Postoperative Ketamine
Time for a Paradigm Shift

Christopher M. Sobey, MD, Adam B. King, MD,† and Matthew D. McEvoy, MD‡*

Thomas Kuhn (1922–1996) is influential in academia for authoring, in 1962, *The Structure of Scientific Revolutions*. In it, he argues that science does not progress as a linear accumulation of new knowledge; rather, disciplines undergo periodic revolutions called "paradigm shifts."[1] A scientific paradigm is a specific theoretical orientation that is built upon a particular epistemology and research methodology and demonstrates the beliefs of a particular scientific community at a particular time in history. As such, paradigms not only provide a framework but also guide the types of questions that will be asked, providing the theoretical basis from which any results are evaluated. According to Kuhn, a scientific paradigm goes through 3 distinct phases. The first is a "prescience" phase defined by a period that lacks a reigning paradigm, but from which the archetype begins to emerge. The second is a "normal science" phase, when research is undertaken to prove and expand the central paradigm by problem solving to approach the "real answer." During this phase, results are evaluated in terms of the paradigm boundaries, and results that do not conform to the paradigm are seen not as refuting the paradigm but as the mistake of the researcher. The final stage, the "crisis" phase, is the point at which enough evidence has been mounted to challenge the reigning paradigm—and at which a new paradigm could emerge to become accepted by the community. Modern health care is at such a point, particularly in the perioperative period, with its understanding of managing analgesia. Opioids, having been used for over a century as the primary means of providing perioperative analgesia, are now being seen as creating significant problems at the individual and societal level.[2] However, a new paradigm for managing and researching perioperative pain is emerging and is yet to be defined.

Despite the mounting evidence against the routine use of opioids, they remain the primary pharmacotherapy for perioperative analgesia. With the expanding literature of the dangers of opioid use, the growing societal consequences of tolerance, abuse, misuse, addiction, and the development of opioid-induced hyperalgesia and chronic postsurgical pain, there is renewed interest in using nonopioid analgesics in the perioperative period.[3,4] In this issue of *Regional Anesthesia and Pain Medicine,* Schwenk et al[5] describe the use of perioperative ketamine. Recent studies have demonstrated the inherent risks of postoperative opioid use contributing to danger in the immediate postoperative period, as well as the rising epidemic of abuse.[2,6] An estimated 4% to 20% of all opioid prescription pills are used nonmedically, accounting for half a billion doses per year of misused opioid prescriptions. In addition, it is reported that 4 of 5 heroin users reported that their opioid use began with prescription pain medication.[7] From 1999 to 2014, more than 165,000 deaths have been attributed to opioid pain medications, and the death rate from opioid abuse continues to climb.[2]

In light of this epidemic, practitioners are consistently examining the proper applications of nonopioid analgesics, including ketamine, as alternative therapies to opioids.[8] Ketamine has been used for acute and postoperative analgesia for over 5 decades.[9] Its ability to produce a dissociative anesthetic state with significant analgesia provides benefits such as sedation with an acceptable operating environment, use as a supplemental analgesic that can dramatically reduce opioid requirement, and the ability to reduce opioid-induced hyperalgesia and tolerance.[10,11] More recently, its use as a low-dose perioperative infusion has demonstrated continued opioid-sparing qualities in the postoperative period based on its primary mechanism of N-methyl-D-aspartate receptor antagonism.[12] Studies promoting the perioperative use of ketamine in attenuating postsurgical pain are present, yet the significant variations in timing and dosing have prevented a unified approach to administration.[13]

One of the factors liming the increased acceptance of ketamine use as an analgesic relates to the concern for development of adverse drug effects (ADEs). The literature surrounding these ADEs is copious. Ketamine-related ADEs are thought to include psychocognitive effects such as hallucinations, cardiovascular effects from inhibition of catecholamine reuptake, neurologic effects such as tonic-clonic movements, and increased intracranial pressure, and the potential for gastrointestinal and respiratory

*Division of Pain Medicine, Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, TN; †Division of Critical Care Medicine, Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, TN; and ‡Division of Multi-specialty Anesthesiology, Department of Anesthesiology, Vanderbilt University School of Medicine.
Accepted for publication April 23, 2016.
Address correspondence to: Matthew D. McEvoy, MD, Division of Multi-specialty Anesthesiology, Department of Anesthesiology, Vanderbilt University School of Medicine (e-mail: matthew.d.mcevoy@vanderbilt.edu).
The authors declare no conflict of interest.

