Ketamine infusion for pain control in elderly patients with multiple rib fractures: Results of a randomized controlled trial

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BACKGROUND: Rib fractures are associated with increased mortality, particularly in the elderly. While opiate-based pain regimens remain the cornerstone of rib fracture management, issues related to opioids have driven research into alternative analgesics. Adjunctive ketamine use in lieu of opioids continues to increase but little evidence exists to support its efficacy or safety within the elderly trauma population.

METHODS: A prospective, randomized, double-blind placebo-controlled trial of elderly patients (age, ≥65 years) with three or more rib fractures admitted to a Level I trauma center was conducted. Exclusion criteria included Glasgow Coma Scale score less than 14, and chronic opiate use. Groups were randomized to either low-dose ketamine (LDK) at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or an equivalent rate of 0.9% normal saline. The primary outcome was reduction in numeric pain scores (NPS). Secondary outcomes included oral morphine equivalent (OME) utilization, epidural rates, pulmonary complications, and adverse events.

RESULTS: Thirty (50.8%) of 59 were randomized to the experimental arm. Groups were similar in makeup. Low-dose ketamine failed to reduce 24-hour NPS or OME totals. Subgroup analysis of 24 patients with Injury Severity Score greater than 15 demonstrated that LDK was associated with a reduction in OME utilization the first 24-hours (25.6 mg vs. 42.6 mg, $p = 0.04$) but at no other time points. No difference in other secondary outcomes or adverse events was noted.

CONCLUSION: Low-dose ketamine failed to affect NPS or OME within the overall cohort, but a decrease in OME was observed in those with an Injury Severity Score greater than 15. Additional studies are necessary to confirm whether LDK benefits severely injured elderly patients. (*J Trauma Acute Care Surg.* 2019;87: 1181–1188. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic, level I.

KEY WORDS: Ketamine; elderly; rib fractures; opioids; trauma.

Rib fractures following thoracic trauma remain a significant issue for those invested in the care of the injured patient.[1] Up to 20% of all admitted trauma patients have rib fractures, and the elderly population is at particular risk for associated pulmonary complications and mortality, an outcome consistently shown across multiple studies.[2–6] Adequate pain control remains the cornerstone of rib fracture management, allowing for effective respiratory therapy in an attempt to decrease the risk of pulmonary complications.[7,8] This is particularly important as highlighted by Wisner in 1990 and again by Bulger in 2000, each of whom demonstrated a lower mortality in elderly patients who underwent epidural catheter placement.[2,3] Unfortunately, epidural catheters are not universally available, are contraindicated in some patients, and have associated complications inherent to the invasive nature of the procedure.[9–11] Even those who qualify for regional pain techniques are often treated using multimodal pain pathways, which remain primarily narcotic based despite increased opioid awareness.[1,12,13] Given the well-described adverse effects of opioids in the elderly population, ample motivation exists to explore the role of nonopioid alternatives in these patients.[14] Ketamine has gained resurgent popularity in the effort to decrease the reliance on opioids for pain control and is being used across a wide range of applications, including trauma, in part because it does not cause respiratory depression even at anesthetic doses.[13,15,16]

As an *N*-methyl-D-aspartate (NMDA) antagonist, ketamine blocks the excitatory transmission of pain signals in the central nervous system through noncompetitive binding.[17,18] Subanesthetic concentrations of the drug (~100–200 mg/mL) produce analgesia and also increase the effectiveness of narcotics,[19] two desired effects that decrease pain while still allowing for patient participation in care. Additionally, these doses are not associated with the classic psychoactive effects (hallucinations, disturbing dreams, delusions, emergence phenomena) that had limited more widespread use of ketamine.[19] Unfortunately, the optimal dose of ketamine for adjunctive pain control has not been identified, but several studies have demonstrated postoperative pain reduction when using doses in the 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ range.[20]

