Out-of-Hospital Intranasal Ketamine as an Adjunct to Fentanyl for the Treatment of Acute Traumatic Pain: A Randomized Clinical Trial

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Study objective: To evaluate if out-of-hospital administration of fentanyl and intranasal ketamine, compared to fentanyl alone, improves early pain control after injury.

Methods: We conducted an out-of-hospital randomized, placebo-controlled, blinded, parallel group clinical trial from October 2017 to December 2021. Participants were male, aged 18 to 65 years, receiving fentanyl to treat acute traumatic pain prior to hospital arrival, treated by an urban fire-based emergency medical services agency, and transported to the region's only adult Level I trauma center. Participants randomly received 50 mg intranasal ketamine or placebo. The primary outcome was the proportion with a minimum 2-point reduction in self-described pain on the verbal numerical rating scale 30 minutes after study drug administration assessed by 95% confidence interval overlap. Secondary outcomes were side effects, pain ratings, and additional pain medications through the first 3 hours of care.

Results: Among the 192 participants enrolled, 89 (46%) were White, (median age, 36 years; interquartile range, 27 to 53 years), with 103 receiving ketamine and 89 receiving placebo. There was no difference in the proportion experiencing improved pain 30 minutes after treatment (46/103 [44.7%] ketamine versus 32/89 [36.0%] placebo; difference in proportions, 8.7%; 95% confidence interval, −5.1% to 22.5%; P=.22) or at any time point through 3 hours. There was no difference in secondary outcomes or side effects.

Conclusion: In our sample, we did not detect an analgesic benefit of adding 50 mg intranasal ketamine to fentanyl in out-of-hospital trauma patients. [Ann Emerg Med. 2024;84:363-373.]

Please see page 364 for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2024.04.018

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INTRODUCTION

Background

Paramedics frequently treat pain after traumatic injuries with parenteral opioids, but many patients experience suboptimal pain control. Ketamine has analgesic and opioid-sparing effects with fewer negative impacts on respiratory or hemodynamic status. The intranasal route of medication administration facilitates timely treatment and may promote faster analgesia.[1] Little data exist that evaluate the combination of fentanyl and ketamine to treat pain in the out-of-hospital setting, and recent evidence-based guidelines for out-of-hospital pain management are silent on intranasal ketamine.[2,3]

Importance

Intranasal ketamine may add an analgesic benefit to fentanyl for pain relief after trauma during out-of-hospital care; defining the efficacy and safety of adding intranasal ketamine to fentanyl is needed.

Goals of This Investigation

We sought to evaluate the addition of a fixed dose of intranasal ketamine or placebo to fentanyl as part of the out-of-hospital treatment of injured patients suffering moderate or severe pain. We hypothesized that the combination therapy would increase the proportion of patients experiencing clinically significant pain reduction 30 minutes after receiving medication compared to patients receiving fentanyl and intranasal placebo.

Editor's Capsule Summary

What is already known on this topic

Ketamine offers analgesia and can be administered intranasally.

What question this study addressed

In traumatized adults receiving out-of-hospital fentanyl, does adding intranasal ketamine 50 mg improve early analgesia?

What this study adds to our knowledge

In this randomized, controlled trial of 192 adults for whom fentanyl (mostly 100 mcg parenterally) was supplemented with intranasal ketamine 50 mg or placebo, the proportions of patients with a 2-point or greater pain score reduction were similar.

How this is relevant to clinical practice

The added benefit of EMS-administered intranasal ketamine after fentanyl for analgesia in those with trauma is small if existent.

MATERIALS AND METHODS

Study Design, Setting, and Organization

We conducted an out-of-hospital randomized, placebo-controlled, blinded, parallel group clinical trial of patients requiring out-of-hospital analgesia for acute traumatic injuries, as previously described; Appendix E1 (available at http://www.annemergmed.com) contains the full study protocol.[4] Enrollment occurred across the City of Cincinnati through a partnership between the Cincinnati Fire Department and the University of Cincinnati Medical Center. The Cincinnati Fire Department is a large, urban, fire-based emergency medical services (EMS) agency that is the sole 911 responder for the City of Cincinnati. All 35 first-responding fire apparatus and 12 ambulances are staffed with at least 1 paramedic, and each unit served as an enrolling vehicle; 6 or more EMS providers, including at least 2 paramedics, responded to the scene of each participant. Cincinnati Fire Department paramedics commonly administer intranasal medications. The University of Cincinnati Medical Center is the only regional adult American College of Surgeons verified Level I trauma center, and the Cincinnati Fire Department delivers 85% of all ground EMS volume to the hospital's emergency department (ED). During the trial, clinical research coordinators continuously staffed the ED.