ISSN: 1098-7339
DOI: 10.1097/AAP.0000000000000429

events.[14] The classic teaching is that the presence of these ADEs is ubiquitous with ketamine use, rather than being dose dependent.[15] This misconception needs to be rectified. Furthermore, some of the traditional dogma has been clearly disproven, such as the increase in intracranial pressure.[16] Another major roadblock to the postoperative use of ketamine is the classification of ketamine as an anesthetic compared with an analgesic. Ketamine has the unique ability to provide both potent analgesia and anesthesia. To date, it is most commonly classified as an anesthetic agent based on these dissociative qualities, and thus its use is often restricted to areas where anesthetic services are either offered or readily available based on hospital policies or state nursing regulations. Obviously, there are pros and cons of these policies, by ensuring safe delivery of medications that could result in an anesthetized state; however, these restrictions do constrain the analgesic options offered in the hospital setting.

In this issue of the *Regional Anesthesia and Pain Medicine*, Schwenk et al provide a large retrospective, observational study that describes the routine use of perioperative ketamine infusions at their institution with 3 defined goals: (1) identifying patients most likely to receive a ketamine infusion, (2) identifying the spine procedures associated with initiating the infusion, and (3) determining the prevalence of ADEs associated with ketamine infusions as well as the frequency of discontinuation following these drug effects.[5] As admitted by the authors, the study is limited in its ability to make generalizations about the benefits of ketamine utilization, such as decreased opioid use, speed of recovery, and improvement of analgesia compared with conventional options, due to the retrospective methodology. However, a primary benefit of this article is in dispelling the pervasive myth that intolerable or significant ADEs always occur with the use of this analgesic. The vast majority of the patients receiving the infusions tolerated them well, and the vast majority of those who experienced adverse effects demonstrated resolution of the unwanted symptoms by discontinuing the infusion. Furthermore, the study demonstrates that doses of less than 5 μg/kg per minute produce few, if any, ADEs. In addition, clinically relevant analgesia was produced at doses of 2 μg/kg per minute. Clarifying this misconception can serve to promote further study of ketamine as a reasonable postoperative analgesic option by breaking down the barriers of use.

The key to mitigating the risks and benefits associated with perioperative nonopioid analgesics lies within determining the dose of these medications that provide adequate pain management, while minimizing the ADEs. In that vein, it has been shown that low-dose ketamine infusions can produce notable analgesia without significant adverse effects, providing a useful tool that continues to be underused.[17] In regard to the lack of ubiquitous acceptance of ketamine in the perioperative period, there is frequently pushback involving multiple components of the postoperative care team, including the hospitals, nursing staff, and pharmacy and therapeutics committees. This is despite evidence that low-dose analgesic infusions can be administered safely and effectively with minimal adverse effects.

As recent evidence shows that massive reductions in perioperative opioid use are not only possible but also associated with improved outcomes,[18] it is time for our specialty to lead the way in promoting a safe pathway for low or no-opioid perioperative analgesia. The evidence espousing the dangers of the status quo use of opioids as a primary analgesic in the postoperative period continues to mount. Despite the significantly higher morbidity and mortality of opioid administration, they remain the most "comfortable" choice of providers. In fact, while the medical literature is littered with peer-reviewed publications warning of the dangers of opioid use,[6] a search for mortality related to ketamine use produces no significant results. In contrast to opioids, the use of intravenous ketamine for acute pain provides the option of effective analgesia without significant adverse effects. As such, we commend Schwenk et al on not only their recent report but also their widespread use of a safer analgesic option. The future of routine perioperative pain management should take note of their findings as one piece in the puzzle and add this to the construction of plans that result in adequate analgesia and reduced ADEs while promoting quicker postoperative functional recovery, a concept that we call optimal analgesia. However, as increased opioid prescribing has led to a direct rise in opioid abuse, there is understandable concern about the misuse of ketamine as a recreational drug.[19] The exact incidence of ketamine abuse is currently unknown, but the possibility for abuse points to the need for using multiple agents for pain control, minimizing exposure and adverse effects from each one.[20] Limiting ketamine use to the inpatient setting should limit both the accessibility to the medication for those at risk, as well as the potential for abuse and misuse.