Our institutional rib fracture guideline utilizes regional anesthesia when conventional pain medications fail to provide adequate analgesia. Low-dose ketamine (LDK) was traditionally reserved for patients who were not candidates for epidural anesthesia or those who had significant pain despite an epidural. Anecdotally, we noted that patients placed on LDK required lower opioid doses to achieve pain control; however, our institutional data regarding the efficacy of ketamine infusions was limited and susceptible to significant selection bias.[13] Similarly, most of the recent publications characterizing the role of ketamine in trauma patient care remain retrospective in nature and subject to those same limitations.[16,21]

Given this lack of prospective data in the use of ketamine for analgesia in patients with rib fractures, we designed a prospective double-blind randomized, placebo-controlled trial to examine the efficacy of LDK as a primary mode of analgesia rather than as salvage therapy. Recognizing that older adults differ in pain perception, management, and potential adverse drug reactions,[22–24] we performed a separate, but concurrent, study for patients 65 ears or older.[25] The elderly study utilized a ketamine dose of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ versus the 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dose in the nonelderly study. In addition to the reasons listed above, the lower dose was chosen due to the known decrease in hepatic clearance seen in the elderly.[26] We hypothesized that the utilization of LDK infusion would improve patient acute pain management and would reduce both numeric pain scores (NPS) and opioid utilization.

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METHODS

Study Design

A prospective, randomized, double-blind, placebo-controlled trial utilizing LDK as an analgesic adjunct among elderly trauma patients (age, ≥65 years) was performed at Froedtert Hospital, an American College of Surgeons verified Level I trauma center that serves the urban and suburban populations of Milwaukee, WI. From August 2015 to June 2018, all elderly blunt trauma patients with three or more rib fractures were screened for eligibility in the study. Patients were excluded from enrollment for any of the following: (1) younger than 65 years, (2) history of adverse reaction to ketamine therapy, (3) Glasgow Coma Scale score less than 13, (4) active acute coronary syndrome, (5) severe hypertension defined as prolonged systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 100 mm Hg, (6) current use of monoamine oxidase inhibitor, (7) chronic opioid use defined by greater than 30 mg oral morphine equivalents (OME) per day for more than 3 weeks, (8) current substance abuse with opioids (prescription, heroin, etc.) or ketamine, (9) inability to communicate with staff, (10) history of psychosis, (11) use of three or more psychotropic medications, (12) active delirium/history of dementia, (13) glaucoma, and (14) prisoners. The study was conducted under the Department of Surgery, Division of Trauma and Critical Care in conjunction with the Departments of Emergency Medicine and Anesthesia at the Medical College of Wisconsin. The institutional review board reviewed and approved the study design. This study was registered with clinicaltrials.gov (NCT02432456).

Randomization and Study Protocol

Following informed consent and enrollment, patients were randomized through Investigational Drug Services to receive an infusion of either LDK (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ based on ideal body weight) or an equivalent volume of placebo (0.9% sodium chloride). Ketamine is indicated for induction and maintenance of anesthesia, and its use in this study as an analgesic at subanesthetic doses is off-label. Infusions were initiated within 12 hours of a patient's arrival to the institution and were continued for a total of 48 hours unless safety concerns prompted early cessation or patients met criteria for discharge. Enrolled subjects were managed using the institutional rib fracture multimodal pain management pathway, which includes opioid and non–opioid-based medical treatments. All participants, care providers, and study staff were blinded from subject assignments unless medical necessity required subjects to be unblinded. Patients were followed throughout their admission and for 30 days after discharge.

Measures

The primary outcome variable evaluated was a reduction in NPS at 24 hours after initiation of the infusion, as calculated using an area under the curve for the pain trajectory during the 12- to 24-hour period. Our institution utilizes a standardized 11-point NPS, which is assessed per unit policy and before/after any pain intervention. The NPS data collected by the nursing staff and recorded throughout the patient's hospital stay were used for statistical analysis. The area under the curve was computed using the trapezoid rule. Linear interpolation was used between the last pain score before the start of the period and the first pain score after the start of the period to obtain the 12-hour pain score, with a similar calculation for the 24-hour score. This measure can be also interpreted as a time-weighted average of pain scores. The use of all pain management medications was recorded, and opiate-based medications were standardized to OME for analysis.