An independent study monitor oversaw protocol compliance and data reporting, and an independent physician medical monitor reviewed all adverse events captured during bedside assessments or through medical record review. A data and safety monitoring board evaluated accruing safety and outcomes data to make recommendations on trial continuation or suspension. No interim statistical analyses were performed, and there were no formal stopping rules. The University of Cincinnati Institutional Review Board and the United States Air Force Human Research Protection Office approved the study. The Food and Drug Administration approved intranasal ketamine administration under an Investigational New Drug application (IND: 131,895). The trial is registered at ClinicalTrials.gov (NCT02866071). This study follows the Consolidating Standards of Reporting Trials reporting guidelines for randomized controlled clinical trials.[5]

Selection of Participants

Between October 2017 and December 2021, adults (18 to 65 years old) experiencing acute moderate/severe pain following a traumatic injury were eligible if paramedics planned to administer fentanyl as part of standard care. To qualify, participants reported self-rated pain prior to treatment of at least 7 of 10 on the verbal numerical rating scale.[6] Complete inclusion and exclusion criteria are shown in the Box. We excluded females because of the inability to perform required rapid pregnancy testing prior to study interventions. Response to the emerging COVID-19 pandemic triggered an enrollment pause between March 13, 2020, and May 31, 2021.

Paramedics screened for eligibility while providing clinical care, including pain management. As soon as feasible, we enrolled eligible participants after paramedics obtained informed consent for research. Multiple paramedics on-scene allowed parallel clinical and research processes (eg, assessing inclusion/exclusion criteria during vascular access, starting consent while providing clinical analgesia). The out-of-hospital-obtained consent covered randomization, study drug administration, primary outcome assessment, out-of-hospital and limited hospital chart review, and other research activities through the first 3 hours of care. After stabilization in the ED, clinical research coordinators approached enrolled participants to obtain a second informed consent for additional assessments and in-depth chart review. The rationale for the consent process has been described in detail.[7]

Reviewing the Cincinnati Fire Department's electronic patient care reporting system for cases of males transported

Box. Inclusion and exclusion criteria.

Inclusion Criteria
Participants must be experiencing pain due to acute trauma (eg, extremity deformity, tourniquet placement, and severe burns).
A verbal numerical rating scale pain score ≥7 prior to any pain medication administration.
Age: 18 through 65 years.
Systolic blood pressure ≥100 mmHg and <180 mmHg.
Transported directly from the scene of injury to the participating ED.
English-speaking.
Male sex.
Receiving fentanyl as part of standard care.
Exclusion Criteria
Participant reported allergy to morphine, fentanyl, or ketamine.
EMS treatment with any ketamine, morphine, or more than 1 dose of fentanyl prior to enrollment.
Inter-facility transfers.
Prisoners or those in police custody.
Paramedic clinical concern of acute agitation or psychosis.
Pain medication not needed in judgment of out-of-hospital provider.
Altered level of consciousness, mental status change, or suspected head injury.
Paramedic clinical concern of circulatory shock.
Inability to provide verbal numerical rating scale score.
Facial injury or suspicion of nasal bone fracture.
Paramedic judgment that participant cannot consent due to underlying cognitive impairment.
Systolic blood pressure ≥180 mmHg.

to University of Cincinnati Medical Center who received fentanyl allowed identification of eligible subjects not enrolled.

Interventions

To avoid delays in care due to research activities, all participants received standard care treatment with fentanyl at the dose and route of the paramedic's discretion based on local protocol. Out-of-hospital clinical protocols designate 25 to 100 mcg as the initial dose of fentanyl, with additional doses as needed; the clinical protocols allow intravenous, intramuscular, intraosseous, or intranasal fentanyl administration.

After paramedics obtained informed consent, participants received a single intranasal dose of 50 mg ketamine (1 mL of 50 mg/mL concentration), or matching volume of saline placebo, using a mucosal atomizer. Treating providers chose all other treatments in the out-of-hospital and hospital settings, including additional pain medications.