We can no longer turn a blind eye to the dangers of routine postoperative opioid use. We should demand that policies are put in place whereby all appropriate and safe treatment options are available throughout the perioperative period. Furthermore, we should lead the way in creating an expectation that care teams ensure the maximum use of nonopioid agents prior to using opioids for managing postoperative pain. Rather than be shackled to opioids by conventional dogma, we should embrace current evidence-based options for the betterment of our patients. This represents a paradigm shift, no less than an analgesic revolution, and it is long overdue.

REFERENCES

1. Kuhn TS. *The Structure of Scientific Revolutions*. 3rd ed. Chicago, IL: University of Chicago Press; 1996.
2. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315:1624–1645.
3. Hayhurst CJ, Durieux ME. Differential opioid tolerance and opioid-induced hyperalgesia: a clinical reality. *Anesthesiology*. 2016;124:483–488.
4. Mauermann E, Filitz J, Dolder P, Rentsch KM, Bandschapp O, Ruppen W. Does fentanyl lead to opioid-induced hyperalgesia in healthy volunteers? A double-blind, randomized, crossover trial. *Anesthesiology*. 2016;124:453–463.
5. Schwenk ES, Goldberg SF, Patel R, et al. Adverse drug effects and preoperative medication factors related to perioperative low-dose ketamine infusions. *Reg Anesth Pain Med*. 2016;41:482–487.
6. Lee LA, Caplan RA, Stephens LS, et al. Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology*. 2015;122:659–665.
7. Kharasch ED, Brunt LM. Perioperative opioids and public health. *Anesthesiology*. 2016;124:960–965.
8. Angst MS, Clark JD. Ketamine for managing perioperative pain in opioid-dependent patients with chronic pain: a unique indication? *Anesthesiology*. 2010;113:514–515.
9. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth*. 1989;36:186–197.
10. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients. *Anesthesiology*. 2010;113:639–646.
11. Laulin JP, Maurette P, Corcuff JB, Rivat C, Chauvin M, Simonnet G. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. *Anesth Analg*. 2002;94:1263–1269.
12. Visser E, Schug SA. The role of ketamine in pain management. *Biomed Pharmacother*. 2006;60:341–348.

13. McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand*. 2014;58:1199–1213.
14. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. *Anesth Analg*. 1998;87:1186–1193.
15. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjunct analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg*. 2004;99:482–495.
16. Mayberg TS, Lam AM, Matta BF, Domino KB, Winn HR. Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. *Anesth Analg*. 1995;81:84–89.
17. Jouqueslet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. *Pain Med*. 2015;16: 383–403.
18. McEvoy MD, Wanderer JP, King AB, et al. A perioperative consult service results in reduction in cost and length of stay for colorectal surgical patients: evidence from a healthcare redesign project. *Perioper Med* (*Lond*). 2016;5:–3.
19. Morgan CJ, Curran HV. Ketamine use: a review. *Addiction*. 2012;107: 27–38.
20. Kalsi SS, Wood DM, Dargan PI. The epidemiology and patterns of acute chronic recreational ketamine use. *Emerg Health Threats J*. 2011;4:7107.

