system side effects in using ketamine as a pain control adjunct have been reported including (dizziness, diplopia, dysphoria, dreams, hallucinations, strange sensation, lightheadedness, sleep difficulties, confusion) (16). However, no significant increase was seen compared to those patients who did not receive ketamine and only opioids for pain control; if anything decreased postoperative nausea and vomiting were associated with the addition of ketamine (16).

Ketamine has been explored in a wide variety of surgical settings. A recent large meta-analysis found that ketamine was more effective in reducing opioid burden in surgeries with more postoperative pain (higher VAS scores) (17). For example, upper abdominal and thoracic procedures showed the greatest decrease in opioid consumption while dental, or head and neck surgery showed a smaller response (17). Within orthopedic surgery, more involved procedures such as spine surgery showed a greater benefit with ketamine those smaller procedures such as arthroscopy (17). As such, we hope to review the most up-to-date prospective clinical trials published on ketamine use in spine surgery to evaluate its efficacy and potential in reducing opioid dependence postoperatively.

Methodology

A PubMed search was performed querying “ketamine”, “spine, and “surgery”. A total of 70 articles resulted, of which 11 prospective randomized control trials were identified. In order to standardize the prospective studies included in this review, several inclusion criteria were established. All studies included patients undergoing an elective spinal procedure (cervical, thoracic, or lumbar

were all included). Both pediatric and adult spinal procedures were included. All studies were required to have clearly defined intraoperative analgesia dosing. Specific dosing and timing of ketamine both intraoperatively and postoperatively had to be described. Lastly, patient-controlled analgesia (PCA) had to be utilized in the postoperative period in order to quantify the primary endpoint of opioid consumption. Based on these criteria, 10 of the 11 prospective randomized control trials identified were included in this review.

Of the studies included, ketamine was administered either as a bolus at incision, a continuous infusion throughout the procedure, or both (*Table 1*). Medication administered by PCA varied between studies and included morphine, hydromorphone, fentanyl, and methadone (*Table 1*). Study enrollment ranged from 22 to 202 subjects, and average age ranged from 14 to 61. All studies included were published between 2004 and 2017.

Ketamine in spine surgery

When looking specifically at spine surgery, the combination of morphine and ketamine has been explored the most in recent randomized control trials. One of the earliest studies to randomize spine surgery patients undergoing elective surgical lumbar discectomy with partial laminectomy and nucleotomy for ketamine administration was performed in 2005 (18). Sixty-nine patients were randomized into three different groups: patients receiving only morphine (control), only ketamine, or a combination of ketamine with morphine 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 (18). Postoperative pain scores (VAS) were significantly lower in the combined KM group versus either the K or M groups. They also found significantly lower incidence of postoperative nausea and vomiting in the KM group versus the M group. Here we see a single dose of ketamine significantly reduce opioid consumption without a significant increase in side effects; this allows one to consider an expanded role for ketamine including as a continuous infusion throughout surgery or even continued into the postoperative period in conjunction with traditional morphine PCAs, which was explored in subsequent randomized control trials.

In 2010, Loftus *et al.* similarly looked at 101 patients

undergoing spine surgery who were randomized to receive either IV ketamine on induction with an infusion until wound closure, or to a control group who only received normal saline during the case. A PCA (either hydromorphone, fentanyl, or morphine) was ordered for all patients postoperatively. Those who received intraoperative ketamine consumed significantly less morphine equivalents postoperatively than the control group at 24 hours (30% reduction, $P=0.032$) and 48 hours (48% reduction, $P=0.029$) (19). Corresponding decreases in PACU pain intensity were also seen in the PACU and at 6 weeks follow-up ($P=0.033$, $P=0.026$ respectively) (19). Of note, this study found a 71% reduction in opiate consumption at 6 weeks follow-up ($P=0.041$) (19). No significant differences were seen in side effects including nausea, constipation, or hallucinations (19).

This study went further to compare the effect on patients after stratifying for preoperative opioid use. Interestingly, after stratifying for preoperative opioid use they found a significant reduction in morphine use at 24 and 48 hours postoperatively in the ketamine group, only in those with a significant history of preoperative opioid use (19). This study explores several key variables: side effects, preoperative opioid use status, and outpatient follow up at 6 weeks. Again, no significant difference is seen in side effects with the use of ketamine. This study also highlights the importance of preoperative screening and a detailed understanding of preoperative opioid use in determining outcomes. Lastly, we see potential long-term benefits of ketamine as illustrated by the decrease in opioid consumption over 6 weeks which has significant implications broadly across all fields.

