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

Thomas W. Carver, MD, Nathan W. Kugler, MD, Janelle Juul, PharmD, William J. Peppard, PharmD, Karin Madsen Drescher, MD, Lewis B. Somberg, MD, Aniko Szabo, PhD, Ziyan Yin, MS, *and* **Jasmeet S. Paul, MD***, Milwaukee, Wisconsin*

AAST Continuing Medical Education Article

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint providership of the American College of Surgeons and the American Association for the Surgery of Trauma. The American College Surgeons is accredited by the ACCME to provide continuing medical education for physicians.

AMA PRA Category 1 Credits™

The American College of Surgeons designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Of the *AMA PRA Category 1 Credit*™ listed above, a maximum of 1 credit meets the requirements for self-assessment.

Credits can only be claimed online

American College of Surgeons
Inspiring Quality:
Highest Standards, Better Outcomes

100+*years*

Objectives

After reading the featured articles published in the *Journal of Trauma and Acute Care Surgery*, participants should be able to demonstrate increased understanding of the material specific to the article. Objectives for each article are featured at the beginning of each article and online. Test questions are at the end of the article, with a critique and specific location in the article referencing the question topic.

Claiming Credit

To claim credit, please visit the AAST website at http://www.aast.org/ and click on the "e-Learning/MOC" tab. You must read the article, successfully complete the post-test and evaluation. Your CME certificate will be available immediately upon receiving a passing score of 75% or higher on the post-test. Post-tests receiving a score of below 75% will require a retake of the test to receive credit.

Disclosure Information

In accordance with the ACCME Accreditation Criteria, the American College of Surgeons, as the accredited provider of this journal activity, must ensure that anyone in a position to control the content of *J Trauma Acute Care Surg* articles selected for CME credit has disclosed all relevant financial relationships with any commercial interest. Disclosure forms are completed by the editorial staff, associate editors, reviewers, and all authors. The ACCME defines a `commercial interest' as "any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients." "Relevant" financial relationships are those (in any amount) that may create a conflict of interest and occur within the 12'months preceding and during the time that the individual is engaged in writing the article. All reported conflicts are thoroughly managed in order to ensure any potential bias within the content is eliminated. However, if you'perceive a bias within the article, please report the circumstances on the evaluation form.

Please note we have advised the authors that it is their responsibility to disclose within the article if they are describing the use of a device, product, or drug that is not FDA approved or the off-label use of an approved device, product, or drug or unapproved usage.

Disclosures of Significant Relationships with Relevant Commercial Companies/Organizations by the Editorial Staff

Ernest E. Moore, Editor: PI, research support and shared U.S. patents Haemonetics; PI, research support, Instrumentation Laboratory, Inc.; Co-founder, Thrombo Therapeutics. Associate Editors David Hoyt, Ronald V. Maier and Steven Shackford have nothing to disclose. Editorial staff and Angela Sauaia have nothing to disclose.

Author Disclosures

Thomas W. Carver, MD and Nathan W. Kugler, MD – a grant from InnovVital.

Reviewer Disclosures

The reviewers have nothing to disclose.

Cost

For AAST members and *Journal of Trauma and Acute Care Surgery* subscribers there is no charge to participate in this activity. For those who are not a member or subscriber, the cost for each credit is $25.

System Requirements

The system requirements are as follows: Adobe® Reader 7.0 or above installed; Internet Explorer® 7 and above; Firefox® 3.0 and above, Chrome® 8.0 and above, or Safari™ 4.0 and above.

Questions

If you have any questions, please contact AAST at 800-789-4006. Paper test and evaluations will not be accepted.

From the Division of Trauma and Acute Care Surgery, Department of Surgery (T.W.C.), Division of Trauma and Acute Care Surgery, Department of Surgery (N.W.K.), Division of Critical Care Pharmacy, Department of Pharmacy (J.J.), Division of Trauma and Acute Care Surgery, Department of Surgery (W.J.P.), Division of Regional Anesthesia and Acute Pain Management, Department of Anesthesia (K.M.D.), Division of Trauma and Acute Care Surgery, Department of Surgery (L.B.S.), Division of Biostatistics (A. S., Z.Y.), and Division of General Surgery, Department of Surgery (J.S.P.), Medical College of Wisconsin, Milwaukee, Wisconsin.

Presented at the 77th Annual Meeting of the American Association for Surgery of Trauma, September 26–29, 2018 in San Diego, California.

Address for reprints: Thomas W Carver, MD, Division of Trauma and Acute Care Surgery, Department of Surgery, Medical College of Wisconsin, 8701 Watertown Plank Rd. Milwaukee, WI 53226; email: tcarver@mcw.edu.

DOI: 10.1097/TA.0000000000002103

BACKGROUND: Rib fractures occur in up to 40% of trauma patients and are associated with increased mortality. Opiate-based pain regimens remain the cornerstone of rib fracture management; however, concerns around opioids have fostered interest in alternative analgesics. Ketamine is currently being used in lieu of opioids, but little evidence exists supporting its use within the trauma population.