BRIEF TECHNICAL REPORT

Adverse Drug Effects and Preoperative Medication Factors Related to Perioperative Low-Dose Ketamine Infusions

Eric S. Schwenk, MD, Stephen F. Goldberg, MD,* Ronak D. Patel, MD,* Jon Zhou, MD,† Douglas R. Adams, BS,* Jaime L. Baratta, MD,* Eugene R. Viscusi, MD,* and Richard H. Epstein, MD‡*

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 3-fold: (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.

(*Reg Anesth Pain Med* 2016;41: 482–487)

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 noncancer chronic pain had taken an opioid in the prior 12 months, an increase of 18.9% from 5 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 with nonopioid 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.[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 3 primary objectives in 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, more than 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 during a 3-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 after 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. The 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, because their postoperative 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, Pennsylvania) and from the pharmacy information system database (Pyxis; CareFusion, San Diego, California). Patients who received intraoperative ketamine boluses but not an infusion were excluded. Data elements analyzed included the date of surgery, age in years, sex, weight, body mass index (BMI), 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

From the *Department of Anesthesiology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA; †Department of Anesthesiology and Pain Medicine, University of California, Davis, Davis, CA; and ‡Department of Anesthesiology, University of Miami, Miami, FL.

Accepted for publication March 2, 2016.

Address correspondence to: Eric S. Schwenk, MD, Department of Anesthesiology, Sidney Kimmel Medical College, Thomas Jefferson University, Suite 8130, Gibbon Bldg, 111 S 11th St, Philadelphia, PA 19107 (e-mail: Eric.Schwenk@jefferson.edu).

Eric S. Schwenk, Stephen F. Goldberg, Ronak D. Patel, Jon Zhou, Douglas R. Adams, Jaime L. Baratta, and Richard H. Epstein have no conflicts of interest to declare. Eugene R. 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.

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.

ISSN: 1098-7339
DOI: 10.1097/AAP.0000000000000416

case scheduling system (ORSOS; McKesson, San Francisco, California). 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 operating room.

Adverse drug effect data were retrieved from the daily notes recorded contemporaneously by the 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 adverse 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, Washington). Odds ratios (OR) were computed using the function *oddsRatio* in the R *mosaic* library, Pearson χ^2 test (with Yate continuity correction), 2-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% confidence interval (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, 60–84 minutes, $P < 10^{-6}$) (Table 1). There were no significant differences in weight or BMI between the 2 groups. Men and women 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 versus not taking a scheduled opioid (OR, 16.09; 95% CI, 11.98–21.59), taking any opioid versus no opioid (OR, 10.25; 95% CI, 7.13–14.75), and taking versus not taking an antidepressant (OR, 2.69; 95% CI, 2.02–3.57) (Table 2). Patients who were taking both a scheduled opioid and an antidepressant were more likely to receive ketamine than those taking just a scheduled opioid (OR, 1.64; 95% CI, 1.11–2.46; 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, 32–67 minutes, $P < 10^{-6}$) (Table 3). There were no significant differences in weight or BMI between the 2 groups. There was a higher proportion of women (difference, 13.3%; 95% CI, 4.3%–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 greater than or equal to 5% prevalence of intraoperative ketamine administration. The 3 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.

Adverse Effects of Low-Dose Ketamine Infusions

There were 31.8% of patients who experienced at least 1 ADE (Table 5). The most frequent ADE was central nervous system excitation (16.2%), followed by sedation (9.4%), and visual disturbances (3.1%). Some patients experienced more than 1 ADE (Table 5). Thirty-seven patients (36.3% of all patients with

TABLE 1. Differences Between All Patients Undergoing Spine Surgery Receiving or Not Receiving a Ketamine Infusion

	Intraoperative Ketamine Infusion			
Variable	**Yes (n = 211)**	**No (n = 4747)**	**Difference (95% CI)**	***P***
Age, y	53.6 ± 0.8	58.0 ± 0.2	4.4 (2.2 to 6.0)	$<10^{-6}$*
Weight, kg	82.8 ± 1.5	85.8 ± 0.3	3.0 (−0.1 to 6.1)	0.054*
BMI, kg/m^2	28.8 ± 0.5	29.5 ± 0.1	0.8 (−0.1 to 1.7)	0.097*
ASA PS				$<10^{-6}$†
1	1 (0.5%)	218 (4.6%)		
2	70 (33.2%)	2541 (53.56%)		
3	137 (64.9%)	1955 (41.2%)		
4	3 (1.4%)	31 (0.7%)		
Scheduled duration, min	293 ± 6	221 ± 1	−72 (−84 to −60)	$<10^{-6}$*

*P value by Student t test.

