Single Dose of Ketamine During Kyphoplasty Procedures Does Not Reduce Postoperative Narcotic Consumption

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This retrospective cohort study aimed to explore the study institution's intraoperative ketamine use during kyphoplasty and compare narcotic requirements in patients who received intraoperative ketamine with those who did not. The authors hypothesized that a single dose of ketamine during kyphoplasty would reduce postoperative narcotic consumption. Included patients underwent kyphoplasty under monitored anesthesia care between 2012 and 2013. Excluded patients were younger than 18 years or had general anesthesia, endotracheal intubation, or major intraoperative complications. Narcotics were converted into morphine equivalents for comparison. Analysis included χ^2, correlation analyses, multivariate regression analysis, and analysis of variance. Overall, 279 patients were included. Men were a minority of the sample, 26.2% (73/279). More than 83% of patients were ASA class 3 (232/279), and more than 50% repaired a single vertebra (154/279). A single dose of ketamine was administered in 15.8% of kyphoplasties, with an average dose of 38.7 mg (range = 2-150 mg). Intraoperative ketamine administration was predictive of decreased intraoperative narcotic requirements ($P < .001$) but was not associated with decreased postoperative narcotic requirements ($P = .442$). Patients remained hemodynamically stable in the preoperative and postoperative period. Ketamine did not reduce postoperative narcotic consumption but reduced intraoperative narcotic consumption in this sample.

Keywords: Intraoperative narcotic consumption, ketamine, kyphoplasty, postoperative narcotic consumption, postoperative pain.

Ketamine, first used in 1964 as an intraoperative anesthetic agent, is a well-established and broadly studied anesthetic and analgesic agent.[1-17] Despite an abundance of literature, ketamine's efficacy to treat perioperative pain in spinal procedures remains controversial, attributed partly to study heterogeneity and lack of dosing standards.[2,3,9,13,14,17] Systematic reviews published in 1999,[14] 2006,[2] and 2011[9] concluded that ketamine appears to reduce postoperative pain intensity and analgesic consumption without significant side effects. However, Bell's group[2] and Schmid et al[14] could not perform meta-analyses on preincisional or perioperative administration, respectively, secondary to vast heterogeneity among the studies. Interestingly, in 2011, Laskowski and colleagues[9] performed a focused meta-analysis on perioperative ketamine use, excluding studies that used any form of regional anesthesia. They reported that the least opioid reduction was found in the most homogeneous groups.[9] Devin and McGirt[3] were not able to determine optimal postoperative pain protocols in spinal surgery because there was a paucity of evidence and conflicting grade I evidence. Indeed, 7 randomized controlled trials examining ketamine's analgesic efficacy in spinal procedures have been performed since 1996 with various study designs, dosing schemes, standard anesthetic techniques, and outcomes.[1,6,7,10-12,15] In 2016, results of a retrospective study with historic controls from a level I trauma center in Canada suggested there was no statistical difference in any analyzed category between conventional postoperative therapy and conventional therapy plus ketamine in patients undergoing spine surgery.[16]

At the current study institution, ketamine is used according to the clinician's discretion. Nurse anesthetists' and anesthesiologists' confidence in and comfort with using ketamine vary, which appears to be a national trend.[8] Conflicting perceptions attributed to knowledge deficits and fears regarding ketamine, among other reasons, were identified in a 2016 survey of the American Society of Pain Management Nurses.[8] Survey respondents included postanesthesia care nurses, nurse anesthetists, and operating room nurses.[8] In their survey, Klaess and Jungquist[8] identified not only vast differences in ketamine dosing regimens but also inconsistent use in each