Randomization and Blinding

The hospital investigational drug pharmacy prepared kits containing the concealed allocated study drug (ketamine or placebo) and all necessary study materials in a 1:1 randomized ratio using permuted small blocks without stratification or control for imbalance. Each EMS unit was stocked with a single study kit, and kit replacement occurred after each enrollment or study drug expiration. We augmented concealment by using the same labeling on vials of study drug, using only a vial number for identification, and placement of the medication vial in a sealed opaque bag in the study kit in a way that prevented it from being seen until the paramedics opened the kit. This randomization and study kit deployment process mirrored several other out-of-hospital trials.[8,9] All paramedics, including those enrolling participants, and all study team members, including those assessing outcomes, were unaware of allocation assignments.

Outcomes and Measurements

The primary outcome was the occurrence of at least a 2-point reduction in pain assessed 30 minutes after study drug administration. We chose this as clinically meaningful based on other out-of-hospital pain trials.[6,10-12] Participants self-reported pain using the Verbal Numerical Rating Scale (VNRS).[6] At the time of study drug administration, paramedics started the study kit's stopwatch; paramedics handed the stopwatch to the research team in the ED at arrival to facilitate timed assessments.

Secondary outcomes were VNRS reported pain at ED arrival, pain control after hospital arrival for 3 hours, and additional pain medication use during out-of-hospital care and through 3 hours of ED care. Clinical research coordinators assessed side effects at arrival and 3 hours after arrival using the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA), the Richmond Agitation-Sedation Scale, and the General Assessment of Side Effects.[13-16] The "general discomfort" item on the SERSDA was not considered an adverse event as participants were not expected to differentiate between discomfort associated with the injury or the treatment. Predefined safety outcomes included laryngospasm, endotracheal intubation (outside of the operating room), hypertension or respiratory depression requiring intervention, anaphylaxis requiring epinephrine, or psychomotor agitation requiring intervention within 6 hours of study drug administration, or any fatal event within 24 hours of study drug administration.

Paramedics obtained initial VNRS and reported any observed adverse events. Clinical research coordinators in the ED obtained research-related information directly from enrolling paramedics and performed all subsequent assessments.

Acute assessments ended if the participant left the ED within 3 hours of arrival, including if they were discharged, taken to an operating room, or transferred to an inpatient setting.

Data Collection and Data Sources

Because the out-of-hospital–obtained consent purposefully omitted Health Insurance Portability and Accountability Act (HIPAA) waiver language, primary data collection relied on direct patient report and study team observation. Limited hospital chart review allowed review of safety and side effect data. Participant report was preferred for all demographic and medical history data points. Assessors noted any inability to answer questions or provide information. Participants consenting for additional assessments also provided HIPAA authorization for a more comprehensive chart review. Blinded clinical research coordinators, trained on the case report forms and supported by a data dictionary, conducted dual chart abstraction with dual data entry, with queries resolved by an adjudicator.

Analysis

We collected and managed study data using Research Electronic Data Capture (REDCap) electronic data capture tools and analyzed these using SPSS version 28 (IBM).[17,18] An intent to treat approach drove primary and secondary outcome comparisons. The primary outcome was assessed at a single point in time and compared between groups using a chi-square test. Differences in proportions and differences in medians, with 95% confidence intervals (CIs), are presented. We expected the response to be 40% in those receiving placebo and 60% in those receiving ketamine (20% absolute difference) based on other research comparing pain management efficacy between participants treated with intravenous morphine alone and intravenous morphine plus intravenous ketamine. With this magnitude of effect, a minimum sample size of 194 (97 per arm) has 80% power to detect the difference between the 2 groups when the critical level of significance is set to 5%. To allow for subject drop-out, protocol deviations, and missing outcome data, we allowed over-enrollment by up to an additional 15% in each arm, for a maximum of 224 subjects. We allowed repeat enrollment and treated each independently.

We also completed a per-protocol analysis that included all randomized participants who correctly received the assigned treatment (study drug or placebo) and did not incur any major protocol deviations or violations, with participants classified according to the treatment they received. Exclusions based on major protocol violations (did not meet eligibility criteria or did not receive study treatments in a manner consistent with the protocol) were adjudicated prior to unblinding.