†P value by χ^2 test with Yate continuity correction.

ASA PS indicates American Society of Anesthesiologists physical status.

TABLE 2. ORs of Receiving a Ketamine Infusion According to Preoperative Medication Use

		Intraoperative Ketamine Infusion		
Preoperative Medication	**Taking**	**No**	**Yes**	**OR (95% CI)**
Scheduled opioid*	No	4325	82	16.09 (11.98–21.59)
	Yes	423	129	
Any opioid†	No	3221	36	10.25 (7.13–14.75)
	Yes	1527	175	
Antidepressant	No	3765	124	2.69 (2.02–3.57)
	Yes	983	87	
Scheduled opioid alone	Yes	274	68	1.64 (1.11–2.46)
Scheduled opioid + antidepressant	Yes	149	61	

*Included oxycodone extended-release, oxycodone (not taken PRN), hydrocodone (not taken PRN), morphine extended-release, oxymorphone extended-release, fentanyl patch, hydromorphone, morphine, and methadone

†Included all "chronic" opioids, as well as the following: oxycodone PRN and hydrocodone PRN.

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 adverse effects at our hospital, whereas 11 patients did not. To view the TJUH ketamine infusion guidelines, see Appendix A.

A postoperative infusion rate more than 20 mg/h was not associated with an increased chance of having the infusion stopped compared with patients receiving less than or equal to 20 mg/h (OR, 0.71; 95% CI, 0.34–1.5). The chance of discontinuation was also not increased with a threshold of 10 mg/h (OR, 0.69; 95% CI, 0.32–1.5).

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 (ie, 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

TABLE 3. Differences Between Spine Patients Taking Scheduled Opioids With or Without Intraoperative Ketamine Infusions

	Intraoperative Ketamine Infusion			
Variable	**Yes (n = 129)**	**No (n = 423)**	**Difference (95% CI)**	***P***
Age, y	53.9 ± 0.8	56.7 ± 0.6	2.8 (0.6 to 5.1)	0.012*
Weight, kg	81.8 ± 1.5	85.8 ± 1.1	4.08 (−0.28 to 8.43)	0.066*
BMI, kg/m^2	28.5 ± 0.4	29.7 ± 0.3	1.24 (−0.14 to 2.50)	0.053*
ASA PS				0.01†
1	0 (0.0%)	11 (2.6%)		
2	36 (27.9%)	171 (40.4%)		
3	90 (69.8%)	234 (55.3%)		
4	3 (2.3%)	7 (1.7%)		
Scheduled duration, min	292 ± 8	243 ± 4	−49 (−67 to −32)	$<10^{-6}$*

**P* value by Student *t* test.

†*P* value by χ^2 test with Yate continuity correction.

ASA PS indicates American Society of Anesthesiologists physical status.

TABLE 4. Specific Spine Procedures and Prevalence of Intraoperative Ketamine Infusion Administration