Variable	Overall (N = 279)	Ketamine (n = 44)	No ketamine (n = 235)
Age, mean (SD), y	77.42 (11.76)	74.75 (12.58)	77.92 (11.56)
Weight, mean (SD), kg	83.86 (112.16)	95.71 (141.60)	81.64 (105.96)
Procedure length, mean (SD), min	59.04 (15.59)	62.48 (18.85)	58.40 (14.87)
VAS pain score, mean (SD)	5.66 (3.23)	6.91 (2.84)	5.43 (3.25)
Hospital stay, mean (SD), d	3.29 (3.14)	3.41 (2.94)	3.26 (3.19)
Morphine equivalents			
Preoperative	1.24 (2.81)	1.42 (3.23)	1.20 (2.73)
Intraoperative	12.34 (7.26)	9.85 (7.94)[a]	12.81 (7.05)
Postoperative	5.78 (9.98)	6.84 (7.43)	5.58 (10.39)
Vertebra repaired, No. (%)			
1	154 (55.2)	25 (56.8)	129 (54.9)
2	92 (33)	14 (31.8)	78 (33.2)
3	30 (10.8)	5 (11.4)	25 (10.6)
4	3 (1.1)	0 (0)	3 (1.3)
ASA class, No. (%)			
1	2 (0.7)	1 (2.3)	1 (0.4)
2	15 (5.4)	2 (4.5)	13 (5.5)
3	232 (83.2)	37 (84.1)	195 (83.0)
4	30 (10.8)	4 (9.1)	26 (11.1)
Epidural block placement, No. (%)			
No	152 (54.5)	27 (61.4)	125 (53.2)
Yes	127 (45.5)	17 (38.6)	110 (46.8)

Table 1. Descriptive Patient Characteristics
Abbreviation: VAS, visual analog scale.
[a]Significantly less than no-ketamine group (P = .013).

state, where some hospitals administer ketamine and others do not, regardless of size or academic affiliation.

The purposes of this study were to explore the study institution's intraoperative ketamine use during kyphoplasty and to compare narcotic requirements in patients undergoing kyphoplasty who received ketamine intraoperatively vs those who did not. The authors hypothesized that intraoperative ketamine administration during kyphoplasty would reduce postoperative narcotic consumption.

Materials and Methods

After institutional review board approval, the authors performed a retrospective chart review of consecutive patients undergoing kyphoplasty at a regional level I trauma center in northeast Ohio. Written informed consent was not required because the authors used preexisting information from medical records.

Included patients underwent a kyphoplasty procedure (*International Classification of Diseases, Ninth Revision* procedure code 81.66) under monitored anesthesia care between January 1, 2012, and May 31, 2013. Excluded patients were younger than 18 years, underwent general anesthesia with endotracheal intubation, had a major intraoperative complication, or had Advanced Cardiac Life Support initiated intraoperatively.

The authors chose the period from January 2012 to May 2013 because the study institution's standard anesthetic technique for kyphoplasty changed from monitored anesthesia to general anesthesia on June 1, 2013. For the purposes of this retrospective chart review, an intraoperative complication was defined as a documented complication in a patient's intraoperative record or postoperative progress note. Patients with intraoperative complications were excluded because these conditions would affect narcotic administration.

The following variables were extracted from the electronic medical record: patient demographics, number of vertebrae repaired, surgery duration, ASA class, and hospital length of stay. Also extracted were total narcotic administration 6 hours preoperatively, intraoperatively, and 6 hours postoperatively; mean arterial pressure and heart rate 6 hours preoperatively and 6 hours postoperatively; intraoperative ketamine administration and total ketamine dose if administered; intraoperative placement of an epidural block; documentation of unwanted events

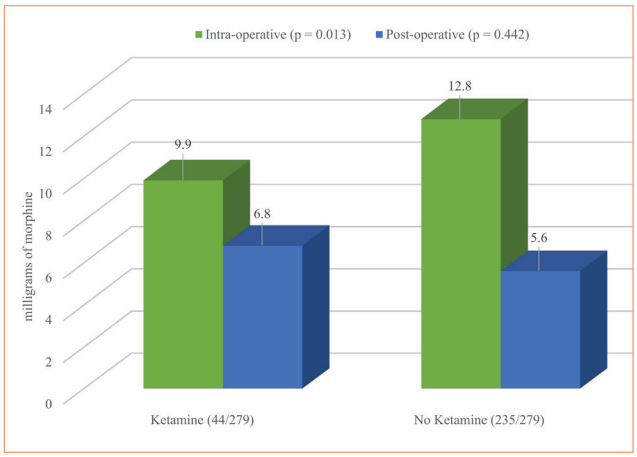

Figure. Mean Intraoperative and Postoperative Narcotic Comparisons in Milligrams of Morphine by Ketamine Administration

(dysphoria, hallucinations, delirium, postoperative intubation, or death). The final variable obtained from the health record was the highest visual analog scale (VAS) pain score 6 hours postoperatively.