RESULTS

Characteristics of Study Subjects

Of 569 males receiving fentanyl as part of out-of-hospital clinical care, 199 were randomized, and 192 were included in the primary analysis (103/192 receiving intranasal ketamine and 89/192 receiving placebo, Figure 1). Two participants were enrolled twice. Figure 1 describes reasons for nonenrollment. Table 1 describes participant and injury characteristics; treatment groups are similar, including body mass and fentanyl dosing.

Participants commonly self-reported history of chronic pain, post-traumatic stress disorder (PTSD), recreational use of pain medications, and use of heroin or other intravenous drugs.

Primary Outcome

Thirty minutes after receiving study medication, 32/89 (36.0%) assigned to placebo and 46/103 (44.7%) assigned to intranasal ketamine reported at least 2 points of pain reduction (difference in proportions, 8.7%; 95% CI, −5.1% to 22.5%; P=.22) (Figure 2 and Table 2).

Secondary Outcomes

Pain over 3 hours of ED care did not differ at any time (Table 2). The proportion of those needing additional pain medications and the total amount of pain medications received did not differ between treatment groups (Table E1, available at http://www.annemergmed.com). Adverse events did not differ between groups (34.8% versus 35.9%; difference in proportions, 1.1%; 95% CI, −12.5% to 14.6%; Table E2, available at http://www.annemergmed.com), and side effects were mostly minor and common and did not differ between groups (Table 3). There were no observed differences between groups in the Richmond Agitation-Sedation Scale at ED arrival or at the end of observation (Table 3).

Per-Protocol Analysis

Table E3 (available at http://www.annemergmed.com) contains characteristics of participants included in the