METHODS: A prospective, randomized, double-blind placebo-controlled trial of adult patients with three or more rib fractures admitted to a Level I trauma center was conducted. Exclusion criteria included age older than 64 years, Glasgow Coma Scale score less than 13, and chronic opiate use. The experimental arm received low-dose ketamine (LDK) at 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ while the placebo cohort received an equivalent rate of 0.9% normal saline. All infusions were continued for 48 hours. The primary outcome was reduction in numeric pain score (NPS) during the first 24 hours. Secondary outcomes studied included oral morphine equivalent (OME) utilization, length of stay, epidural rates, pulmonary complications, and adverse events.

RESULTS: Forty-five (49%) of 91 patients were randomized to the experimental arm. Both groups were similar in makeup. Overall, 74.7% were male, had a median age of 49 years, and an Injury Severity Score (ISS) of 14. Low-dose ketamine was not associated with a significant reduction in 24-hour NPS or OME totals. Subgroup analysis of 45 severely injured patients (ISS, >15) demonstrated that LDK was associated with a significant reduction in OME utilization during the first 24 hours (35.7 vs. 68, $p = 0.03$), 24 hours to 48 hours (64.2 vs. 96, $p = 0.03$), and overall (152.1 vs. 198, $p = 0.048$). No difference in other secondary outcomes or adverse events was noted.

CONCLUSION: Low-dose ketamine failed to decrease NPS or OME within the overall cohort, but a decrease in OME was observed among patients with an ISS greater than 15. Confirmatory studies are necessary to determine if LDK is a useful adjunct among severely injured patients. (*J Trauma Acute Care Surg.* 2019;86: 181–188. Copyright © 2018 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic study, level II.

KEY WORDS: Ketamine; trauma; rib fractures; pain management; opioids.

Rib fractures are present in nearly half of patients with multiple injuries and are a major contributor to mortality in this patient group.[1,2] Management of rib fractures has consistently focused on aggressive pain treatment, which allows the patient to perform effective respiratory therapy in an attempt to decrease the risk of pulmonary complications.[1,3] Decades of research have gone into determining the optimal treatment for patients with rib fractures, including a variety of pain medications and regional anesthetic techniques, such as intercostal blocks and epidurals.[4,5] Unfortunately, previous meta-analyses demonstrated that epidurals have no effect on mortality[6] and that not every patient is a candidate for epidural placement.[6,7] Even with the use of epidurals and multimodal analgesic therapy, opioids continue to anchor rib fracture pain management protocols.[6,8–10] The side effects and dependency issues associated with opioids have created an interest in the use of nonnarcotic medications, and ketamine is increasingly being used as an alternative to opioids.[11,12]

Our institutional rib fracture guideline utilizes regional anesthesia when scheduled nonopioids and as-needed opioids 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 its use. Anecdotally, we noted that patients placed on LDK required lower opioid doses to achieve adequate analgesia; 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 regarding the role of ketamine in trauma patient care remain retrospective in nature and subject to those same limitations.[12,14]

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.

METHODS

Study Design

A prospective, randomized, double-blind, placebo-controlled trial utilizing LDK as an analgesic adjunct among adult trauma patients was performed at Froedtert Memorial Lutheran Medical Center, an American College of Surgeons verified Level I trauma center that serves the urban and suburban populations of Milwaukee, WI. From August 2015 to December of 2017, all adult blunt trauma patients with three or more rib fractures were screened for eligibility in this study. Patients were excluded from enrollment for any of the following: (1) age, 65 years or older; (2) history of adverse reaction to ketamine therapy; (3) Glasgow Coma Scale, 13 or less; (4) active acute coronary syndrome; (5) severe hypertension defined by prolonged systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 100 mm Hg; (6) current use of monoamine oxidase inhibitors; (7) chronic opioid use defined by 30 mg or greater oral morphine equivalents (OME) per day for 3 weeks or longer; (8) current substance abuse with opiates (prescription and/or heroin) or ketamine; (9) inability to communicate with staff; (10) history of psychosis; (11) use of three or more psychotropic medications; (12) active delirium/dementia; (13) glaucoma; (14) pregnancy; and (15) 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 (NCT 02432456) and funded through institutional grant funding (Research Affairs Committee grant 3307034).

Randomization and Study Protocol

Following informed consent and enrollment, patients were randomized through the Investigational Drug Services to receive an infusion of either LDK (2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or similar volume of

placebo (0.9% sodium chloride), the dosing of which was based on ideal body weight. 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 departmental thoracic trauma pain management pathway which includes opiate and non–opiate-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 was a reduction in numeric pain scores (NPS) at 24 hours after initiation of the infusion as calculated using an area under the curve for the pain trajectory during the 12-hour to 24-hour period. Our institution utilizes a standardized 11-point NPS, which is assessed per unit policy at regular intervals and before/after any pain intervention. Numeric pain score 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 the pain scores. The use of all pain management medications was recorded, and opiate-based medications were standardized to OME for analysis.

