7-1-2016

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Institutional Affiliation of Manuscript:
Sidney Kimmel Medical College, Thomas Jefferson University

Source of Funding:
Departmental funding

Portions of this manuscript were presented at the 2013 annual meeting of the American Society of Anesthesiologists and at the 2014 spring meeting of the American Society of Regional Anesthesia and Pain Medicine.

Conflicts of Interest:
Eric Schwenk, Stephen Goldberg, Ronak Patel, Jon Zhou, Douglas Adams, Jaime Baratta, and Richard Epstein have no conflicts of interest to declare.

Eugene Viscusi has served as a consultant for AcelRx, Medicines Company, Mallinkrodt, Trevena, Cara Pharmaceuticals, and Astra Zeneca. He has received grant money in the past from AcelRx and Pacira. He has been a paid lecturer for AcelRx, Merck, Salix, and Mallinkrodt.

Abstract

High-dose opioid administration is associated with significant adverse events. Evidence suggests that low-dose ketamine infusions improve perioperative analgesia over conventional opioid management, but usage is highly variable. Ketamine's adverse drug effects (ADEs) are well known, but their prevalence during low-dose infusions in a clinical setting and how often they lead to infusion discontinuation are unknown. The purposes of this study were threefold: 1) to identify patient factors associated with initiation of ketamine infusions during spine surgery; 2) to identify specific spine procedures in which ketamine has been used most frequently; and 3) to identify ADEs associated with postoperative ketamine infusions and which ADEs most frequently led to discontinuation. Spine surgery was chosen because of its association with moderate to severe pain and a relatively high use of ketamine infusions in this population at our hospital.

Introduction

Patients presenting for surgery due to conditions associated with chronic pain frequently are being treated with opioids, often at alarmingly high doses. One study of Medicaid enrollees found that 63.5% of patients with non-cancer chronic pain had taken an opioid in the prior 12 months, an increase of 18.9% from five years prior.[1] Yet despite escalating doses of opioids, patients continue to report that their chronic pain is not well controlled.[2] At the same time, serious adverse drug effects (ADEs) associated with opioids, including fatal respiratory depression, continue to be a serious concern.[3] In patients chronically taking opioids, tolerance to respiratory depression is incomplete[4] and such patients have an increased risk of overdose and death compared to non-opioid users.[5] Analgesic alternatives to opioids are, therefore, highly desirable.

One such alternative during the perioperative period is ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist. A role of the NMDA receptor in the development of opioid tolerance was suggested by studies from several decades ago.[6,7] Ketamine is a potent analgesic that does not cause respiratory depression, and may improve postoperative analgesia while reducing opioid consumption.[8,9] As an additional potential benefit, recent evidence suggests that intravenous (IV) ketamine may decrease the incidence of persistent postsurgical pain (PPSP).[10] Ketamine infusions at our institution have been used both intraoperatively by the anesthesia team and postoperatively by the acute pain management service (APMS) as part of an opioid-sparing strategy in complex, opioid-tolerant patients.

We had three primary objectives of the current study: 1) to identify factors associated with current decisions by anesthesiologists to initiate ketamine during spine

surgery; 2) to identify specific spine procedures in which ketamine has been used most frequently; and 3) to identify ADEs associated with all postoperative ketamine infusions and which ADEs most frequently led to discontinuation. This information is necessary for us to design prospective, randomized clinical trials comparing IV ketamine to placebo in opioid-tolerant patients. Spine surgery was chosen to study in detail because it is typically associated with moderate to severe postoperative pain, over 50% of our ketamine use has been in spine surgery, and this is a high-volume service at our institution. We retrospectively analyzed the preoperative medications and surgical details of all patients over a three-year period who underwent any type of elective spine surgery and also examined a sample of postoperative patients from all surgical specialties who received ketamine infusions for the presence of ADEs and classified them.

Methods

This study was approved by the Thomas Jefferson University institutional review board without requirement for written patient consent.

All patients admitted on the day of surgery following elective spine surgery by an orthopedic surgeon or neurosurgeon under general anesthesia between January 1, 2012 and March 21, 2015 at Thomas Jefferson University Hospital (TJUH) were studied. TJUH is a major academic medical center, as well as a regional spinal cord trauma center with a high spine surgery volume. Patients undergoing microdiscectomy at our hospital are usually cared for on an outpatient basis, and therefore most of those patients were not included, since their post-operative data were not available. Demographic data, preoperative medications, and dose and timing data related to ketamine infusions were retrieved from the hospital's anesthesia information management system (Innovian®, Dräger, Telford, PA) and from the pharmacy information system database (Pyxis®, CareFusion, San Diego, CA). Patients who received intraoperative ketamine boluses but not an infusion were excluded. Data elements analyzed included the date of surgery, age in years, gender, weight, body mass index, American Society of Anesthesiologists (ASA) physical status, scheduled duration of surgery, primary surgical service, and preoperative medications. Preoperative opioids were classified as being taken on a "scheduled" or "as needed" basis (Table 2). Planned procedures (using locally defined, procedure-specific codes) were queried from the operating room case scheduling system (ORSOS®, McKesson, San Francisco, CA). All planned, elective spine surgeries requiring hospital admission (but not emergencies or cases booked as "add-ons") were included for analysis. The decision to start an intraoperative ketamine infusion at our hospital was

made by the attending anesthesiologist for the case. Data retrieved from the pharmacy information system were aligned with patient anesthesia records to determine if postoperative ketamine infusions had been started intraoperatively or initiated after the patient left the OR.

