Ketamine infusion for pain control in severely injured patients: Results of a randomized controlled trial

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BACKGROUND: Opiate-based pain regimens remain the cornerstone of pain management following traumatic injury, but issues related to opioids have driven research into alternative analgesics. Adjunctive ketamine has been increasingly used to decrease opioid use, but little evidence exists to support its efficacy within the trauma population.

METHODS: A prospective, randomized, double-blind placebo-controlled trial of severely injured (Injury Severity Score [ISS], ≥15) adult patients (aged 18–64 years) admitted to a Level 1 trauma center was conducted. Exclusion criteria included Glasgow Coma Scale score of <14, ISS of <15, pregnancy, and chronic opiate use. All patients were prescribed a patient-controlled analgesia in addition to being randomized to either adjustable dose ketamine starting at 3 μg/kg/min or an equivalent rate of 0.9% normal saline. Study drug and patient-controlled analgesia titration were allowed as part of a treatment algorithm. The primary outcome was reduction in oral morphine equivalent (OME) utilization at 24 hours.

RESULTS: We performed a planned interim analysis upon reaching a predetermined enrollment goal. Forty-two of 78 patients (53.8%) were randomized to the experimental arm. Both groups were similar in makeup and had a median ISS of 22 (19, 28.5). The median OMEs in adjustable dose ketamine and placebo groups were 110.6 (55.7, 191.7) and 99.2 (50.6, 172.6), respectively ($p = 0.85$). No significant difference in OME was found in 24- to 48-hour or the entire 48-hour study period. Adjustable dose ketamine had no impact on pain scores throughout the study period when compared with placebo (4.9 vs. 4.7, $p = 0.95$). These findings met the futility cutoff, and enrollment was terminated.

CONCLUSION: Adjustable dose ketamine failed to reduce OME totals or pain scores in a severely injured trauma cohort when compared with placebo at any time point. Additional studies are necessary to determine if there is any benefit for adjuvant ketamine in different trauma subpopulations. (*J Trauma Acute Care Surg.* 2025;98: 858–866. Copyright © 2025 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level I.

KEY WORDS: Ketamine; trauma; severe injury; pain management; opioids.

Pain is an unavoidable part of trauma, but balancing adequate treatment of acute posttraumatic pain and minimizing opioid use remain a challenge for the provider caring for the injured.[1] With an estimated 6% to 12% of trauma patients persistently using opioids 6 months after an injury, a clear incentive exists to identify effective nonopioid medications for the treatment of acute pain.[2] Despite the incorporation of multimodal pain management strategies at most trauma centers, opioids are frequently administered throughout an admission, and approximately 73% of patients are discharged with an opioid prescription.[3]

The adverse effects and dependency issues associated with opioids are well-known; however, poorly controlled pain also has significant consequences,[4] including lower quality-of-life scores, impaired physical function, development of chronic pain, and increased rates of posttraumatic stress disorder.[5,6] In light of these issues, ketamine, a phencyclidine derivative with potent analgesic effects, has seen a resurgence in use over the past decade because of its safety profile and unique mechanism of action.[7–10] By antagonizing *N*-methyl-D-aspartate receptors, ketamine decreases pain transmission but also acts on opioid, cholinergic, and monoaminergic receptors, any of which may affect a patient's analgesic response.[11–13] Ketamine infusions decrease postoperative opioid use,[14–16] and their role in trauma care continues to be explored.[17–21]

Our institution uses a multimodal regimen for pain control in all trauma patients and employs regional anesthesia techniques when opioids fail to provide adequate analgesia. For those patients with poorly controlled pain despite these methods, adjustable dose ketamine (ADK) infusions are prescribed. While many publications on ketamine in trauma patient care are retrospective in nature,[17,19,22] recent randomized trials have demonstrated mixed results.[23–25] In a 2019 publication, Carver et al.[24] found that low-dose ketamine infusions did not impact pain scores or the amount of opioids used in patients with rib fractures, but a significant reduction in opioid use was seen within a subgroup of patients with severe injury (Injury Severity Score [ISS], >15). Based on those findings, a prospective, double-blind, randomized, placebo-controlled trial was performed to examine the efficacy of ADK to decrease opioid consumption in severely injured patients.

PATIENTS AND METHODS

Study Design

Using the 46% reduction in oral morphine equivalent (OME) at 24 hours in patients with an ISS of >15 demonstrated in the adult ketamine trial,[24] we hypothesized that ADK would decrease the opioid use of severely injured patients by 30% at 24 hours after initiation of the infusion. To test this hypothesis, a prospective, randomized, double-blind, placebo-controlled trial using ADK as an analgesic adjunct among adult trauma patients with severe injury (ISS, >15) was performed at an American College of Surgeons–verified Level I trauma center. From January 2021 to February 2024, all adult trauma patients (18–64 years of age) were screened for eligibility in this study. To be included, the patient had to be within 24 hours of arrival, admitted to the Trauma Service and had an estimated ISS of >15. The estimated ISS was calculated based on imaging and clinical findings (Supplemental Digital Content, Supplementary

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This study was presented at the 2024 American Association for Surgery of Trauma Annual Meeting, September 2024, in Las Vegas, Nevada.