Secondary outcomes evaluated for the trial included NPS values at 48 hours, opioid consumption measured in OME at 24 and 48 hours, total OME, intensive care unit (ICU)/hospital length of stay, rate of epidural placement, pulmonary complications, and other adverse events. Patients were monitored throughout their hospitalization for specific complications, including nausea, pruritus, respiratory depression, sedation level, and presence of disturbing dreams or hallucinations. Those who exhibited signs of delirium were screened by the clinical nursing staff utilizing the institution's approved Confusion Assessment Method in the ICU tool.[27] Demographics including age, mechanism of injury, sex, chest Abbreviated Injury Scale, Injury Severity Scale (ISS), number of rib fractures, presence of a flail chest or pulmonary contusion, and tobacco use were also recorded.

Sample Size Calculation

A clinically significant reduction in NPS is defined as a two-point reduction on the 11-point scale.[28–30] The sample size was calculated based on previous institutional pain data which assumed a between-patient standard deviation of 2.5 points. Using this initial assumption, the sample size was calculated at 26 patients per group for 80% power at an alpha of 0.05. Planned enrollment was set at 60 patients to allow for an estimated 15% attrition rate. Recalculation of the sample size was performed at the end of enrollment given that estimates were used during the study design. The between-patient standard deviation of the NPS was lower than estimated (only 1.6), which meant that the enrollment we achieved had over 90% power to detect a 1.5-point difference.

Statistical Analysis

Demographic and other baseline data, such as trauma characteristics, as well as outcome measures, are presented overall and by treatment group. Categorical data were analyzed using Fisher's exact test for between-group comparisons. Between-group comparisons of numeric data with approximately symmetric distribution was performed using Student's two-sample *t* test. Skewed outcomes, such as length of stay and cumulative OME, and ordinal measures, such as ISS, were compared using Wilcoxon rank-sum test. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Sixty-one patients were enrolled, and 59 randomized to either the placebo or experimental (LDK) arm. Thirty (50.8%) patients were randomized to the experimental arm (Fig. 1). Overall, 59.3% of patients were male, with a median age of 74 years (interquartile range [IQR], 65–96 years) and a median ISS of 13 (IQR, 4–48). Falls were the most common mechanism of injury (50.8%), with no significant differences in demographics or