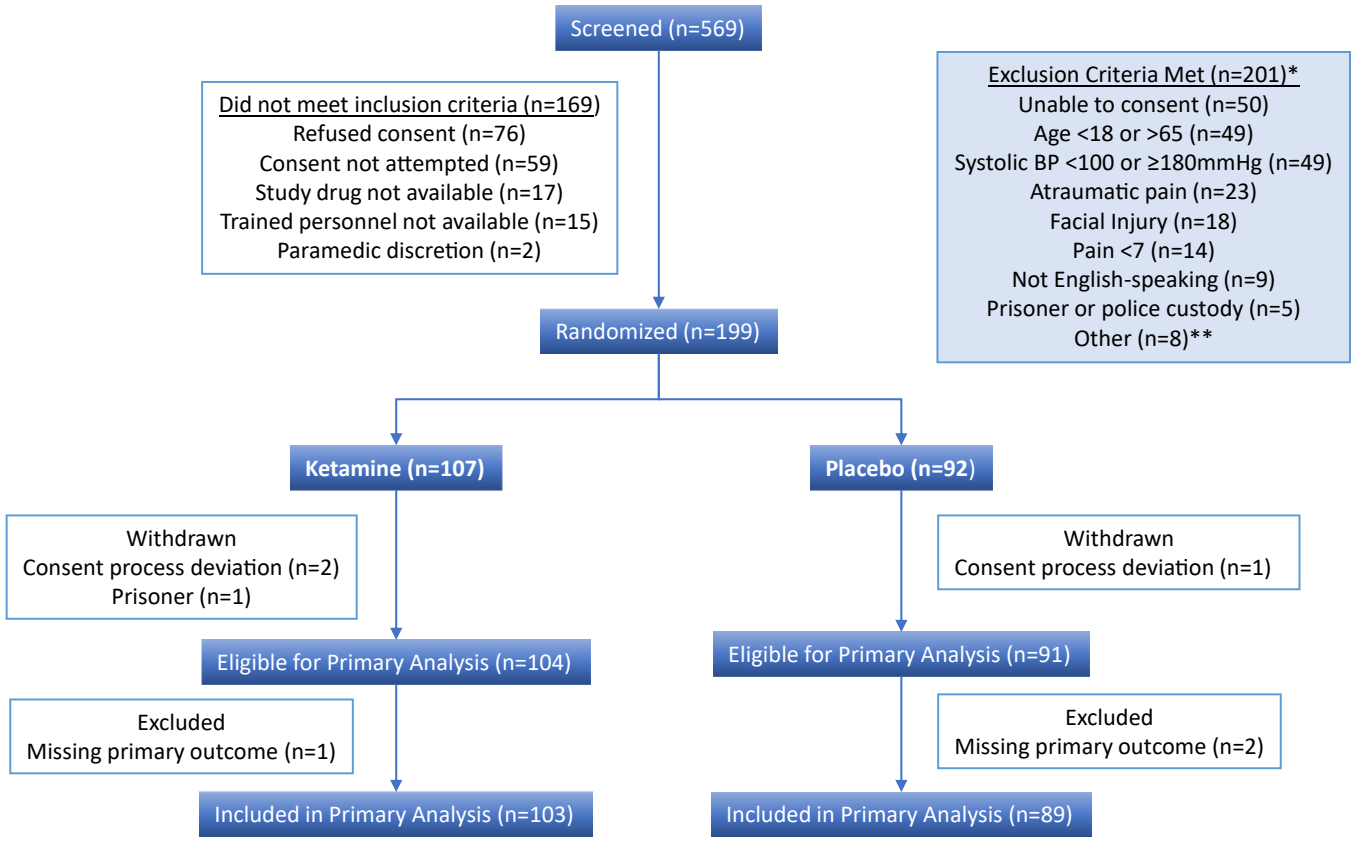

Figure 1. Flow of participants. *Some participants met more than 1 exclusion criteria. **Other exclusion criteria met were treatment with morphine or multiple doses of fentanyl prior to enrollment (n=3), paramedic clinical concern for shock (n=3), reported allergy (n=1), or inter-facility transfer (n=1). *BP*, blood pressure.

per-protocol analysis (ketamine [n=95] or placebo [n=85]). Thirty minutes after receiving study medication, 31/85 (36.4%) assigned to placebo and 43/95 (45.2%) assigned to intranasal ketamine reported at least 2 points of pain reduction (difference in proportions, 8.8%; 95% CI −5.5% to 23.1%; *P*=.24).

LIMITATIONS

We observed an unexpected imbalance in allocation between ketamine and placebo. The data and safety monitoring board did not recommend any changes to our allocation/randomization strategy after scheduled reviews. We used the same study drug deployment strategy for this trial as we have in other out-of-hospital randomized controlled trials: our investigational drug pharmacy issued one study kit per EMS vehicle based on a randomization/allocation schedule, crews used that single kit to enroll a subject, and kits were replaced after an enrollment or after study drug expiration.[8,9] Block randomization does not guarantee a perfect balance because of the need for study kit replacement, as the replacement may be in a different randomization block. The blocking enforces some balance, but by design, assignments within a block may not have been used. We note that there was not an imbalance of subjects lost after randomization (4 versus 3, Figure 1).

Some participants may have displayed nystagmus after receiving ketamine, and clinicians or study team members at bedside may have seen this phenomenon. We purposefully omitted this side effect from study-related trainings of paramedics and the study team members performing assessments, but observation may have resulted in unintentional unblinding. Because our primary outcome relied on self-reporting of pain, and not a researcher's observation, bias is unlikely.

DISCUSSION

In this out-of-hospital randomized clinical trial of adults receiving out-of-hospital fentanyl after injury, the addition of 50 mg intranasal ketamine did not statistically improve the proportion of patients with improved pain scores. We powered the study to detect a 20% absolute difference in proportion of patients experiencing pain reduction, thought to be large enough to justify the operational cost of changing out-of-hospital clinical protocols. We observed

Table 1. Participant characteristics by study group.