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Data 2, http://links.lww.com/TA/E366). Patients were excluded from enrollment for any of the following: (1) age 65 years or older, (2) estimated ISS of <15, (3) history of adverse reaction to ketamine therapy, (4) Glasgow Coma Scale score of ≤13, (5) active acute coronary syndrome, (6) severe hypertension defined by prolonged systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg, (7) current use of monoamine oxidase inhibitors, (8) chronic opioid use defined by ≥30 mg OMEs per day for ≥3 weeks, (9) current substance abuse with opiates (prescription and/or heroin) or ketamine, (10) inability to communicate with staff, (11) history of psychosis, (12) active delirium/dementia, (13) glaucoma, (14) pregnancy, and (15) prisoners.

Randomization and Study Protocol

A randomization table for 152 patients was created using a web-based generator. The randomization table was divided into 38 blocks of four with two placebo and two ketamine assignments arranged randomly within each block. Unblinded pharmacy staff used the printed randomization sheet in Investigational Drug Services to implement the random allocation sequence as each patient was enrolled in the study. The randomization plan was kept in a locked study binder that was only available to unblinded pharmacy personnel. Blinded study personnel were not given access to the randomization plan until after the study was closed.

Following informed consent and enrollment, patients were randomized through the Investigational Drug Services to receive an infusion of either ADK (starting at 3 μg/kg/min) or similar volume of placebo (0.9% sodium chloride), the dosing of which was based on ideal body weight. Initial study design called for randomization within 12 hours of arrival to the institution, but because of difficulty in enrollment, this was amended to 24 hours after arrival. Infusions were required to be initiated within 24 hours of a patient's arrival to the institution and were continued for a total of 48 hours unless clinical conditions or patient request prompted early cessation.

Pain management was addressed using the divisional pain management pathway, which includes opiate- and nonopiate-based medical treatments. To limit variation in opioid prescribing patterns, all subjects were given a patient-controlled analgesia (PCA) with specified initial dosing parameters (Fig. 1). A hydromorphone PCA was used preferentially, but a morphine