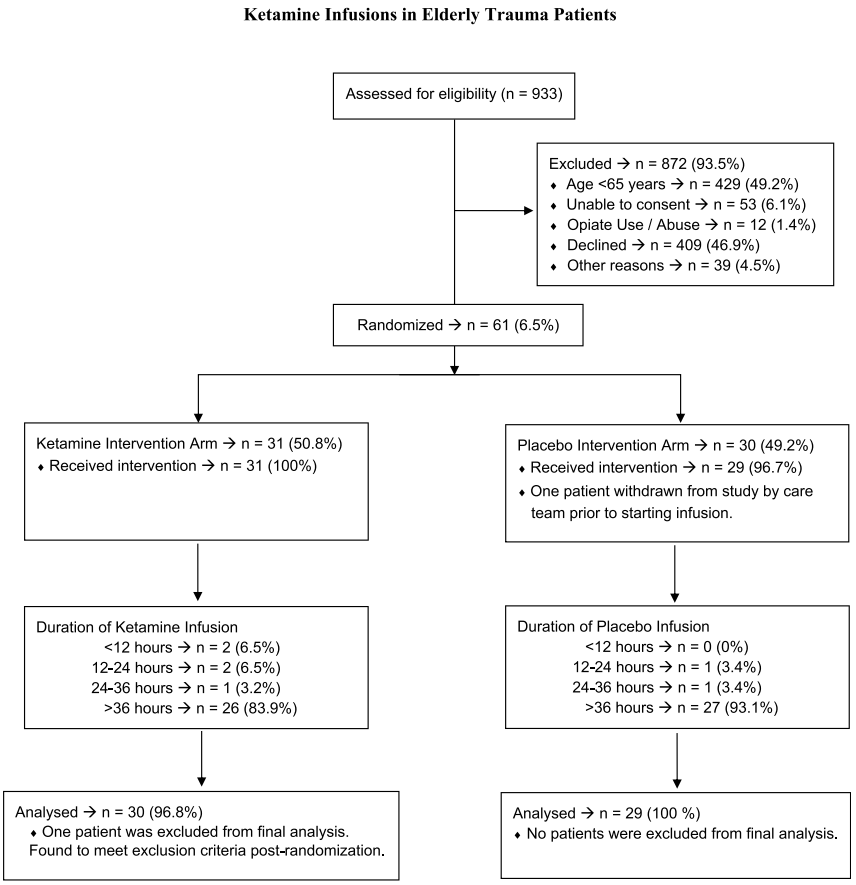

Figure 1. CONSORT flow diagram.

injury characteristics between groups (Table 1). One (1.7%) patient completed less than 12 hours of the infusion, two (3.4%) patients completed less than 24 hours, and 53 (89.8%) patients completed longer than 36 hours of the infusion, but no difference in the infusion duration was noted between groups. As part of our multimodal pain treatment guideline for patients with rib fractures, oral acetaminophen, muscle relaxants, and nonsteroidal anti-inflammatory medications are prescribed unless contraindicated. There was no statistical difference in the use of any of these medications in our patient population. Additionally, intercostal nerve blocks were performed on 14 (46.7%) LDK patients and 18 (62.1%) in the placebo arm ($p = 0.17$).

Regarding the primary outcome, no difference was noted in NPS at 12 hours, 24 hours, or 48 hours. Similarly, no difference was noted in OME totals at 12 hours, 24 hours, 48 hours, or during the cumulative hospitalization (Table 2). A subset analysis was completed to further explore whether LDK had any effect on NPS or OME in patients with isolated rib fractures, those admitted to the ICU vs. the ward, or those with an ISS ≥15 (Table 3). Low-dose ketamine failed to decrease NPS within any of those patient groups and there was actually a lower NPS in the severely injured (ISS ≥15) placebo group at 48 hours (4.4 vs. 6.0, $p = 0.007$). A significant reduction in OME was noted in severely injured patients receiving LDK, but only at the 12-hour to 24-hour time-frame (Fig. 2). Other secondary outcomes are reported in Table 4. Of note, adverse events were not significantly different between groups, nor were the rates of epidural placement (13.3% vs. 20.7% of LDK and placebo patients, respectively).

DISCUSSION

Our article presents the results of a randomized, double-blinded controlled trial of LDK for the treatment of pain in elderly trauma patients with at least three rib fractures. This trial was pragmatically designed to include not just patients with isolated rib fractures, but the population with multiple injuries typically seen in trauma centers. While no difference was noted in NPS or OME within the entire cohort at 12 hours, 24 hours, or 48 hours, LDK significantly reduced OME utilization in severely injured patients (ISS ≥15) at the 12-hour to 24-hour period. In contrast to the nonelderly (<65 years) cohort, the opioid sparing effect was not demonstrated beyond this initial time point.[25] The OME reduction was not related to admission to the intensive care unit or general trauma ward, which suggests that our findings are based on the patients' cumulative injuries and not simply an effect of where they were cared for. Unfortunately, we could not determine if a specific additional injury (i.e., long bone fracture or abdominal injury) in addition to the rib fractures contributed to this finding. Confounding this further is that the typical pain threshold is significantly increased in patients older than 60 years, which suggests that they may have a decreased sensitivity to