Procedure	No. Cases	Intraoperative Ketamine Infusion	
		n	%
Primary spine procedures			
Image-guided posterior thoracic/lumbar decompression/fusion	46	8	17.4
Anterior/posterior thoracic/lumbar fusion	37	5	13.5
Anterior/posterior cervical fusion	137	15	10.9
Anterior thoracic/lumbar fusion	136	12	8.8
Posterior thoracic/lumbar fusion	148	10	6.8
Anterior/posterior lumbar fusion	202	8	4.0
Posterior cervical fusion	275	10	3.6
Anterior minimally invasive/posterior lumbar decompression and fusion	69	2	2.9
Transforaminal lumbar interbody fusion	663	18	2.7
Posterior lumbar fusion	500	11	2.2
Anterior cervical fusion	1154	17	1.5
Posterior lumbar discectomy/laminectomy/decompression	473	4	0.8
Revision spine procedures			
Revision lateral anterior/posterior lumbar decompression/fusion	10	3	30.0
Revision posterior thoracic/lumbar fusion	88	22	25.0
Revision anterior/posterior cervical fusion	22	4	18.2
Revision anterior/posterior thoracic/lumbar fusion	14	2	14.3
Irrigation and drainage of thoracic/lumbar spine, removal of hardware	17	1	5.9
Revision posterior lumbar fusion	69	3	4.3
Revision anterior cervical fusion	65	2	3.1
Revision transforaminal lumbar interbody fusion	48	1	2.1

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 antidepressants and scheduled opioids was not surprising as the link between chronic pain, antidepressants, 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, antidepressant 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 per hour 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

TABLE 5. Adverse Drug Effects Occurring in 321 Patients During Low-Dose Postoperative Ketamine Infusion Administration on General Medical Floors

Adverse Event	Patients With ADE, n, % (95% Binomial CI)	Discontinued Ketamine Infusions in Patients With Specified ADE, Proportion, % (95% Binomial CI)
CNS excitation*	52, 16.2% (12.3%–20.7%)	18/52, 34.6% (22.0%–49.1%)
Sedation	30, 9.4% (6.4%–13.1%)	12/30, 40.0% (22.7%–59.4%)
Visual disturbances	10, 3.1% (1.5%–5.7%)	2/10, 20.0% (2.5%–55.6%)
Hemodynamic instability†	9, 2.8% (1.3%–5.3%)	2/9, 22.2% (2.8%–60.0%)
Nausea	9, 2.8% (1.3%–5.3%)	1/9, 11.1% (0.3%–48.3%)
Other	25, 7.8% (5.1%–11.3%)	2/25, 8.0% (1.0%–26.0%)
At least 1 ADE	102, 31.8% (26.7%–37.2%)	37/102, 36.3% (27.0%–46.4%)

*Delirium, agitation, dysphoria, hallucinations, and vivid dreams.

†Tachycardia, hypertension, and hypotension.

CNS indicates central nervous system.

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

Using the data from this observational study, we are currently designing a prospective, randomized trial comparing intraoperative 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 (ie, anterior/posterior procedures or procedures involving 2 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.

REFERENCES

1. Sullivan MD, Edlund MJ, Fan M, DeVries A, Braden JB, Martin BC. Trends in use of opioids for non-cancer pain conditions from 2000–2005 in commercial and Medicaid insurance plans: the TROUP study. *Pain*. 2008; 138:440–449.
2. Fredheim OMS, Mahic M, Shurtveit S, Dale O, Romundstad P, Borchgrevink PC. Chronic pain and use of opioids: a population-based pharmacoepidemiological study from the Norwegian Prescription Database and the Nord-Trondelag Health Study. *Pain*. 2014;155:1213–1221.
3. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11:S105–S120.
4. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction*. 1999;94:961–972.
5. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose. *Ann Intern Med*. 2010;152:85–92.
6. Trujillo KA, Akil H. Inhibition of morphine tolerance and dependence by the NMDA antagonist MK-801. *Science*. 1991;251:85–87.
7. Elliott K, Minami N, Kolesnikov YA, Pasternak GW, Inturrisi CE. The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, NG-nitro-L-arginine, attenuate analgesic tolerance to the mu-opioid morphine but not to kappa opioids. *Pain*. 1994; 56:69–75.
8. 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: 639–646.
9. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth*. 2011;58: 911–923.
10. McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand*. 2014;58:1199–1213.
11. Urban MK, Ya Deau JT, Wukovits B, Lipnitsky JY. Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. *HSS J*. 2008;4:62–65.
12. 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;12:1276–1283.
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. Walid MS, Zaytseva NV. Prevalence of mood-altering and opioid medication use among spine surgery candidates and relationship with hospital cost. *J Clin Neurosci*. 2010;17:597–600.
15. Rasmussen KG. Psychiatric side effects of ketamine in hospitalized medical patients administered subanesthetic doses for pain control. *Acta Neuropsychiatr*. 2014;26:230–233.
16. Porter SB, McClain RL, Howe BL, et al. Perioperative ketamine for acute postoperative analgesia: the Mayo Clinic-Florida experience. *J Perianesth Nurs*. 2015;30:189–195.
17. Villasenor A, Ramamoorthy A, Silva dos Santos M, et al. A pilot study of plasma metabolomic patterns from patients treated with ketamine for bipolar depression: evidence for a response-related difference in mitochondrial networks. *Br J Pharmacol*. 2014;171:2230–2242.