A study by Perello *et al.* looked at the pediatric population undergoing spine surgery for AIS, with patients ages 10 to 18. They looked at 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. Although 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 also had no significant difference than the control group, which speaks to concerns regarding

Table 1 Literature review of ketamine use in spinal surgery

Authors	Number [mean age], years	Surgery	Ketamine dosing	Patient-controlled analgesia (PCA)	Main outcome (postoperative opioid consumption)
Aveline <i>et al.</i>	69 [47]	Lumbar discectomy w/ partial laminectomy and nucleotomy	Bolus at incision: 0.15 mg/kg	Morphine PCA: 1 mg/dose, Q7 min lockout; M: Morphine bolus before incision: 0.1 mg/kg; K: Ketamine bolus before incision: 0.15 mg/kg; MK: Morphine bolus before incision: 0.1 mg/kg + Ketamine bolus before incision: 0.15 mg/kg	M: Significant decrease: I cumulative consumption of morphine PCA in MK v. M, K at 24 h
Loftus <i>et al.</i>	102 [51]	Elective back surgery	Bolus at induction: 0.55 mg/kg; Continuous infusion intraoperatively to wound closure: 10 mcg/kg/min	Opioid PCA (hydromorphone, morphine, fentanyl)	Significant decrease: In cumulative consumption of morphine equivalent at 24 h, 48 h, 6 weeks
Perello <i>et al.</i>	48 [14]	Deformity correction (mean 11 levels fused)	Bolus at induction: 0.5 mg/kg; Continuous infusion intraoperatively to 72 h postoperatively: 2 µg/kg/min	Morphine PCA: 20 µg/kg/dose q5 min lockout; Continuous infusion (Morphine) 5 µg/kg/h to 72 h postoperatively	No significant decrease: In cumulative consumption of morphine PCA
Garg <i>et al.</i>	66 [36]	Elective lumbosacral spine surgery	Bolus postoperatively: 0.25 mg/kg; Continuous infusion intraoperatively to 24 h postoperatively: 0.25 mg/kg	Rescue dose (Morphine) 3 mg/dose PRN	Significant decrease: In rescue morphine bolus use in ketamine group at 12 h, 24 h, 48 h
Nitta <i>et al.</i>	49 [61]	Spine surgery	Bolus at induction: 10 mg; Continuous infusion intraoperatively for surgery duration: 2 mg/kg/h; Combined in PCA: 2 mg/dose	M: Morphine PCA: 2 mg/dose q10 min lockout; MK: Morphine PCA: 2 mg/dose q10 min lockout + Ketamine 2 mg/dose + Clonidine premedication 4 µg/kg	Significant decrease: In cumulative consumption of morphine in MCK v. M, MK, MC at 24, 36, 48, 60 h
Yamauchi <i>et al.</i>	200 [59]	Posterior cervical, posterior lumbar spinal surgery	Bolus at incision: 1 mg/kg; K1: Continuous infusion intraoperatively for 24 h: 42 mcg/kg/h; K2: Continuous infusion intraoperatively for 24 h: 83 mcg/kg/h	Fentanyl PCA: 0.5 µg/kg/dose q6 min lockout 0.5 µg/kg/h continuous infusion (48 h)	Significant decrease: In fentanyl consumption in K2 group in cervical patients; Significant decrease: In fentanyl consumption only at 6 h postop timepoint for K2 group in lumbar patients
Song <i>et al.</i>	50 [58]	Lumbar surgery	Bolus at induction: 0.3 mg/kg; Combined in PCA: 0.3 mg/kg/dose	Fentanyl PCA: 20 µg/kg/dose	Significant decrease: Cumulative fentanyl dose consumption at 48 h
Urban <i>et al.</i>	26 [51]	1–2 level posterior lumbar fusion	Bolus at induction: 0.2 mg/kg; Continuous infusion intraoperatively; for 24 h: 2 mcg/kg/h	Hydromorphone PCA: 0.5 mg/dose q5 min lockout	No significant decrease: In hydromorphone consumption
Subramaniam <i>et al.</i>	30 [57]	Lumbar/thoracolumbar laminectomy	Bolus at induction: 0.15 mg/kg; Continuous infusion intraoperatively to 24 h postoperatively: 2 µg/kg/min	Hydromorphone PCA: 0.125 mg/dose q5 min lockout	No significant decrease: In cumulative consumption of hydromorphone PCA at 48 h
Pacreu <i>et al.</i>	22 [57]	–	Bolus at induction: 0.5 mg/kg; Combined in PCA: 0.25 mg/dose	ME: Methadone PCA: 0.5 mg/dose q10 min lockout; MK: Methadone PCA: 0.25 mg/dose + Ketamine 0.25 mg/dose	Significant decrease: In cumulative consumption of methadone PCA at 24 h, 48 h

the safety of ketamine in analgesia (especially in younger patients) (20).