TABLE 1. Demographics and Injury Characteristics of Subjects

Demographics	Total	Ketamine	Placebo	*p* Value
Patients, n (%)	59 (100)	30 (50.8)	29 (49.2)	1.00
Sex, n (%) Male	35 (59.3)	15 (50)	20 (69)	0.19
Age: median (IQR), y	74 (65–96)	75 (65–90)	73 (65–96)	0.76
BMI, median (IQR)	27.7 (20.6–39.7)	29.2 (22.5–38)	26.8 (20.6–39.7)	0.35
No. rib fractures mean (SD)	6.3 (3.0)	6.1 (2.6)	6.5 (3.4)	0.60
Flail chest, n (%)	13 (22)	4 (13.3)	9 (31)	0.13
Chest tube, n (%)	14 (23.7)	4 (13.3)	10 (34.5)	0.07
ISS, median (IQR)	13 (4–48)	13 (4–41)	14 (9–48)	0.40
ISS >15, n (%)	24 (40.7)	10 (33.3)	14 (48.3)	0.29
AIS ≥ 2 only, n (%)	16 (27.1)	9 (30)	7 (24.1)	0.77
ICU admission, n (%)	51 (86.4)	25 (83.3)	26 (89.7)	0.71
Mechanism of injury, n (%)				0.17
MVC	20 (33.9)	9 (30)	11 (37.9)	
Fall	30 (50.8)	16 (53.3)	14 (48.3)	
MPC	2 (3.4)	1 (3.3)	1 (3.4)	
Other	7 (11.9)	4 (13.3)	3 (10.3)	
Duration of infusion, n (%)				1.00
< 12 h	1 (1.7)	1 (3.3)	0 (0)	
< 24 h	2 (3.4)	1 (3.3)	1 (3.3)	
> 36 h	53 (89.8)	26 (86.7)	27 (93.1)	

BMI, body mass index; fx, fracture; AIS, Abbreviated Injury Scale; MVC, motor vehicle crash; MPC, motor vehicle vs. pedestrian crash; AUC, area under the curve; SD, standard deviation.

pain.[24] There are several proposed mechanisms for altered pain perception in older patients; one pertinent to this study is the role of the NMDA receptor in the process.[31] The NMDA receptors are involved in the initiation and continuation of central sensitization in response to nociceptive stimuli, and hypoactivity at the receptor site results in decreased sensitization and pain sensitivity.[32,33]

Adverse effects associated with ketamine are common when utilized for induction of anesthesia or procedural sedation, but those doses are much higher (up to 4.5 mg/kg) than those used for pain management.[26] As found in other studies, we demonstrated a low rate of side effects in the ketamine group, providing additional evidence regarding the safety of LDK infusions.[34,35] Similarly, we expected a low incidence of psychomimetic effects due to the lower dose of ketamine used in this study. While not statistically significant, the incidence of oversedation, respiratory distress, and delirium were higher in the placebo group. These findings provide evidence of the benefits of LDK aside from improvements in NPS or OME; theoretically, any decrease in opioids should lower the risk of respiratory depression and delirium and may explain why each of these was higher in the placebo group.

TABLE 2. NPS and OMEs in All Subjects

Outcome	Total	Ketamine	Placebo	*p*-Value
NPS AUC, mean (SD)				
12–24 h	5.3 (1.6)	5.4 (1.9)	5.2 (1.3)	0.61
24–48 h	4.7 (1.7)	5.1 (1.7)	4.4 (1.6)	0.17
OME: median (IQR), mg				
12–24 h	22.5 (0–203)	21.3 (0–203)	30.0 (0–131)	0.41
24–48 h	30.0 (0–765)	25.0 (0–765)	44.0 (0–302)	0.19
Total	73.9 (0–988)	67.5 (0–988)	86.8 (0–376)	0.38