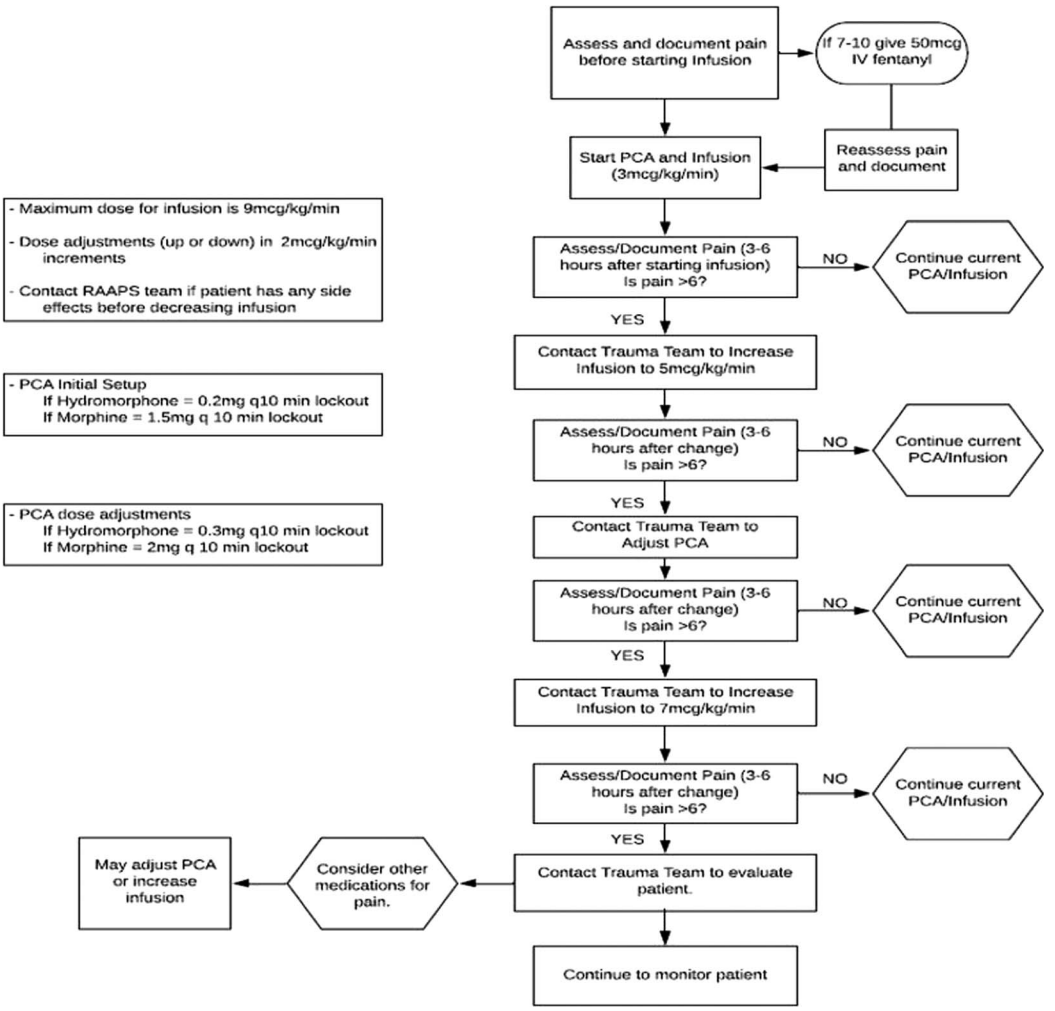

Figure 1. Pain treatment algorithm.

PCA was allowed if a hydromorphone allergy or intolerance was present. Prior to starting the investigational infusion, a single intravenous push of 50 μg of fentanyl was administered to any patient with a numeric pain score (NPS) of 7 to 10.

Adjustments to both the investigational drug infusion (maximum 9 μg/kg/min) and the PCA were allowed depending on the needs of the patient, but adjustments to these medications followed a treatment algorithm (Fig. 1). Patients who were deemed to be in severe pain (NPS 7–10) could also receive a single bolus dose of an opioid while awaiting the adjustments to their PCA/investigational infusion. Regional anesthesia could be used during the study period for those people with pain difficult to control despite escalation along the treatment algorithm. At the completion of the 48-hour infusion, the inpatient team had the option of transitioning the patient from the PCA to oral pain medications and could start an ADK infusion if desired.

Safety/Monitoring Protocol

All patients enrolled in the study were followed by both the Trauma Service and the Regional Anesthesia and Acute Pain Service who assessed the patient for adverse events related to the infusion or PCA. Specifically, patients were assessed for nausea, pruritus, respiratory depression, sedation level, and presence of disturbing dreams or hallucinations. In addition, each patient was monitored by the nursing staff according to the institutional ketamine medication administration guideline. Any concern for an adverse event related to a study medication prompted an evaluation by the Regional Anesthesia and Acute Pain Service and Trauma Services to determine if the adverse event was related to the study infusion or PCA. Based on their assessment, the infusion (or PCA) could be left at the current rate, decreased, or stopped. If stopped, the patient was reassessed within 2 hours to determine if the symptoms had resolved or improved. If improved (or if the symptoms were mild), the infusion (or PCA) was restarted at a lower rate/dose. If an infusion was stopped for more than 4 hours or if symptoms persisted/worsened, the investigational infusion was discontinued. If the symptoms were felt to be related to the PCA, the PCA was adjusted. If symptoms related to the PCA persisted, a different PCA medication was ordered.