ADE data were retrieved from the daily notes recorded contemporaneously by the Acute Pain Management Service (APMS) nurses on a consecutive sample of 321 patients who received a postoperative ketamine infusion while on the APMS from January 1, 2011 through December 31, 2013. Patients from all surgical subspecialties were included for the ADE analysis, not just those undergoing spine procedures. All APMS nurses had undergone training on the management of ketamine infusions, including the recognition of side effects. No special monitoring, such as telemetry or intensive care, has been required at our institution for patients receiving ketamine. Criteria for discontinuation of ketamine infusions included the patient requesting discontinuation due to ADEs or the patient's primary service requesting discontinuation.

Data were extracted and prepared for analysis using SQL Server 2008 R2 (Microsoft, Redmond, WA). Odds ratios (OR) were computed using the function *oddsRatio* in the R *mosaic* library, Pearson's chi-square test (with Yate's continuity correction), two-group Student t tests (with the Satterthwaite approximation), and local polynomial regression fits using the functions *chisq.test*, *t.test*, and *loess*, respectively, in the R *stats* library (R v3.2.0, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics and Preoperative Medications Associated with Ketamine Administration

There were 4958 patients who underwent elective spine surgery under general anesthesia during the study interval, 4748 of which were entered into our electronic preoperative anesthesia system and had data available for analysis, and 211 of whom received an intraoperative infusion of ketamine. Among all patients, those receiving ketamine were younger (difference = -4.4 years, 95% CI -2.2 to -6.0 years, $P < 10^{-6}$), had a higher ASA Physical Status ($P < 10^{-6}$), and were scheduled for surgeries of longer estimated duration (difference = 72 minutes, 95% CI 60 to 84 minutes, $P < 10^{-6}$), (Table 1). There were no significant differences in weight or BMI between the two groups. Males and females were represented equally (difference = -0.40%, 95% CI -3.1% to 2.3%, $P = 0.77$).

Medication factors at the time of the preoperative evaluation associated with a greater likelihood of receiving an intraoperative ketamine infusion were taking vs. not taking a scheduled opioid (OR 16.09, 95% CI 11.98 to 21.59), taking any opioid vs. no opioid (OR 10.25, 95% CI 7.13 to 14.75), and taking vs. not taking an anti-depressant (OR 2.69, 95% CI 2.02 to 3.57) (Table 2). Patients who were taking both a scheduled opioid and an anti-depressant were more likely to receive ketamine than those taking just a scheduled opioid (OR 1.64, 95% CI 1.11 to 2.46; Table 2).

Among the 552 patients who were taking a scheduled opioid at the time of the preoperative evaluation, those receiving a ketamine infusion were younger (difference = -2.8 years, 95% CI -0.6 to -5.1 years, $P = 0.012$), had a higher ASA Physical Status ($P = 0.01$), and were scheduled for surgeries of longer estimated duration (difference = 49

minutes, 95% CI 32 to 67 minutes, $P < 10^{-6}$), (Table 3). There were no significant differences in weight or BMI between the two groups. There was a higher proportion of females (difference = 13.3%, 95% CI 4.3 to 22.3%, $P = 0.005$).

Surgical Procedures Associated with Ketamine Administration

There were 20 distinct spine procedures (12 primary spine procedures and 8 revision spine procedures) identified in the database (Table 4). Of these, there were 10 procedures that had ≥ 5% prevalence of intraoperative ketamine administration. The three most commonly performed of these 10 were posterior thoracic/lumbar fusion (N = 148 cases), anterior thoracic/lumbar fusion (N = 136 cases), and anterior/posterior cervical fusion (N = 137 cases). Specific spine procedures are displayed in Table 4 according to primary or revision status.

Side Effects of Low-Dose Ketamine Infusions

There were 31.8% of patients who experienced at least one ADE (Table 5). The most frequent ADE was CNS excitation (16.2%), followed by sedation (9.4%) and visual disturbances (3.1%). Some patients experienced more than one ADE (Table 5). Thirty-seven patients (36.3% of all patients with an ADE) experienced ADEs severe enough to have resulted in discontinuation of the ketamine infusion. The reasons for infusion discontinuation are described in Table 5. Sedation was the ADE most likely to result in ketamine discontinuation. Of the 37 patients whose infusions were discontinued, 35 of them reported resolution of symptoms after the infusion was stopped. Twenty-six patients received benzodiazepines, commonly used for treatment of side effects at our hospital,

while 11 patients did not. To view the TJUH ketamine infusion guidelines, see Appendix A.