Characteristic	Placebo	Ketamine
Number included	89	103
Age (y), median (IQR)	33 (25-50)	42 (30-53)
Race, n (%)		
Black	49/89 (55)	45/103 (44)
White	35/89 (39)	54/103 (52)
Other	3/89 (2)	3/103 (3)
Unknown	2/89 (2)	1/103 (1)
Ethnicity, n (%)		
Not Hispanic or Latino	83/89 (93)	101/103 (98)
Unknown	4/89 (4)	2/103 (2)
Hispanic or Latino	2/89 (2)	0/103 (0)
Weight documented (n)	83	97
Weight (kg), median (IQR)	82 (73-95)	83 (75-99)
Pretreatment pain assessment, median (IQR)	10 (9-10)	10 (9-10)
Medication and ED arrival time documented (n)	88	101
Study medication to ED arrival (min), median (IQR)	14 (9-20)	14 (10-18)
Initial out-of-hospital vital signs		
Heart rate documented (n)	83	84
Heart rate (beats/min), median (IQR)	93 (82-101)	93 (78-103)
Systolic blood pressure documented (n.)	67	79
Systolic blood pressure (mmHg), median (IQR)	140 (126-152)	142 (127-160)
Diastolic blood pressure documented (n)	62	71
Diastolic blood pressure (mmHg), median (IQR)	90 (76-95)	85 (80-98)
Mean arterial pressure, median (IQR)	107 (93-115)	106 (93-120)
Injury type,* n/N (%)		
Blunt injury		
Fall	21/65 (32)	32/76 (42)
Machinery	3/65 (5)	6/76 (8)
Motor vehicle collision	13/65 (20)	10/76 (13)
Motorcycle	5/65 (8)	5/76 (7)
Other	10/65 (15)	8/76 (11)
Pedestrian struck	2/65 (3)	8/76 (11)
Assault	9/65 (14)	5/76 (7)
Bicycle	2/65 (3)	2/76 (3)
Penetrating injury		
Gunshot wound	18/25 (72)	14/27 (52)
Stabbing (knife)	2/25 (8)	3/27 (11)
Impalement	1/25 (4)	1/27 (4)
Other	4/25 (16)	9/27 (33)
Out-of-hospital fentanyl administration		
Intramuscular (n)	12	17
Intramuscular dose (mcg), median (IQR)	100 (50-100)	100 (100-100)
Intramuscular dose (mcg/kg), median (IQR)	1.0 (0.6-1.3)	1.1 (0.9-1.2)
Intravenous (n)	44	52
Intravenous dose (mcg), median (IQR)	100 (50-100)	100 (100-100)
Intravenous dose (mcg/kg), median (IQR)	1.1 (0.6-1.3)	1.1 (0.9-1.3)
Intranasal (n)	15	16

Table 1. Continued.

Characteristic	Placebo	Ketamine
Intranasal dose (mcg), median (IQR)	50 (50-50)	100 (50-100)
Intranasal dose (mcg/kg), median (IQR)	0.6 (0.5-0.8)	1.0 (0.6-1.4)
Intraosseous (n)	1	1
Intraosseous dose (mcg)	100	100
Intraosseous dose (mcg/kg)	1.4	1.6
Missing route (n)	17	17
Missing route dose (mcg), median (IQR)	100 (50-100)	100 (100-100)
Missing route dose (mcg/kg), median (IQR)	1.1 (0.6-1.3)	1.1 (1.0-1.3)
Self-reported chronic pain and opioid use		
Chronic pain, with or without medication, n/N (%)	28/86 (33)	25/98 (26)
Care seeking with a pain specialist or pain management, n/N (%)	12/83 (14)	8/96 (8)
Use of pain medications for reasons other than pain, or use of heroin, n/N (%)	10/86 (12)	17/98 (17)
Heroin/IVDU, n/N (%)	8/82 (10)	14/95 (15)
Reported diagnosis of PTSD, with or without medication, n/N (%)	6/86 (7)	6/97 (6)
Injury Severity Scale documented (n)[†]	69	81
Injury Severity Scale score, median (IQR)	4 (4-9)	4 (2-9)
Injury Severity Scale score 15+, n/N (%)	2/69 (3)	5/81 (6)
ED disposition,[‡] n/N (%)		
Admit ED observation	4/70 (6)	5/83 (6)
Admit medical floor	22/70 (31)	29/83 (35)
Admit ICU	2/70 (3)	3/83 (4)
Admit operating room	8/70 (11)	14/83 (17)
Discharge AMA	1/70 (1)	0/83 (0)
Discharge home	33/70 (47)	32/83 (39)

AMA, Against medical advice; *IQR*, interquartile range; *IVDU*, intravenous drug use.
*Multiple injury types are possible.
[†]Injury Severity Scale data were collected only for participants providing consent for additional medical record review.
[‡]ED disposition was collected only for participants providing consent for additional medical record review.

that 9% more people may experience a meaningful reduction in their pain with the addition of ketamine; we cannot speculate whether this difference would be durable in a larger sample or be clinically meaningful for those overseeing care. Using our findings, a trial to confirm a 10% treatment effect would need an estimated sample size of 750 participants.