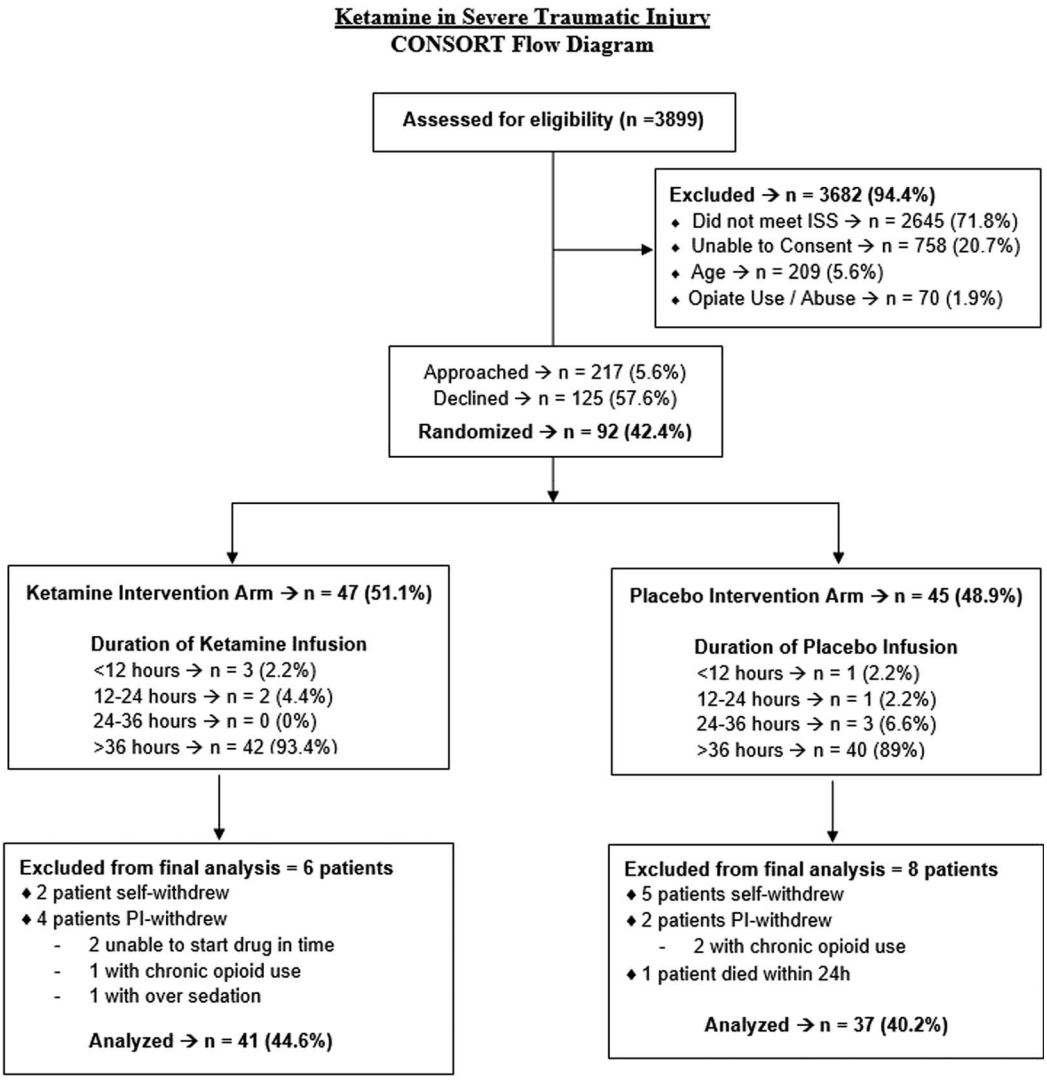

Figure 2. Study Consolidated Standards Of Reporting Trials (CONSORT) diagram.

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. The institutional review board reviewed and approved the study design (IRB000317017). This study was registered with clinicaltrials.gov (NCT no. 04274361) and funded through an institutional grant (Comprehensive Injury Center Award). This study used the Consolidated Standards Of Reporting Trials reporting guidelines for reporting parallel group randomized trials (Supplemental Digital Content, Supplementary Data 3, http://links.lww.com/TA/E367). The use of adjunctive ketamine infusions for pain is not Food and Drug Administration approved and is considered "off-label."

Measures

The use of all pain management medications was recorded, and opiate-based medications were standardized to OME for analysis. The primary outcome was difference in total OME at 24 hours. We felt that this would represent a marker of the effectiveness of ADK on a patient's pain control without relying on the NPS given the inherent subjectivity of pain score reporting.

Secondary outcomes for the trial included reduction in OME from 24 to 48 hours, total OME for the entire 48-hour period, and for the hospitalization. In addition, NPSs were followed after initiation of the infusion, for the entire 48-hour period. Our institution uses a standardized 11-point NPS, which is assessed per unit policy at regular intervals and before/after any pain intervention. Patients who were intubated after enrollment had their pain scores documented using the Critical-Care Pain Observation Tool, which is the standard nursing assessment used in our critical care units.[26] Rates of the aforementioned medication-related complications and PCA-related information, including number of demands and demand deliveries, were also collected. Other outcome measures included intensive care unit (ICU) and hospital length of stay, epidural placement rate, and discharge disposition. Demographics including age, mechanism of injury, sex, body mass index, Abbreviated Injury Scale score, and calculated ISS were all recorded.