Secondary outcomes for the trial included reduction in NPS at 48 hours, opioid consumption in OME at 24 hours and 48 hours, total OME, intensive care unit (ICU) and hospital length of stay, epidural placement rate, 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 tool. Demographics, including age, mechanism of injury, sex, chest Abbreviated Injury Score, Injury Severity Score (ISS), number of rib fractures, presence of a flail chest or pulmonary contusion, and tobacco use, were also recorded.

Sample Size Calculation and Interim Blinded Analysis

A clinically significant reduction in NPS was defined as a two-point reduction on the 11-point scale.[15–17] The original

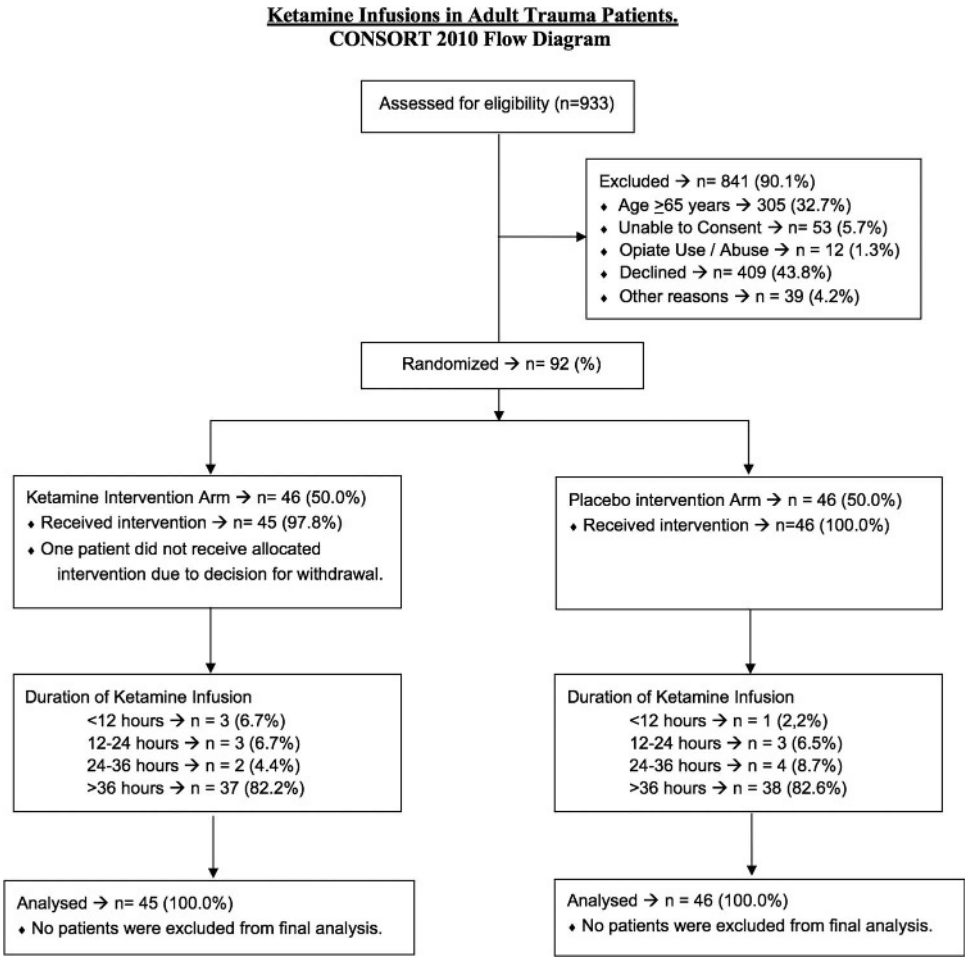

Figure 1. CONSORT study enrollment overview.