The VAS pain score is a common method of assessing patients' pain. The patient assigns a number for pain intensity from 0 to 10, with 0 being no pain and 10 being the worst pain imaginable. The authors chose a 6-hour postoperative period because ketamine has a half-life less than 6 hours.[18] It is unlikely that ketamine administered as a single dose would influence pain scores and narcotic administration after the 6-hour postoperative period. For consistency, the authors applied the 6-hour window to the preoperative period as well.

Data were entered into a spreadsheet (Excel 2010, Microsoft Corp, Redmond, WA) and imported into statistical analysis software (SPSS 17.0, SPSS Inc, Chicago, IL) for data analysis. All recorded narcotics were converted into morphine equivalents (MEQ) to allow comparison across groups. Patients who did and who did not receive ketamine intraoperatively were compared with statistical control for confounding variables. Analysis included χ^2, correlation analyses, multivariate regression analysis, and analysis of variance. Statistical significance was established with $\alpha \leq .05$.

Results

Overall, 338 charts were reviewed and 279 patients were included. The most common reason for exclusion was general anesthesia with endotracheal intubation. Two patients were excluded because of a major intraoperative complication; neither had received ketamine. Males accounted for a minority of the sample, 26.2% (73/279). More than 83% of patients were ASA class 3 (232/279), and 55.2% were repairing a single vertebra (154/279). Other patient characteristics are displayed by group in Table 1. There were no continuous ketamine infusions administered in this sample. A preincisional, single dose of ketamine was administered in 15.8% of the kyphoplasties included (44/279). The average ketamine dose among the 44 patients who received it was 38.7 mg, ranging from 2 mg to 150 mg. When ketamine was calculated as a weight-based dose, the average dose was 0.53 mg/kg with a range from 0.01 mg/kg to 1.64 mg/kg.

All patients were hemodynamically stable in the preoperative and postoperative periods. Heart rate and mean arterial pressure did not significantly vary between patients who did and did not receive ketamine intraoperatively. Heart rate and mean arterial pressure in the postoperative period were similar to the preoperative period among all groups, and there were no unwanted events (dysphoria, hallucinations, delirium, intubations, or deaths) documented in the postoperative period. In the 6-hour preoperative period, there was no difference in narcotic consumption between patients who received intraoperative ketamine (1.42 MEQ, SD = 3.23) and patients who did not (1.20 MEQ, SD = 2.73, t [df = 277] = –0.472, P = .637).

Increased intraoperative narcotic consumption was associated with higher preoperative morphine requirements, longer procedures, younger age, lower ASA class, and male gender (all $P < .05$). Epidural block placement, postoperative pain scores, and number of vertebrae repaired were not associated with intraoperative narcotic requirements. Patients who received a single dose of ketamine required significantly less intraoperative narcotics than patients who did not receive ketamine: 9.85 MEQ (SD = 7.94) vs 12.81 MEQ (SD = 7.05), t (df = 277) = 2.51, P = .013 (Figure).

In multivariate regression analysis with forward selection (Table 2), longer procedures (β = 0.08), younger patients (β = –0.23), and any ketamine use (β = –4.01) was predictive of decreased intraoperative narcotic requirements (model F = 20.13, $P < .001$, R^2 = 0.180). Intraoperative placement of an epidural block did not significantly affect intraoperative narcotic administration. Patients without an epidural block consumed 11.85 MEQ (SD = 6.36) and patients with an epidural consumed 12.93 MEQ (SD = 8.21), t (df = 277) = –1.24, P = .218.