TABLE 1. Demographics and Baseline Study Variables

Variable	Total, N = 78	Ketamine, n = 42	Placebo, n = 36	*p*
Age, median (Q1, Q3), y	32 (21, 44)	31.5 (20, 44)	32.5 (25, 43.3)	N/A
Sex, males, n (%)	51 (65.4)	27 (64.3)	24 (66.7)	N/A
BMI, median (Q1, Q3), kg/m^2	28.2 (23.8, 33.1)	27.2 (22.6, 32.3)	29.3 (25.5, 33.1)	N/A
ICU admission, n (%)	42 (53.8)	19 (45.2)	23 (63.9)	N/A
Mechanism of injury, n (%)				
GSW	13 (16.7)	5 (11.9)	8 (22.2)	N/A
MVC	33 (42.3)	18 (42.9)	15 (41.7)	
MCC	12 (15.4)	5 (11.9)	7 (19.4)	
Fall	8 (10.3)	7 (16.7)	1 (2.8)	
Other	12 (15.4)	7 (16.7)	5 (13.9)	
ISS, median (Q1, Q3)	22 (19, 28.5)	22 (19, 27)	22.5 (18.8, 29.3)	N/A
AIS, median (Q1, Q3)				N/A
Chest	3 (1, 3)	3 (1.5, 3)	3 (1.5, 4)	
Abdomen	3 (0, 4)	3 (0, 4)	1 (0, 4)	
Extremity	2 (1, 3)	1 (0, 4)	2 (0, 3)	
Rib fractures, n (%)	57 (73)	30 (71)	27 (75)	N/A
Study drug dose, μg/kg/min				
Median (Q1, Q3)	3 (3, 5)	3 (3, 5)	4(3, 5)	0.53
Study drug duration, h				
Median (Q1, Q3)	47.9 (47.3, 48.1)	47.9 (47.4, 48.1)	47.9 (47.2, 48.1)	0.97
RAAPS consult, n (%)	74 (94.9)	40 (95.2)	34 (94.4)	>0.99
OR timing during infusion, n (%)				
0–24 h	22 (28.2)	12 (28.6)	10 (27.8)	0.2
24–48 h	9 (11.5)	6 (14.3)	3 (8.3)	
0–48 h	31 (39.7)	18 (42.9)	13 (36.1)	
Operations during infusion, n (%)	31 (39.7)	18 (42.9)	13 (36.1)	0.65
Orthopedic	22 (70.9)	12 (66.7)	10 (76.9)	
Abdominal	6 (19.4)	3 (16.7)	3 (23.1)	
Thoracic	1 (3.2)	0 (0)	1 (7.7)	
Spine	2 (6.4)	1 (5.6)	1 (7.7)	
Other	3 (9.7)	1 (5.6)	2 (15.4)	
>1 Operation	4 (12.8)	1 (5.6)	3 (23.1)	

GSW, gun shot wound; MVC, motor vehicle crash; MCC, motorcycle crash; AIS, Abbreviated Injury Scale; BMI, body mass index; N/A, not available; RAAPS, Regional Anesthesia and Acute Pain Service; OR, operating room.

Sample Size Calculation and Interim Blinded Analysis

Sample Size and Power

Based on a previous ketamine trial in adults with rib fractures,[24] we expected a 30% reduction in OME. Assuming a log-normally distributed outcome with a 75% coefficient of variation, using an 80% power and a one-sided *t* test on the log-transformed OME values at a significance level of 2.5%, we determined that 119 subjects would need to be randomized accounting for an interim analysis. A planned interim analysis of the primary endpoint would be performed when 80 randomized subjects had completed the trial. Following the interim analysis, the trial could be stopped for either efficacy or futility, which was determined using the error spending function approach described by DeMets and Lan.[27] The Hwang-Shih-DeCani spending function with γ equal to -2 for β-spending and -4 for α-spending was used to determine the appropriate statistical significance levels for each analysis.[28]

Statistical Analysis

Statistical analysis was performed using a modified intent-to-treat approach, meaning that only patients who received study infusion would be analyzed. Demographic and other baseline data such as trauma characteristics, as well as outcome measures, are presented overall and by treatment group. Categorical data, presented by frequencies and percentages, were analyzed using Pearson's χ^2 test or with Fisher's exact test for between-group comparisons. Numeric data with approximately symmetric distribution were summarized using mean and standard deviation and compared between groups using Student's two-sample *t* test. Skewed outcomes were summarized using median and interquartile range (IQR) and compared with Wilcoxon rank-sum test. Oral morphine equivalent was represented and analyzed using both the sum total and as a log of sum total for day 1, day 2, and combined days 1 and 2, with the log-scale analyses considered primary. All analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

At the time of the interim analysis, 92 patients had been enrolled, and 47 were randomized (51.1%) to the experimental arm. Fourteen patients were excluded after enrollment, and 78 patients (42 in the experimental arm) were included in the analysis (Fig. 2). Overall, 65.4% of patients were male, with a median age of 32 years (IQR, 21–44 years), and a median ISS of 22 (IQR, 19–28.5). Fifty-three percent of patients were admitted to the ICU from the emergency department. Motor vehicle collision was the most common mechanism of injury (42.3%), followed by gunshot wound (16.7%) and motorcycle crash (15.3%). There were no significant differences in demographics or injury characteristics in either group (Table 1). A complete listing of all injuries can be found in Supplemental Digital Content (Supplementary Data 4, http://links.lww.com/TA/E368). Four patients (5.1%) completed <12 hours of the infusion, three patients (6.3%) completed 12 to 24 hours, and 82 patients (88.6%) completed >36 hours of the infusion, but no difference in the infusion duration was noted between groups. As part of our multimodal pain treatment guideline, oral acetaminophen, nonsteroidal anti-inflammatory medications, muscle relaxants, and gabapentin are typically prescribed unless contraindicated. There was no difference in the use of any of these medications in the patient cohorts. Seven patients had undergone epidural catheter placement for pain control. Three patients (two in the placebo group and one in the ketamine group) had their epidurals placed before enrollment. The four patients who underwent epidural placement after enrollment were all in the placebo group ($p = 0.04$). Three