TABLE 1. Demographics and Injury Characteristics of Subjects

Demographics	Total	Ketamine	Placebo	*p*
Patients, n (%)	91 (100)	45 (49.4)	46 (50.6)	1.00
Sex, n (%)				1.00
Male	68 (74.7)	34 (75.6)	34 (73.9)	
Female	23 (25.3)	11 (24.4)	12 (26.1)	
Age, median (IQR)	49 (18–65)	46 (18–61)	50 (20–65)	0.10
BMI, median (IQR)	29 (18.3–51.7)	29 (18.3–51.7)	28.5 (18.7–50)	0.83
No. rib fractures mean (SD)	6.4 (3.2)	6.4 (3.2)	6.4 (3.3)	0.95
Flail chest, n (%)	26 (28.6)	15 (57.7)	11 (42.3)	0.36
Chest tube, n (%)	32 (35.2)	14 (43.8)	18 (56.2)	0.51
ISS, median (IQR)	14 (9,38)	17 (9,34)	13 (9,38)	0.29
ISS >15, n (%)	45 (49.5)	26 (57.8)	19 (42.2)	0.29
AIS ≥ 2 only, n (%)	24 (26.4)	9 (37.5)	15 (62.5)	0.24
ICU admission, n (%)	46 (50.5)	21 (45.7)	25 (54.3)	0.53
Mechanism of injury, n (%)				0.93
MVC	41 (45.1)	21 (46.7)	20 (43.5)	
Fall	25 (27.5)	11 (24.4)	14 (30.4)	
MCC	15 (16.5)	8 (17.8)	7 (15.2)	
Other	9 (9.9)	5 (11.1)	5 (10.9)	
Duration of infusion, n (%)				0.72
< 12 hours	4 (4.4)	3 (6.7)	1 (2.2)	
< 24 hours	10 (11)	6 (13.4)	4 (8.7)	
> 36 hours	75 (82.4)	37 (82.2)	38 (82.6)	

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

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. Given differences in patient populations, there was concern that the actual variability would be different, thus an internal pilot was incorporated into the study.[18] When 50% of the patients had been randomized, the primary outcome was evaluated. A blinded sample size recalculation was performed using the original target effect size of two-point difference and the observed standard deviation of the pooled data adjusted for the expected treatment difference using Zucker's formula:

$$S^2_{adj} = S^2 - \left(n_1 * d^2\right) / [n_1 - 1]$$

where $d = 2$ is the expected treatment difference. Recruitment did not stop during the recalculation phase. Sample size revision did not allow for a decrease of the study sample size, only for a potential increase. This approach maintains the overall type I error rate but protects against moderate underestimation of the between-patient variability. The interim sample size recalculation resulted in a revised sample size of 82 total patients to achieve 80% power.

TABLE 2. NPS and OMEs in All Subjects

Outcomes	Total	Ketamine	Placebo	*p*
NPS AUC, mean (SD)				
12–24 hours	5.9 (2.0)	5.7 (2.1)	6.1 (2)	0.36
24–48 hours	5.7 (2.0)	5.6 (2)	5.8 (1.9)	0.77
OME, mean (SD), mg				
12–24 hours	57.3 (57.1)	50.5 (42.1)	64.1 (68.4)	0.79
24–48 hours	99.6 (157.2)	85.9 (105.9)	113.0 (195.3)	0.63
Total	207.5 (227.2)	184.2 (144.4)	230.4 (285.9)	0.98

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 are presented by

TABLE 3. Results of Subset Analysis

Outcomes	Total	Ketamine	Placebo	*p*
OME ISS < 15, mg (SD)				
12–24 hours	46.0 (48.3)	50.4 (35.2)	42.8 (56.1)	0.10
24–48 hours	80.1 (107.4)	84.4 (72.8)	77.1 (127.5)	0.28
Total	172.0 (183.0)	189.4 (140.3)	161.3 (209.7)	0.12
OME ISS ≥ 15, mg (SD)				
12–24 hours	69.0 (63.3)	50.5 (47.2)	94.3 (74.3)	0.03
24–48 hours	119.5 (194.9)	87.0 (126.1)	164.1 (259.0)	0.03
Total	242.9 (262.3)	180.3 (150.0)	328.5 (351.4)	0.048
OME rib fx only, mg (SD)				
12–24 hours	36.3 (36.3)	54.0 (48.9)	25.7 (22.0)	0.11
24–48 hours	53.8 (55.3)	80.1 (73.1)	38.0 (35.5)	0.14
Total	135.1 (131.9)	199.0 (177.1)	96.8 (80.4)	0.11
OME ICU admits, mg (SD)				
12–24 hours	73.2 (68.1)	62.8 (50.6)	85.0 (83.7)	0.62
24–48 hours	169.9 (283.5)	111.4 (138.8)	169.9 (283.5)	0.68