This study has several limitations. First and foremost, the use of NPS as the primary outcome presents challenges. Pain is subjective and difficult to assess, particularly in patients with multiple injuries. We were unable to have "thoracic pain scores" consistently recorded separate from the "global pain score" that a patient reported. Ultimately, we had to use either the thoracic or global "pain score" as recorded by the nursing staff. In addition, there was no assessment made regarding the amount of patient effort, strength of cough, or degree of "splinting" either at rest or during respiratory therapy. Another potential weakness is the lack of standardization of the pain regimen used in this study. Although there were no differences in nonopioid medications used in the two cohorts, the influence of the various combinations of medications on pain scores or OME totals could not be determined. In addition, a transition to oral narcotics was permitted to prevent increasing length of stay. Oral narcotic dosing is less variable, and the elderly demonstrate decreased ability to clear opioids,[36–38] each of which could have decreased the potential impact of LDK on daily OME. Since decreased utilization of opioids was our overall goal, future studies on the use of ketamine in trauma patients should focus on reduction in OME. Additionally, studies utilizing physiologic outcomes (such as vital capacity, incentive spirometry) or dynamic pain scores.

Finally, it should be noted that the protocol did not allow for titration of the ketamine infusion. The ketamine infusion was intentionally set at a low fixed dose of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and underdosing may have led to the lack of differences in OME and NPS between groups. A lower dose of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was empirically selected for this trial given ketamine's extensive hepatic metabolism and the concern of decreased hepatic blood flow

TABLE 3. Results of Subset Analysis

Outcome	Total	Ketamine	Placebo	*p* Value
OME ISS <15: median (IQR), mg				
12–24 hours	16.0 (0–67.8)	18.0 (0–67.8)	10.0 (0–47)	0.35
24–48 hours	15.1 (0–136.8)	18.8 (0–136.8)	15.0 (0–75)	0.60
Total	55.0 (0–300.7)	63.8 (0–300.7)	43.2 (0–177)	0.24
OME ISS ≥15: median (IQR), mg				
12–24 h	31.0 (0–203)	25.6 (0–203)	42.6 (4–131)	0.04
24–48 h	54.3 (0–765)	41.3 (0–765)	67.5 (16–302)	0.13
Total	142.0 (0–988)	97.5 (0–988)	168.0 (35–376)	0.10
NPS AUC ISS ≥15, mean (SD)				
12–24 h	5.6 (1.2)	5.8 (1.3)	5.5 (1.1)	0.59
24–48 h	5.0 (1.4)	6.0 (0.6)	4.4 (1.4)	0.01
OME Rib fx only: median (IQR), mg				
12–24 h	20.7 (0–60.4)	30.0 (0–60.4)	10.0 (0–45)	0.20
24–48 h	21.3 (0–90)	27.5 (0–90)	7.5 (0–75)	0.34
Total	63.8 (0–169)	67.5 (0–169)	38.0 (0–159)	0.24
OME ICU admits: median (IQR), mg				
12–24 h	25.4 (0–203)	22.5 (0–203)	31.9 (0–131)	0.35
24–48 h	30.0 (0–765)	20.0 (0–765)	49.7 (0–302)	0.07
Total	86.8 (0–988)	67.5 (0–988)	132.5 (0–376)	0.25

and liver function in the elderly population.[26,39] In a Cochrane review analyzing ketamine for acute postoperative pain, dosing of ketamine varied from 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[40] The heterogeneity of dosing indicates that the optimal dose of adjunct ketamine has not been determined, but inter-patient variability in response to ketamine has been reported[41] and infusion rates as low as 1.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ have been shown to improve postoperative pain control in the elderly.[42] That said, data supporting adjunct ketamine use in elderly patients are lacking, and consensus guidelines offer no guidance on the use of, or the optimal dose of, ketamine in patients older than 65 years.[43] Future studies using higher doses of ketamine or the ability to titrate a ketamine infusion based on an individual's response to the drug may improve treatment efficacy, and the lack of significant adverse side effects at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is further evidence to support increasing the ketamine dose.