TABLE 2. Oral Morphine Equivalents, Pain Scores, and PCA-Related Outcomes

Variable	Total, N = 78	Ketamine, n = 42	Placebo, n = 36	*p*
OME outcomes				
Day 1 OME, median (Q1, Q3)	99.7 (53.2, 191.7)	110.6 (55.7, 191.7)	99.2 (50.6, 172.6)	0.93
Day 2 OME, median (Q1, Q3)	85.1 (41.8, 149.7)	75.4 (39.1, 194)	87.1 (42.4, 120.9)	0.64
Days 1 and 2 OME, median (Q1, Q3)	183 (97.2, 352.4)	184.2 (92.8, 414.3)	183 (125.6, 306.8)	0.96
Total hospital OME, median (Q1, Q3)	409 (248.8, 778.5)	411 (261.5, 1072.8)	398 (216.8, 711.6)	0.52
Discharge OME, median (Q1, Q3)	30 (8.1, 37.5)	30 (8.1, 30)	30 (13.1, 40.3)	0.38
Pain score outcomes				
Day 1 NPS, median (Q1, Q3)	4.6 (3.3, 6)	4.4 (3.8, 5.9)	4.8 (2.9, 6.3)	0.72
Day 2 NPS, median (Q1, Q3)	4.8 (2.7, 5.8)	4.7 (2.7, 5.4)	4.9 (3, 5.9)	0.76
Days 1 and 2 NPS, median (Q1, Q3)	4.8 (3.3, 5.83)	4.9 (3.4, 5.5)	4.7 (3.2, 6)	0.95
PCA-related outcomes				
Day 1, median (Q1, Q3)				
Demands/shift	25 (12.8, 45)	31.5 (14, 51.8)	21.5 (9.5, 39.8)	0.09
Deliveries/shift	21 (11, 33.3)	24 (11, 39.5)	18 (9.3, 29.3)	0.18
Day 2, median (Q1, Q3)				
Demands/shift	23 (10, 46)	27 (11, 57)	21 (8.5, 37)	0.29
Deliveries/shift	18 (7, 28)	16 (9, 36.3)	18 (7, 25.5)	0.83
Days 1 and 2, median (Q1, Q3)				
Demands/shift	43 (25, 98)	55 (27.5, 105.8)	37 (22.5, 74.5)	0.1
Deliveries/shift	34 (22, 61)	35 (23.3, 76.5)	34 (20, 55)	0.43

epidurals were placed on day 1, and one epidural was placed after the study infusion ended.

Nine patients underwent an operation prior to enrollment (four in the ketamine group and five in the placebo group, $p = 0.43$). Within the placebo group, these operations included an amputation, two damage-control laparotomies, an arm debridement, and a mandible fixation. Within the ketamine group, these operations included external fixation of a pelvis, external fixation of a lower extremity, a brachial artery repair, and a lower extremity washout. Notably, each of these patients underwent an additional operation during the study infusion. Thirty-one subjects underwent operations during their study infusion (Table 1). Most of these procedures were orthopedic in nature (71%), and 13% of patients had more than one operation during their study infusion. There were no statistical differences between groups in those undergoing operations during the study infusion. The timing of operations performed during the study infusion was also not statistically different between groups. Specifically, 28.6% of ketamine and 27.8% of placebo patients underwent an operation in the first 24 hours of the infusion, 14.3% and 8.3% in the second 24 hours of the infusion, and 42.9% and 36.1% at any point during the 48-hour infusion time ($p = 0.2$).

Regarding the primary outcome, no significant difference was noted in median OME totals in the first 24 hours, 24 to 48 hours, or total 48 hours. There were no significant differences in total OME for the entire hospitalization or in discharge OME. No difference was noted in median NPS at the first 24 hours, 24 to 48 hours, or the total 48 hours. There were no significant differences in PCA demands, PCA deliveries, or highest rate of investigational drug (Table 2, Fig. 3). There were no differences in other secondary outcomes or medication-related adverse events between groups (Table 3). To evaluate the effect that an epidural may have had on the study