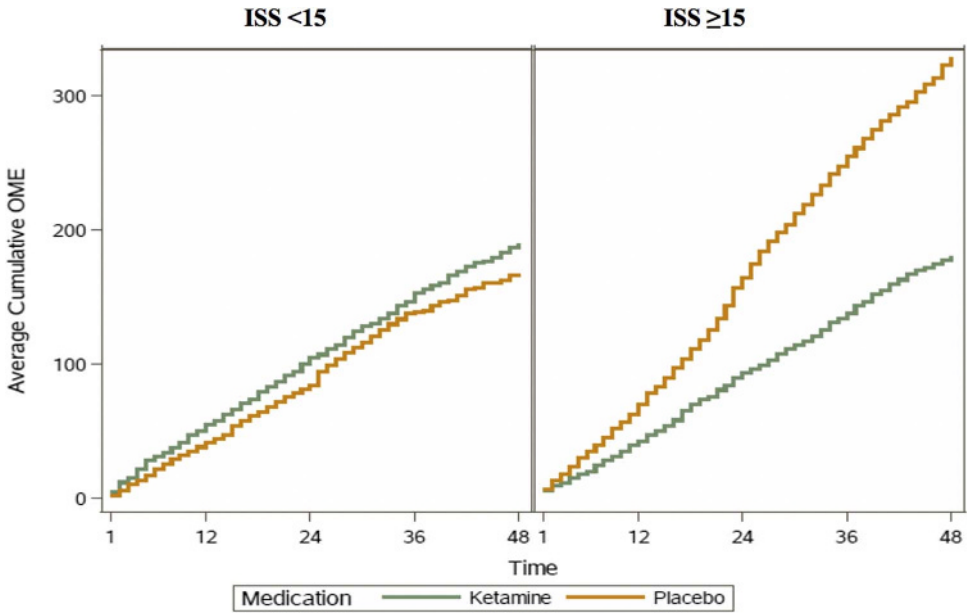

Figure 2. Total OME in subset of ISS.

frequencies and percentages, with Fisher's exact test for between-group comparisons. Numeric data with approximately symmetric distribution, including the primary outcome, was summarized using mean and standard deviation, and compared between groups using Student's two-sample *t*-test. Skewed outcomes, such as length of stay and cumulative OME, and ordinal measures, such as ISS, were summarized via median and interquartile range (IQR) with Wilcoxon's rank-sum test for comparisons. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Ninety-two patients were enrolled, and 91 randomized to either the placebo or experimental (LDK) arm. Forty-five (49%) patients were randomized to the experimental arm (Fig. 1). Overall, 74.7% of patients were male, had a median age of 49 years (IQR, 18.0–65.0), and had a median ISS of 14 (IQR, 9.0–38.0). Motor vehicle collision was the most common mechanism of injury (45.7%). There were no significant differences in demographics or injury characteristics in either group (Table 1). Four (4.4%) patients completed less than 12 hours of the infusion, 10 (11%) patients completed less than 24 hours, and 75 (82.4%) patients completed more 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, nonsteroidal anti-inflammatory medications, and muscle relaxants are typically prescribed unless contraindicated. There was no statistical difference in the use of any of these medications in our patient population. Similarly, intercostal nerve blocks were performed on 11 (24.4%) LDK patients and 13 (28.3%) in the placebo arm ($p = 0.81$).

Regarding the primary outcome, no difference was noted in NPS at 0 hour to 12 hours, 12 hours to 24 hours, 24 hours, or 48 hours. Similarly, no difference was noted in OME totals at 12 hours, 24 hours, or 48 hours (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, ICU versus ward admissions, and those with an ISS greater than 15 (Table 3). While LDK failed to decrease NPS within any of those patient groups (data not shown), a significant reduction in OME was noted in severely injured (ISS > 15) patients receiving LDK (Fig. 2). Other secondary outcomes are reported in Table 4. Of note, adverse events were not significantly different between groups nor was the rate of epidural placement (15.6% vs. 6.5% of LDK and placebo patients, respectively.)

TABLE 4. Secondary Outcomes

Outcomes	Total	Ketamine	Placebo	*p*
Length of stay, median (IQR)	5.0 (1.0–33.0)	5.0 (1.0–20.0)	4.0 (1.0–33.0)	0.83
Epidural placed, n (%)	10 (10.9)	7 (15.6)	3 (6.5)	0.18
Unplanned ICU admit, n (%)	3 (3.3)	0 (0)	3 (6.5)	0.24
Respiratory failure, n (%)	5 (5.5)	2 (4.4)	3 (6.5)	1.00
Sedation, n (%)	5 (5.6)	1 (2.2)	4 (8.7)	0.36
Hallucinations, n (%)	1 (2.2)	0 (0)	1 (2.2)	1.00

DISCUSSION

Our article presents the results of the first randomized, double-blinded controlled trial of LDK for the treatment of pain in trauma patients with at least three rib fractures. This trial was pragmatically designed to include not just patients with isolated rib fractures, but the multiple-injured population 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). Interestingly, the OME reduction was not related to admission to the ICU or general trauma ward, which suggests that our findings are related to 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.

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.[19] As noted in other studies, we also demonstrated a low rate of other side effects in the ketamine group, which provides additional evidence regarding the safety of LDK infusions.[20,21] Similarly, we expected a low incidence of psychomimetic effects due to the dose of ketamine used in this study, and the incidence of oversedation and respiratory distress were both higher (but not significantly) 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 may explain why more episodes of respiratory distress were noted in the placebo group.