CONCLUSION

Despite the current emphasis on multimodal analgesic therapy, opioids still remain the foundation for treatment of rib fracture related pain.[12] Given the side effects, dependency issues, and nationwide opioid crisis, we must continue to seek alternate medications to treat pain in the injured patient.[44]

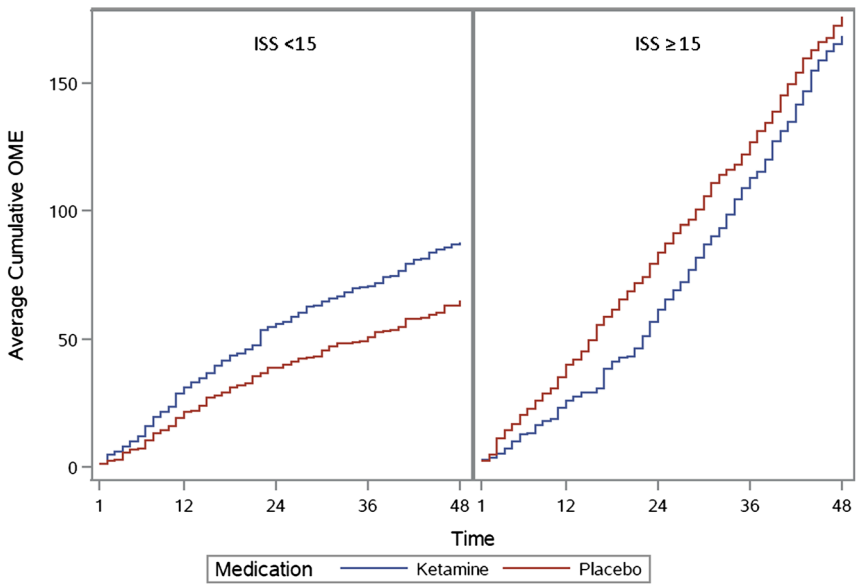

Figure 2. Total OME in ISS subset.

TABLE 4. Secondary Outcomes

Outcome	Total	Ketamine	Placebo	*p* Value
Length of stay, median (IQR)	5 (2–109)	5 (2–50)	6 (2–109)	0.89
Epidural placed, n (%)	10 (16.9)	4 (13.3)	6 (20.7)	0.51
Unplanned ICU admit, n (%)	1 (1.7)	0 (0)	1 (3.4)	0.49
Respiratory failure, n (%)	0 (0)	0 (0)	0 (0)	1.00
Sedation, n (%)	3 (5.1)	1 (3.3)	2 (6.9)	0.61
Hallucinations, n (%)	4 (6.8)	2 (6.7)	2 (6.9)	1.00
Delirium, n (%)	4 (7.1)	1 (3.6)	3 (10.7)	0.61

We report the results of a randomized double-blind placebo-controlled trial of LDK in multiply injured elderly patients with three or more rib fractures. Although there was no difference in NPS or OME for the entire cohort, we noted a reduction in OME in severely injured patients (ISS ≥ 15). Low-dose ketamine may result in decreased opioid consumption within a group of severely injured patients, but additional studies will be necessary to confirm this finding.

AUTHORSHIP

The overall project design was performed by N.W.K., T.W.C., K.M.D., and J.S.P. The literature search was a joint effort of all authors included on the trial. Data collection was performed by N.W.K., J.J., W.J.P., K.B., and T.W. C. Sample size calculation, statistical methodology, and data analysis was performed by A.S. and L.R. Data interpretation was performed by all listed authors on the study. Writing of the article and critical revision of the article was performed by all the listed authors.

DISCLOSURE

None of the authors have any financial and personal relationships with other people or organizations that could potentially and inappropriately influence their work and conclusions on this topic. T.W.C. and N.W.K. are paid consultants for InnoVital Systems Inc. but these disclosures are not relevant to this study. The remaining authors have no financial disclosures. This trial was funded through internal support from the Department of General Surgery at the Medical College of Wisconsin.

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