Postoperative narcotic consumption was associated with pain scores, preoperative narcotic requirements, intraoperative narcotic consumption, number of repaired vertebrae, and age (all $P < .05$). Procedure length, gender, ASA class, weight, and epidural block placement were not associated with postoperative narcotic requirements. The average postoperative narcotic dose was 6.84 MEQ (SD = 7.43) when patients received intraoperative ketamine, and 5.58 MEQ (SD = 10.39) when patients did not receive intraoperative ketamine (t [df = 277] = –0.77, P = .442; see Figure). Multivariate regression analysis with forward selection (Table 3) revealed that higher preoperative narcotic doses (β = 1.35), higher pain scores

Variable	Unstandardized β coefficient	Standard error	Standardized β coefficient	P
Constant	25.88	3.02	8.58	< .001
Age	–0.23	0.03	–0.37	< .001
Ketamine use	–4.01	1.10	–0.20	< .001
Procedure length	0.08	0.03	0.17	.002

Table 2. Factors Predicting Intraoperative Narcotic Consumption (N = 279)[a]
[a] R^2 = 0.180.

Variable	Unstandardized β coefficient	Standard error	Standardized β coefficient	P
Constant	–3.33	1.51		.028
Preoperative narcotics	1.35	0.19	0.38	< .001
Visual analog scale	0.86	0.17	0.28	< .001
Vertebra repaired	1.67	0.70	0.12	.019

Table 3. Factors Predicting Postoperative Narcotic Consumption (N = 279)[a]
[a] R^2 = 0.301.

(β = 0.06), and greater number of repaired vertebrae (β = 0.167) were predictive of increased narcotic use in the postoperative period (model F = 38.73, P < .001, R^2 = 0.301). Receiving an intraoperative epidural block did not significantly affect postoperative narcotic consumption. Patients with and without an epidural block consumed similar amounts of postoperative narcotics: 5.90 MEQ (SD = 13.01) vs 5.68 MEQ (SD = 6.49), respectively, t (df = 277) = –0.19, P = .853.

Discussion

The purposes of this retrospective cohort study were to explore the study institution's intraoperative ketamine use during kyphoplasty and to compare narcotic requirements in patients who received intraoperative ketamine with those who did not. The authors hypothesized that intraoperative ketamine administration during kyphoplasty would reduce postoperative narcotic consumption. In the current study observing a homogeneous group of mostly elderly patients with multiple comorbid conditions, a single dose of ketamine during kyphoplasty was not associated with reduced narcotic consumption or reduced VAS pain scores in the 6-hour postoperative period, but it reduced intraoperative narcotic consumption.

Less than one-fourth (16%) of the current sample received ketamine, and in those who did, the weight-based doses of ketamine administered ranged from 0.01 mg/kg to 1.64 mg/kg. The small percentage of patients receiving ketamine confirms that clinicians at the study institution are divided regarding intraoperative ketamine use. The wide ketamine dosing range found in 44 patients is in accordance with Klaess and Jungquist's[8] 2016 survey results that demonstrated administration inconsistencies and a myriad of dosing calculations used in practice.

Despite various study designs across the literature, the current findings were more in-line with investigators who found no difference in postoperative pain.[12,15,16] Nitta and colleagues[12] investigated continuous intraoperative and postoperative ketamine administration in spinal surgeries. They reported no difference in patient-controlled analgesia or VAS pain scores in their prospective, randomized investigation, but they excluded ASA class 3 patients and those who had preoperative analgesia.[12] Subramaniam et al[15] similarly conducted a prospective, randomized trial of continuous intraoperative and postoperative ketamine infusion in major spine surgeries. They included ASA class 3 and opioid-tolerant patients but also reported no difference in postoperative analgesia.[15] The retrospective study by Vaid et al[16] of opioid-tolerant adults undergoing spinal surgery demonstrated that the addition of a continuous ketamine infusion to a conventional postoperative pain regimen also did not reduce pain scores and opioid consumption. The current study's results mirror the findings of Garcia-Navia et al,[5] who concluded that single ketamine doses did not reduce postoperative pain or opioid consumption but did reduce intraoperative opioid requirements in gynecologic procedures.