Other studies included comparisons of morphine with other combinations of medications. One recent study in 2016 by Garg *et al.* combined morphine with either ketamine and midazolam or a dexmedetomidine drip. The cumulative morphine requirement, as well as mean pain-free period, was significantly lower with the ketamine and dexmedetomidine groups relative to a control group, with no significant increase in relevant side effects (21). Another study by Nitta *et al.* combined morphine PCA with either a control infusion, clonidine premedication, ketamine intraoperatively and postoperatively, or ketamine with the addition of clonidine premedication, and found that the morphine/clonidine/ketamine group had a significantly lower cumulative morphine requirement than the morphine only group starting 12 hours postoperatively. Pain scores at rest, at 24 hours postoperatively and at 48 hours postoperatively for the morphine and morphine/ketamine group were lower than those receiving clonidine, however pain scores with movement had no significant differences (22).

Ketamine in combination with other PCA medications other than morphine have also been looked at. A large study in 2008 looked at 202 patients undergoing either cervical or lumbar surgery. Patients were on a fentanyl drip with PCA demand dosing with the addition of either ketamine at 42 or 83 mcg/kg/h. Patients were also able to request NSAIDs every 8 hours as well. This study added another level of complexity by stratifying patients based on anatomic location of surgery. Cervical patients had significantly lower pain scores at the higher ketamine dose versus the control group or the lower ketamine dose group at 24 hours postoperatively. Fentanyl consumption was also significantly lower in the higher ketamine dose group. NSAID consumption in the higher ketamine dose group was also lower for cervical patients. For lumbar patients, the higher ketamine dose group showed significantly lower fentanyl consumption only at 6 hours. This study looked at several variables not previously addressed including variable ketamine dosing, anatomic surgical location, as well as supplemental NSAID use (23). A similar study looked at patients on a fentanyl-based PCA versus those given ketamine IV bolus after induction in addition to ketamine in the fentanyl PCA. This study focused on side effects, namely postoperative nausea/vomiting. They found that the incidence was similar in a high-risk group (female, non-smoking patients). They also found significantly lower fentanyl consumption over 48 hours in the ketamine group (24).

When combined with a hydromorphone PCA, a smaller study of 26 patients undergoing 1 or 2 level lumbar fusions (narcotic-tolerant) found that patients given ketamine at induction and for the following 24 hours had significantly less pain in the first postoperative hour and at postoperative day 1 (POD1), both at rest and while working with physical therapy (25). Though the ketamine group did require less hydromorphone overall, the differences were not statistically significant (25). Another study looked at hydromorphone PCAs in combination with ketamine infusion both intraoperatively and for the first 24 hours postoperatively; all patients in this study additionally received epidural bupivacaine in the surgery however. This study on the other hand found no difference in pain scores at rest or movement, or differences in hydromorphone consumption between the control and ketamine groups (26).

The final combination studied was the use of ketamine in conjunction with a methadone PCA. Ketamine was administered in a bolus after intubation and as a continuous infusion throughout the surgery. Pacreu *et al.* found that the methadone with ketamine (MK) group required more remifentanyl at induction versus methadone only, however the MK group attempted less doses with PCA postoperatively. The MK group received 70% less methadone via PCA at 24 hours and significantly less at 48 hours postoperatively as well. The ketamine group also had attempted significantly less doses (27).

Of the 10 prospective studies included in this study, 7 trials found a significant decrease in opioid consumption postoperatively at varying timepoints when ketamine was incorporated in some form into the analgesia regimen (18,19,21-24,27). On the other hand, 3 of the prospective studies reviewed found no significant change in opioid consumption (20,25,26), including the only study performed exclusively in a pediatric population (20). In all these studies, no significant side effects were seen with the addition of sub-anesthetic doses of ketamine either intraoperatively or postoperatively. 2 of the studies stratified for those patients who were opioid-tolerant preoperatively and found lower opioid consumption (19) and decreased pain scores postoperatively (25).

Conclusions

The opioid epidemic continues to grow in the United States and will require a multi-faceted approach to address, from identifying vulnerable patients to implementing effective addiction recovery options. As surgeons, one

major contribution that can be made is at the front end, to reduce the number of people exposed to opioids in the first place – decreasing the need for pain medication in the postoperative period and finding alternatives to opioids will be critical towards reaching this goal. Ketamine has shown great promise in this respect, specifically following spine surgery. Randomized control trials exploring the efficacy of ketamine in postoperative pain control following spine surgery have only been sporadically performed over the last 15 years, and though the results have varied slightly most of the studies show significant reduction in postoperative opioid consumption with the adjunct of ketamine with minimal adverse side effects. The studies reviewed here illustrate the complexity and difficulty in performing a comprehensive study, addressing variables such as dosing, timing, administration, and supplemental medication. With further study of ketamine and other medication alternatives to opioids, the hope is to eliminate postoperative pain control as a gateway into the ever-growing opioid crisis.

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Footnote

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