Another benefit of ketamine, aside from its direct analgesic effects, is the action that ketamine plays in the physiologic response to pain.[22] Painful stimuli activate NMDA receptors and produce hyperexcitability of the dorsal root neurons, which leads to central sensitization, "wind-up" phenomenon, and pain memory.[22] As a noncompetitive antagonist of NMDA receptors, ketamine can prevent central sensitization caused by stimulation of peripheral nociception and block the "wind-up" phenomenon by blunting the excitatory neurotransmitter glutamate.[11] These effects are not completely understood but may be relevant when one considers that a single dose of ketamine at the time of surgery has been shown to limit the future development of chronic pain and to reduce neuropathic pain.[23]

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 tried to have "thoracic pain scores" recorded separately from the "global pain score" that a patient reported. However, separating out pain scores was inconsistent despite several study protocol information sessions and, ultimately, we had to use either the thoracic or global "pain score" as recorded by the nursing staff. Additionally, this study allowed the treating provider to use any medications within the multimodal rib fracture pain management order set. Since there was no difference in the medications prescribed within the groups, we do not think this had any impact on the study results but cannot say this definitively. Not standardizing the pain regimen is another potentially confounding variable. Intravenous opioid medications were recommended while the investigational drug was infusing, but a transition to oral narcotics was permitted to prevent increasing length of stay. Oral narcotic doses and frequency are less variable, which could decrease the effect on OME.

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 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and underdosing may have led to the lack of differences in OME and NPS between groups. 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 1 $mg \cdot kg^{-1} \cdot min^{-1}$.[22] The heterogeneity of dosing indicates that the optimal dose of adjunct ketamine has not been determined, but interpatient variability in response to ketamine has been reported.[24] Ketamine appears to work on several receptors including NMDA, cholinergic, and monoaminergic receptors, any of which may affect a patient's analgesic response to ketamine.[25] 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 demonstrate a significant benefit.

CONCLUSION

Despite the current emphasis on multimodal analgesic therapy, opioids still remain the foundation for treatment of rib fracture related pain.[6] Given the side effects, dependency issues, and nationwide opioid crisis, we must continue to seek alternate medications to treat pain in the injured patient.[26] We report the results of the first randomized double-blind placebo-controlled trial of LDK in multiply injured 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). LDK 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., 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. and T.W.C. Sample size calculation, statistical methodology, and data analysis was performed by A.S. and Z.Y. 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.
The authors have no conflicts of interest.
Source of Funding: This trial was funded through institutional grant funding (Research Affairs Committee grant 3307034).
Financial Disclosures: T.W.C. and N.W.K. are paid consultants for InnoVital Systems Inc. The remaining authors have no financial disclosures.

REFERENCES

1. Brasel KJ, Guse CE, Layde P, Weigelt JA. Rib fractures: relationship with pneumonia and mortality. *Crit Care Med*. 2006;34(6):1642–1646.
2. Flagel BT, Luchette FA, Reed RL, Esposito TJ, Davis KA, Santaniello JM, Gamelli RL. Half-a-dozen ribs: the breakpoint for mortality. *Surgery*. 2005; 138(4):717–723; discussion 723–5.