Although adding intranasal ketamine did not prove effective in any measured outcome, ketamine did not increase the risk of important adverse events. Importantly, we observed no difference in sedation after receiving ketamine and fentanyl, and no episodes of laryngospasm or emergence phenomenon occurred. These findings suggest that a single 50 mg intranasal dose of ketamine appears safe.

Our novel feature is use of paramedics in the United States to obtain informed consent for research prior to hospital arrival and without support from a dedicated study team. Our out-of-hospital enrollment captures early treatment at the point of injury and during transport, which is more generalizable for out-of-hospital care considerations than traditional acute pain research that frequently enrolls participants in the ED and excludes those receiving out-of-hospital pain management.[19-23]

Although national model EMS protocols and evidence-based guidelines recommend ketamine as an adjunct to opioids, opinions diverge on the use of ketamine when administered via the intranasal route in part because high-quality data are lacking.[3,24-26] Our single fixed dose of 50 mg intranasal ketamine was specifically chosen to reflect Trauma Combat Casualty Care (TCCC) recommendations, and the dosing mirrors existing clinical practices by EMS agencies.[27] Because out-of-hospital providers poorly estimate weight and commonly commit

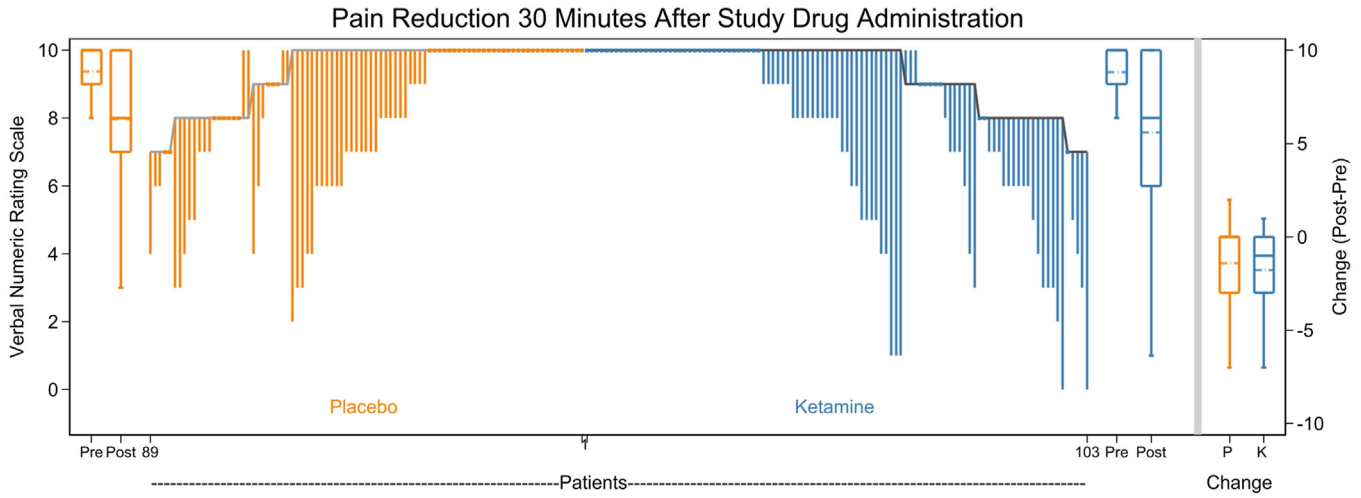

Figure 2. Absolute change from baseline stated verbal numerical rating scale, assessed 30 minutes after receiving study drug. The central parallel line plot shows the verbal numerical rating scale for each participant at baseline and 30 minutes after receiving study drug. The box-whisker plots demonstrate within- and between-group differences. *K*, ketamine; *P*, placebo.

math errors, fixed dose and volume strategies are recommended.[28-30] Based on an estimated 40% bioavailability of ketamine after intranasal administration, our 50 mg intranasal dose translates to the typical intravenous dose range of 0.1 to 0.3 mg/kg range for treating pain in an adult weighing 67 to 200 kg.[24,31,32]

A Canadian trial found that more patients experienced pain relief when intranasal ketamine was added to nitrous oxide, although the dose of ketamine was higher (0.75 mg/kg versus our median 0.6 mg/kg); adverse events were also more common than observed here.[12] After enrollment in this trial concluded, TCCC guidelines increased the recommended fixed dose of intranasal ketamine to 50 to 100 mg, and this higher dose may provide additional analgesia than we observed.[33] Intranasal administration of any medication requires skill, and poor technique may result in drug condensing in the posterior nasopharynx instead of being distributed along the nasal mucosa for rapid absorption. At least 31 participants received intranasal fentanyl as part of initial care, which may have saturated the nasal mucosa prior to ketamine administration, although route of fentanyl administration was similar between groups.