Observations reported in this retrospective chart review are plausible. Ketamine's short duration of action may provide therapeutic benefit within a limited timeframe,[18] with a subsequent "rebound" increase in opioid requirement once the effects have subsided. All ketamine doses administered in this investigation were preincisional, 1-time doses. This may explain why use of intraoperative narcotics was reduced in the ketamine group, but postoperative narcotic consumption was similar between groups. Another explanation is selection bias; patients who received ketamine intraoperatively may have been opioid tolerant. Preoperative pain scores and data on opioid tolerance were not collected for the

current investigation, but 6-hour preoperative narcotic consumption was not significantly different between groups. It is reasonable to assume that most, if not all, patients included in this retrospective chart review were being treated for back pain in the weeks or months before their procedure. Because ketamine use is according to the anesthesiologist's or nurse anesthetist's discretion at the study facility, it is likely that patients who received ketamine were under the care of an anesthesiologist or nurse anesthetist who was confident in and comfortable with the agent. Another consideration is timing of ketamine administration. In the current effort, the intraoperative ketamine administration was preincisional. Administering ketamine as a continuous infusion during the procedure may have led to better pain management in the postoperative period.[1,6,7,10,11]

Despite the lack of an opioid-sparing effect in the postoperative period, the results of the current study suggest there is a clinically important opioid-sparing effect intraoperatively. When intraoperative narcotics are reduced, respiratory and airway integrity are preserved. Given the known respiratory depression due to opioid use, ketamine administration may be a beneficial adjunct to avoid intubation in monitored anesthesia care surgical cases, especially in an elderly population with moderate to high operative risks. Importantly, no hemodynamic instability or adverse events related to intraoperative ketamine use were observed. This is particularly noteworthy given the mostly elderly population with multiple comorbidities.

This retrospective chart review is unique for 4 reasons. First, the authors examined ketamine use in kyphoplasty procedures. A PubMed search using the text terms *ketamine* and *kyphoplasty* yielded no pertinent publications. To the authors' knowledge, the efficacy of ketamine in kyphoplasty has not been specifically reported. Second, all 7 randomized controlled trials examining ketamine use in spinal procedures included patients who underwent surgery with general endotracheal anesthesia.[1,6,7,10-12,15] The patients examined in the current study had monitored anesthesia care; the authors excluded any patients who received general anesthesia. Third, more than 90% of patients included in the current study were ASA class 3 or 4. In all 7 randomized controlled trials, patients with ASA classes 3 and 4 were either excluded[1,6-7,12] or represented less than half of all included patients.[10,11,15] Fourth, the average patient age was 77 years in the current study. In all 7 randomized controlled trials, 65 years was the average age,[6,7,10-12,15] and the maximum age was 75 years.[1] Klaess and Junquist's[8] survey respondents indicated that in practice, 55% of patient's receiving ketamine were 65 years or older. It seems that previously studied populations are not wholly representative of most patients who receive ketamine in practice. The current retrospective cohort study provides enlightening real-world information in an understudied population. The results warrant ketamine practice standardization and further research in ketamine's efficacy for the geriatric population in a randomized controlled design. Future research could include investigating ketamine efficacy during other monitored anesthesia cases.

Among this study's limitation is its retrospective nature. As previously mentioned, ketamine use in kyphoplasty procedures at the study facility is according to the clinician's discretion. Secondary to clinician preference and a lack of practice standardization, there is inherent selection bias. Rationale behind who received and did not receive ketamine, as well as the dose administered, could not be determined. Another limitation is the small sample of patients receiving ketamine intraoperatively, and the wide dosing range observed in the patients who received it. This can be attributed to an absence of widely accepted guidelines regarding optimal dose, route, or length of therapy when ketamine is used off-label as an analgesic[8]; even the prescribing information acknowledges that dosage recommendations cannot be absolutely fixed when used as an anesthetic.[18] As mentioned in the discussion, the authors did not collect preoperative pain scores or preoperative opioid tolerance variables. Knowing these patient characteristics may have provided further insight into the results. In the present study, only a 6-hour postoperative period was examined because of the short half-life of ketamine.[18] Observing narcotic use for a 24-hour period may have suggested different results, but based on ketamine's short half-life and the single-dose administration, extending the period to 24 hours may have inappropriately confounded narcotic consumption by collecting data that were not temporally associated with ketamine's known pharmacokinetics. Despite the limitations, this investigation provides valuable, clinically meaningful insight into real-world ketamine use in this understudied patient population.

Conclusion

A single, intraoperative, preincisional dose of ketamine did not reduce postoperative narcotic consumption, but reduced intraoperative narcotic administration, without unwanted side effects in this study group. The results strengthen the need for standardization of ketamine practice.

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