3. Peek J, Smeeing DPJ, Hietbrink F, Houwert RM, Marsman M, de Jong MB. Comparison of analgesic interventions for traumatic rib fractures: a systematic review and meta-analysis. *Eur J Trauma Emerg Surg*. 2018.
4. Thiruvenkatarajan V, Cruz Eng H, Adhikary SD. An update on regional analgesia for rib fractures. *Curr Opin Anesthesiol*. 2018;31(5):601–607.
5. Bulger EM, Edwards T, Klotz P, Jurkovich GJ. Epidural analgesia improves outcome after multiple rib fractures. *Surgery*. 2004;136(2):426–430.
6. Karmakar MK, Ho AM. Acute pain management of patients with multiple fractured ribs. *J Trauma*. 2003;54(3):615–625.
7. Bugaev N, Breeze JL, Alhazmi M, Anbari HS, Arabian SS, Holewinski S, Rabinovici R. Magnitude of rib fracture displacement predicts opioid requirements. *J Trauma Acute Care Surg*. 2016;81(4):699–704.
8. Galvagno SM Jr, Smith CE, Varon AJ, Hasenboehler EA, Sultan S, Shaefer G, To KB, Fox AD, Alley DE, Ditillo M, et al. Pain management for blunt thoracic trauma: a joint practice management guideline from the eastern Association for the Surgery of Trauma and Trauma Anesthesiology Society. *J Trauma Acute Care Surg*. 2016;81(5):936–951.
9. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' committee on regional anesthesia, executive committee, and administrative council. *J Pain*. 2016; 17(2):131–157.
10. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the in tensive care unit. *Crit Care Med*. 2013;41(1):263–306.
11. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth*. 2011;58(10): 911–923.
12. Walters MK, Farhat J, Bischoff J, Foss M, Evans C. Ketamine as an analgesic adjuvant in adult trauma intensive care unit patients with rib fracture. *Ann Pharmacother*. 2018;52(9):849–854.
13. Mulllins C, Kugler N, Luc M, Peppard W. Adjunct ketamine infusions provide improved acute traumatic and post-surgical pain management. *Crit Care Med*. 2015;43(12):283.
14. Losing AK, Jones JM, Keric A, Briggs SE, Leedahl DD. Ketamine infusion therapy as an alternative pain control strategy in patients with multi-trauma including rib fracture; case report and literature review. *Bull Emerg Trauma*. 2016;4(3):165–169.
15. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2):149–158.
16. Holdgate A, Asha S, Craig J, Thompson J. Comparison of a verbal numeric rating scale with the visual analogue scale for the measurement of acute pain. *Emerg Med*. 2003;15(5–6):441–446.
17. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Ann Emerg Med*. 2001;38(6):633–638.
18. Friede T, Kieser M. Sample size recalculation in internal pilot study designs: a review. *Biom J*. 2006;48(4):537–555.
19. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. *Clin Pharmacokinet*. 2016;55(9):1059–1077.
20. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. *Pain Med*. 2015;16(2):383–403.
21. Pruskowski KA, Harbourt K, Pajoumand M, Chui SJ, Reynolds HN. Impact of ketamine use on adjunctive analgesic and sedative medications in critically ill trauma patients. *Pharmacotherapy*. 2017;37(12):1537–1544.
22. Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). *Acta Anaesthesiol Scand*. 2005;49(10):1405–1428.
23. Sleigh J, Harvey M, Voss L, Denny B. Ketamine—more mechanisms of action than just NMDA blockade. *Trends Anaes Crit Care*. 2014;4(2–3):76–81.
24. Rabben T, Skjelbred P, Oye I. Prolonged analgesic effect of ketamine, an *N*-methyl-D-aspartate receptor inhibitor, in patients with chronic pain. *J Pharmacol Exp Ther*. 1999;289(2):1060–6.
25. Strigo IA, Duncan GH, Bushnell MC, Boivin M, Wainer I, Rodriguez Rosas ME, Persson J. The effects of racemic ketamine on painful stimulation of skin and viscera in human subjects. *Pain*. 2005;113(3):255–264.
26. Chaudhary MA, Scully R, Jiang W, Chowdhury R, Zogg CK, Sharma M, Ranjit A, Koehlmoos T, Haider AH, Schoenfeld AJ. Patterns of use and factors associated with early discontinuation of opioids following major trauma. *Am J Surg*. 2017;214(5):792–797.

DISCUSSION

Dr. David A. Spain (Stanford, California): Thank you, Drs. Rotondo and Reilly and the Program Committee for the privilege of discussing this outstanding work.

I hope you noticed that Dr. Kugler was up here at the ready as the prior discussion was closing. It's like having short turnover time in the OR – doesn't always happen, but it's beautiful when you get it. I had the privilege of hearing Dr. Kugler present this work at the Wisconsin State COT Chapter Meeting a few months ago, and he did an excellent job today as well.

The group from Medical College of Wisconsin are to be congratulated for doing what few of us have: conducting a prospective, randomized, blinded trial. The amount of work required to pull this off is incredible, and they are really to be commended. And I would like to thank Dr. Kugler for his excellent presentation. I have just a few quick questions for you, Dr. Kugler:

1. At our hospital, the pain scores by convention are recorded by the nurses with the patient at rest; if you're in bed, not doing a whole lot, you may not have a lot of pain. Do you have any data on the activity level of your patients in these two groups? Were patients on ketamine more likely to be up and walking around?

2. Did you look at respiratory function in these patients? We have been using inspiratory volumes with an incentive spirometer to determine if we have good pain control, and it seem to correlate. Do you have any experience with this?

3. You mentioned that this is a low to medium dose of ketamine. Will your group continue these efforts, maybe with a dose escalation protocol?

4. And then, finally, rib fractures are very challenging and may take a long time for patients to recover their projected normal activities. You have gone through all this effort to set up a mechanism to study these patients and shown you can conduct prospective randomized trials; so what's next on your research agenda for these patients?

With both the nationwide opioid crisis and the opioid shortage, non-narcotic alternatives to pain control are becoming increasingly important. The group from the Medical College of Wisconsin are to be congratulated for tackling such a difficult problem and I look forward to their continued efforts in this area. Thank you very much.

Dr. Kimberley A. Davis (New Haven, Connecticut): This was a beautifully presented study. I have a quick question for you. Have you adjusted your pain regimen or standardized your protocols, particularly in the more severely injured patients?

Dr. Eileen M. Bulger (Seattle, Washington): Just a quick question. I'm concerned about the 43 percent of your patients that declined enrollment in the study. Did you look at that group to see if they are any different than the cohort that you studied?

Dr. Doulas J. E. Schuerer (St. Louis, Missouri): Again, trying to be brief, I was curious about resource utilization. When we use ketamine, it's usually on people who can't get the other type

of drips or are narcotic users, but they have to stay in the ICU while on the ketamine drip; as opposed to epidural when they can be on the floor. Does this protocol increase your use of ICUs?