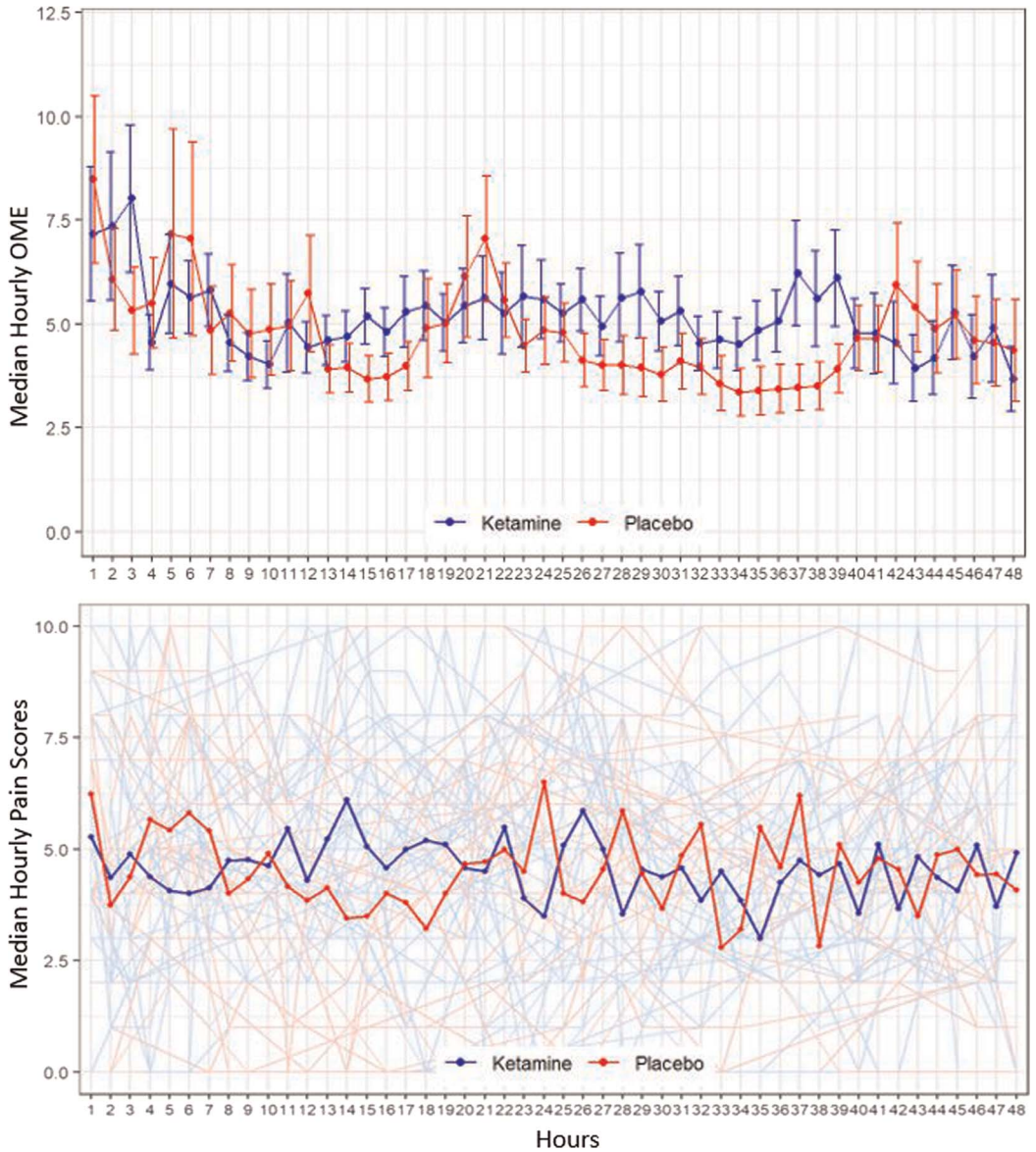

Figure 3. Median OME and pain scores per hour.

TABLE 3. Hospital and Medication-Related Outcome Variables

Variable	Total, N = 78	Ketamine, n = 42	Placebo, n = 36	*p*
Hospital outcomes				
Length of stay, median (Q1, Q3), d	7.5 (5, 12.8)	7.5 (4.3, 12)	7.5 (5.8, 15)	0.41
ICU length of stay, median (Q1, Q3), d	1 (0, 3)	0.5 (0, 3)	1 (0, 2.5)	0.57
DC destination				0.67
Home	63 (80.8)	34 (81)	29 (80.6)	
SNF/rehab	11 (14.1)	5 (11.9)	6 (16.7)	
Other	4 (5.1)	3 (7.1)	1 (2.8)	
Medication-related adverse events				
Nausea, n (%)				0.18
Absent	54 (69.2)	33 (78.6)	21 (58.3)	
Present, no therapy	11 (14.1)	4 (9.5)	7 (19.4)	
Present, therapy effective	12 (15.4)	5 (11.9)	7 (19.4)	
Present, therapy ineffective	1 (1.3)	0 (0)	1 (2.8)	
Respiratory depression, n (%)	2 (2.6)	0 (0)	2 (5.6)	0.21
Sedation, n (%)				0.3
No sedation noted	47 (60.3)	23 (54.8)	24 (66.7)	
Sedation documented	31 (39.7)	19 (45.2)	12 (33.3)	
Sedation requiring transfer	0 (0)	0 (0)	0 (0)	
Pruritus, n (%)				0.56
Absent	67 (85.9)	36 (85.7)	31 (86.1)	
Present, no therapy	9 (11.5)	4 (9.5)	5 (13.9)	
Present, therapy effective	2 (2.6)	2 (4.8)	0 (0)	
Reported hallucinations and/or disturbing dreams, n (%)	9 (11.5)	6 (14.3)	3 (8.3)	0.49
Reported vivid dreams, n (%)	3 (3.8)	2 (4.8)	1 (2.8)	>0.99

DC, discharge; SNF, skilled nursing facility.

outcomes, we removed patients with an epidural and performed a separate analysis. No statistical difference between groups in OME, PCA demands/deliveries, or pain scores was noted (Supplemental Digital Content, Supplementary Data 5, http://links.lww.com/TA/E369).