Appendix A

Thomas Jefferson University Hospital
Acute Pain Management Service Policy and Procedure
Ketamine Infusion Guidelines for Opioid-Tolerant Postoperative Patients, Palliative Care Patients, and Intractable Migraine Headache Patients

Purpose:
To provide guidelines for the acute pain management service nursing staff caring for patients receiving ketamine to treat intractable migraine headaches, poorly controlled pain due to opioid tolerance, or as a palliative care treatment. Infusion may be initiated in adult general care units as well as intermediate and intensive care units.
Procedure (Opioid Tolerant and Headache):

1. All patients will be monitored according to opioid monitoring guidelines, even if the patient is not receiving an opioid (may occur with intractable migraine headache patients). Minimal monitoring is q4hr: RR, BP, pain and sedation levels.
2. Initial bolus dosing is 10–15 mg IVP, MR × 1. Dose must be administered by APMS physician.
3. Initiate infusion at 5 mg/h. Maximum dose is 1 mg/kg per hour. Dose titration may only be done by APMS physicians or nurses.
4. Assess patient's pain using 0–10 scale (0 = no pain, 10 = worst pain imaginable).
5. If patient using opioids appropriately and reports greater than 5 of 10 pain:
   a. Bolus patient with ketamine 10 mg.
   b. If no response in 10 minutes, may repeat bolus of ketamine 10 mg.
   c. After bolus, increase rate of ketamine infusion by 5 mg/h (not to exceed 1 mg/kg per hour unless approved by APMS physician).
   d. May be repeated as needed, but no more frequently than every 60 minutes.
6. Document therapy and outcome on Titrating Analgesia flow sheet. When a ketamine bolus is administered or the rate is changed, the following information is recorded on the Titrating Analgesia flow sheet:
   a. Date/Time
   b. Medication (name and dose)
   c. Pain score assessment, HR, BP pre-bolus
   d. Patient response to therapy; pain score, HR, BP post-bolus
7. When a ketamine bolus is administered, it will be signed out by the APMS nurse on the electronic medical record.
8. When no pain relief achieved after 2 boluses:
   a. Notify APMS physician for further instructions.
   b. In headache patients, the Neurology Headache Physician will be notified if the patient has dose-limiting adverse effects or is reaching the upper limits of dosing and continues to have inadequate pain relief.
9. If patient experiences side effects, such as hallucinations, tremors, diplopia or confusion, from a ketamine bolus:
   a. Verify that the patient is receiving a benzodiazepine. If the patient is not receiving a benzodiazepine, notify the APMS physician or attending neurologist for headache patients.
   b. APMS nurse will remain with the patient and provide comfort and reassurance. Most adverse effects are self-limiting and will usually subside within 10–15 minutes after receiving a bolus dose. If adverse effects do not subside, notify APMS or Neurology attending physician.
   c. APMS nurses may decrease infusion by 50% as per APMS physician order.

If an APMS physician wants a ketamine infusion discontinued, the APMS nurse may discontinue the order in Jeff Chart as a protocol user. The Neurology Headache Physician will discontinue ketamine infusions for headache patients.