Dr. Krista L. Kaups (Fresno, California): I'm curious to know why you excluded the patients over 65. Sometimes those are the most challenging patients to develop pain regimens for, so it would have made sense to include those patients.

Dr. Walter L. Biffl (San Diego, California): Very nicely done study. Quick question and comment. How did the morphine requirement translate to the post-discharge environment? Did you do follow-up?

And I think a lot of people in this room probably saw a paper published in the last year in the *Annals* about spin in randomized trials that are negative, and this was a negative trial – you found a difference in a sub-group of a secondary outcome – so, your conclusion in the abstract, which a lot of people will limit their reading to that, I would temper it a little bit. I don't think we've demonstrated it's a useful adjunct yet. Congratulations, again.

Dr. William S. Hoff (Bethlehem, Pennsylvania): Just to take it a step further from my colleagues' discussions. Two of your exclusions were some of the more challenging patients that we have: the elderly and the chronic opioid abuser. Do you have any plans now that you have these results to perhaps look at those specific populations? Thank you.

Dr. Nathan Kugler (Milwaukee, Wisconsin): Thank you for the wonderful questions. So, should I address these we'll start at the top.

So, pain scores in terms of resting versus dynamic at our institution are certainly a challenge, as I think they are at most institutions. We relied heavily on the nurses in terms of reporting all pain scores.

We were unable to tease out, even in a prospective fashion, whether or not these were all up and ambulating versus sitting down.

I think that's a focus of a future study that we're looking to incorporate, in terms of are patients able to get up and move around easier with this low-dose ketamine component.

Certainly, we know that all of our patients are enrolled with early physical therapy and early ambulation is a part of all of those patients' care throughout the hospital stay, but unfortunately that data, we were unable to look at this separately.

With respect to respiratory function, Incentive Spirometry is certainly one of the things that patients are encouraged to utilize by both the nurses as well as our providers. In this study, however, we utilized vital capacity, which is an indexed measure based off of each patient.

All patients enrolled in the study had chest trauma monitoring protocol, which is a standardized protocol utilized in our institution, that is a respiratory therapist-driven protocol.

What we did find when we looked at the vital capacities between the separate cohorts is that there was no significant difference at the initial onset of vital capacity between the placebo and the ketamine group. And as we followed it through, we did not see any statistically significant difference between the vital capacities achieved while on the infusion.

With respect to the ketamine dosage that was utilized within the trial, we relied on our anesthesia colleagues, which we'll sort of talk about this in a different component, to help guide the study, as they are sort of the masters of ketamine at our institution and the gatekeepers to utilization in the hospital.

The group that we worked with had limited experience with this as an analgesic, particularly in a trauma patient population, so the dose that was fixed was based on a retrospective study that we looked at that appeared to be safe as well as predominantly effective.

Since the sort-of onset of this trial, they've become a lot more comfortable with utilization of ketamine, and thus they've started to increase their doses, even just since this trial was finished.

With respect to the future directions for this, I think that we have isolated a group within our sub-group analysis that suggest that severely injured patients may have a potential benefit to the use of low-does ketamine.

We utilized rib fractures as a proxy to severely injured patients, and it was of our interest due to the complexity of managing rib fracture patients' pain. Certainly moving forward, looking at severely injured patients as a different cohort as a whole, will be a key and a challenge to designing the future trials of this.

With respect to why a patient declined enrollment within the study, so this was difficult to assess, but for the most part, there seemed to be a large portion of patients who were unfamiliar with the drug or had concerns given the drug.

Patients were approached in the Emergency Department in an attempt to enroll them early within a 12-hour time frame to start the drug, which may have been a limiting factor, given, sort of, they just experienced a trauma, and now they're being approached about a research study.

With respect to ketamine and ICU utilization, so, when we looked at our disposition from the Emergency Department, we found there was no significant difference between ICU and floor dispositions between the placebo versus the ketamine group.

Our institution does allow the utilization of a ketamine infusion at a fixed dose on the floor, so we did not require ICU admission for all of these patients, unless they needed ICU admission for other injury-related purposes.

With respect to the question of why to exclude patients over the age of 65, at our institution, we have two separate chest trauma monitoring and thoracic management protocols based on age.

Age of 65 or greater has a different pain medication regimen as well as some different adjuncts; thus, we felt that it was important to separate these two out so that we had a consistent study group.

We did, in fact, perform the same exact trial within the cohort at 65 years or older, which that trial has now concluded at the same time as this, but that data is still being analyzed, so hopefully we'll have that to follow.

With respect to transition to post-discharge and whether or not this affected the overall requirements for patients and follow-up, we chose not to look at how much patients were discharged on due to the fact that this is somewhat provider-dependent; however, we have a subsequent, an additional trial that's going on to look at the quality of life as well as their overall outcomes.

Thank you, and I'd be happy to take any questions after.