Using the error-spending function, with interim analysis after 78 subjects, the one-sided *p* value cutoff for declaring efficacy was 0.006, and the cutoff for stopping due to futility was 0.167. Based on the results of this interim analysis, the study reached exceeded the identified threshold for futility, and enrollment was terminated.

DISCUSSION

This article presents the results of a randomized, double-blinded, controlled trial of ADK for the treatment of pain in severely injured patients. This trial included the multiply injured population typically seen in trauma centers and was also designed to address limitations found in other ketamine studies, including allowing ketamine dose adjustments, higher initial ketamine dose, and a standardized PCA regimen. Despite these study adjustments, we found no significant difference in OME or NPS at any time point.

While adverse effects associated with ketamine are common when used for induction of anesthesia or procedural sedation,[12] we again demonstrated that ADK had a low rate of side effects, despite the higher rate of ketamine infusion. This article provides additional evidence regarding the safety of ADK infusions considering that almost 50% of ADK patients were admitted to the general ward.[18,29] Specifically, the incidences of hallucinations and respiratory distress were both low in the entire study cohort, and the two patients with respiratory distress were in the placebo group. Any decrease in opioids could explain this finding, but since the OME were almost identical between groups, the occurrence of respiratory depression in the placebo group was most likely related to chance.

Despite the lack of measurable outcome differences in the ADK group, there are theoretic benefits related to the role ketamine plays in the physiologic response to pain.[14] Painful stimuli activate *N*-methyl-D-aspartate receptors and produce hyperexcitability of the dorsal root neurons, which leads to central sensitization, "wind-up" phenomenon, and pain memory.[13,14] Central sensitization can be blocked by ketamine by blunting the effect of the excitatory neurotransmitter glutamate.[16] While not entirely understood, this 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, common issues faced by trauma patients.[11]

Limitations

This study has several limitations. Despite attempts to standardize the treatment of patient's pain, there were several episodes in which a patient's pain score was ≥7, but no changes to their treatment regimen were performed. This occurred despite monthly education sessions for both the provider and nursing teams regarding the importance of assessing and adequately treating pain. Pain is subjective and difficult to assess, particularly in patients with multiple injuries, and is occasionally undertreated when the patient's pain score does not match their behavior.[30] Ultimately, the decision to adjust the medications was left to the bedside team who was responsible for assessing the patient, but this deviation could have resulted in more opioid use in the ADK group, especially if the ketamine dose was not maximized. Another limitation was that the treating provider could use any combination of medications within the multimodal pain management order set. While no difference was noted in the medications prescribed within the groups, we cannot say for certain that this variation did not have any impact on the study outcome. In addition, because of recruitment-related issues, the study enrollment period was amended from 12 hours to 24 hours after arrival. There is a possibility that patients enrolled within a longer period after their trauma had differences in their opioid needs, depending on how well their pain was controlled prior to the initiation of the infusion. Some of the patients went to the operating room during the study period, and we were unable to control for the beneficial (or detrimental) consequences of the procedure on their pain. Finally, this study only evaluated the short-term effect of ADK on pain and opioid use, and there may be long-term benefits that have not been elucidated. Despite these limitations, we think that the strengths of the study overcome many of the limitations noted in previous ketamine trials. This study allowed for titration of both the ADK infusion and PCA, had a higher starting dose of the ketamine

infusion, allowed for patient care in both ICU and acute care settings, and had near universal involvement of the Pain Service.

CONCLUSION

Complete elimination of opioids in the treatment of traumatic pain has proven to be very difficult, despite the current emphasis on multimodal analgesic therapy.[31] Given the known consequences of opioid use, we had hoped to demonstrate a benefit of ketamine on opioid reduction in this population. The results of this randomized, double-blind, placebo-controlled trial of ADK in severely injured patients demonstrated no measurable decrease in OME or NPS within the first 24 or 48 hours after injury. There may still be a role for ketamine in the care of the trauma patient as not all benefits are directly measurable, and we know that posttraumatic recovery is a prolonged dynamic process. To further explore the potential long-term benefits of ADK, we are evaluating the role of ADK in quality-of-life following severe injury.

AUTHORSHIP

T.W.C., W.J.P., C.T., T.A.d.R.-C., and R.T. performed the overall project design. T.W.C., W.J.P., J.A.G., and M.M.-W. performed the data collection. A.S. and Y.Y. performed the sample size calculation, statistical methodology, and data analysis. All authors performed the data interpretation. Writing of the article and critical revision of the article was performed by all the listed authors.

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DISCLOSURE

Conflict of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/E370).

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