A postoperative infusion rate above 20 mg/hr was not associated with an increased chance of having the infusion stopped compared to patients receiving ≤ 20 mg/hr (OR 0.71, 95% CI 0.34 to 1.5). The chance of discontinuation was also not increased with a threshold of 10 mg/hr (OR 0.69, 95% CI 0.32 to 1.5).

Discussion

In this observational study, we found that patients who received intraoperative ketamine infusions tended to be younger, sicker, and undergoing spine procedures of longer duration (i.e., more complex) than those who did not. Patients who received ketamine infusions were more likely to be taking preoperative opioids, and this increased if patients were taking opioids on a scheduled basis.

We found that patients who were most likely to receive ketamine were those undergoing the most complex spine procedures, often involving both an anterior and posterior component or a revision procedure (Table 4). Previous studies examining ketamine in spine surgery have yielded conflicting results regarding postoperative opioid consumption.[8,11-13] The lack of consistent findings may have resulted, in part, from combining potentially different procedures, listed as "lumbar fusion,"[8] "lumbar or thoracolumbar laminectomy and fusion,"[12] or "elective spine surgery."[13] Our data, however, suggest that anesthesiologists viewed patients undergoing longer, complex procedures differently than less complex cases. For example, one of the most common procedures, primary posterior lumbar fusion, had a low prevalence of ketamine administration, suggesting that providers believed conventional opioid analgesia was adequate. Patients who may benefit most from ketamine should be targeted for future studies examining important long-term outcomes of interest. Those patients undergoing presumably less painful procedures with lower incidence of persistent postsurgical pain, such as primary posterior lumbar fusion or anterior cervical fusion, may be able to be managed with conventional therapy. Consistent with previous studies,[9] the more complex

and painful spine procedures were the ones most likely to be associated with ketamine administration as a continuous infusion.

The apparent increased prevalence of ketamine use in patients taking both anti-depressants and scheduled opioids was not surprising as the link between chronic pain, anti-depressants, opioids, and spine surgery has been described.[14] Although it is impossible to determine retrospectively if this combined therapy factored into the decision-making process by the anesthesia team, anti-depressant use is a potential confounder that should be controlled for in future studies comparing ketamine to other therapies.

Our results also confirm the tolerability of ketamine's ADEs in a clinical setting (Table 5). This agrees with clinical trials in which up to 0.25 mg/kg/hr have been tried without major ADEs.[13] Our observed prevalence of central nervous system ADEs (16.2%) is similar to the 22% retrospectively described by Rasmussen.[15] Thus, consideration of a variable-rate postoperative ketamine infusion in a treatment arm of a randomized clinical trial is reasonable. Our ADE data confirm those from Mayo Clinic, Jacksonville[16] but go a step further in describing the specific ADEs, their prevalence, and the rate of discontinuation in a daily clinical practice in which the infusion rates are adjusted frequently.

Discontinuation of ketamine due to ADEs was unrelated to the maximum dose, a somewhat surprising finding. Several factors may have played a role in this, including ADEs resulting from simultaneous administration of opioids and benzodiazepines, as well as variable patient sensitivity to ketamine, some of which may be related to individual changes at the cellular level.[17] There may be other unidentified factors as well.

Because 35 out of the 37 patients had resolution of symptoms once the infusions were stopped, this suggests that the side effects were at least partially due to ketamine.

Using the data from this observational study, we are currently designing a prospective, randomized trial comparing intra- and postoperative ketamine infusions to placebo in opioid-tolerant patients undergoing complex spine surgery with particular focus on long-term outcomes. Only complex spine procedures that are more likely to result in severe pain will be included (i.e. anterior/posterior procedures or procedures involving two or more spine areas, such as thoracic and lumbar). We will use the frequency of ADEs encountered to guide the process of obtaining informed consent. The ADE data could also be used as a guide for any hospitals considering starting a ketamine service on the general medical floors.

Our study may have limited generalizability in that the decision to start an intraoperative ketamine infusion was made at the discretion of the attending anesthesiologist for the case. Thus, our findings may not apply to all practices. Second, some patients may have been inappropriately placed in the "scheduled" opioid group rather than the "as needed" group or vice versa due to documentation issues or patients misrepresenting their opioid use.

In conclusion, we confirmed that postoperative ketamine infusions may be given safely on general medical floors without special monitoring or intensive care, and intraoperative infusions tend to be started for patients taking opioids, especially scheduled opioids. Our data provide guidance both for hospitals considering the use of ketamine infusions and for the design of future prospective, randomized clinical trials looking at long-term benefits of ketamine or its ADEs.

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