Our 36% response with fentanyl is comparable to other studies comparing usual out-of-hospital pain analgesia to ketamine.[12] The proportion self-reporting recreational use of pain medications, heroin, and/or other intravenous drugs mirrors findings of urine drug screens in trauma patients; underlying opiate tolerance may be a factor in how much analgesia is achieved with the first dose(s) of fentanyl.[34] Although seemingly high, the proportion of participants in our cohort with self-reported pre-existing PTSD and chronic pain symptoms (7% and 29%, respectively) reflects the estimated prevalence in the United States.[35,36]

Despite the relevance of hyperacute enrollment to inform evidence-based practice in the out-of-hospital setting, certain regulatory obligations dictated some methodological choices and constrained the population

Table 2. Reported pain reduction of 2 or more points between the Verbal Numerical Rating Scale obtained prior to out-of-hospital treatment (baseline) and at each time point over up to 3 hours.

	Placebo, n/N (%)	Ketamine, n/N (%)	Difference (%)	95% CI
30 min after dose (primary outcome)	32/89 (36)	46/103 (45)	9	−5% to 23%
30 min after ED arrival	30/83 (36)	44/96 (46)	10	−5% to 24%
60 min after ED arrival	39/81 (48)	47/94 (50)	2	−13% to 17%
90 min after ED arrival	34/72 (47)	47/87 (54)	7	−9% to 22%
120 min after ED arrival	41/74 (55)	47/82 (57)	2	−14% to 18%
150 min after ED arrival	40/66 (61)	45/80 (56)	-5	−20% to 12%
180 min after ED arrival	34/61 (56)	44/71 (62)	6	−11% to 23%

Table 3. Proportion of participants rating side effects as "bothersome" or "very bothersome" at the time of ED arrival.*

	Placebo, n/N (%)	Ketamine, n/N (%)	Difference (%)	95% CI
SERSDA†				
Fatigue	9/83 (11)	7/96 (7)	−4%	−12% to 5%
Dizziness	1/83 (1)	8/96 (8)	7%	1% to 13%
Nausea	2/83 (2)	4/96 (4)	2%	−3% to 7%
Headache	2/82 (2)	5/96 (5)	3%	−3% to 8%
Feeling of unreality	2/83 (2)	4/96 (4)	2%	−3% to 7%
Changes in hearing	1/83 (1)	0/96 (0)	−1%	−4% to 1%
Changes in vision	0/83 (0)	2/96 (2)	2%	−1% to 5%
Mood change	3/83 (4)	9/95 (9)	6%	−1% to 13%
Generalized discomfort	28/83 (34)	25/95 (26)	−7%	−21% to 6%
Hallucination	0/83 (0)	0/95 (0)	0%	0% to 0%
Dry mouth	20/83 (24)	19/95 (20)	−4%	−16% to 8%
Additional side effects				
Abdominal pain	3/82 (4)	0/95 (0)	−4%	−8% to 0%
Breathing problems	3/83 (4)	1/95 (1)	−4%	−7% to 2%
Vomiting	1/83 (1)	0/95 (0)	−1%	−4% to 1%
Skin rash or itching	0/83 (0)	0/95 (0)	0%	0% to 0%
Agitation	9/83 (11)	5/95 (5)	−6%	−14% to 3%
Irritability, nervousness	8/83 (10)	7/95 (7)	−2%	−11% to 6%
Anxiety	5/83 (6)	7/95 (7)	1%	−6% to 9%
RASS‡				
Alert and calm on arrival (RASS=0)	57/88 (65)	53/102 (52)	−12.8%	−26.7% to 1.1%
Alert and calm at 3 h (RASS=0)	40/79 (51)	59/93 (63)	12.8%	−1.9% to 27.6%

RASS, Richmond Agitation-Sedation Scale.
*Side effects were not obtained from 13 participants (6 placebo; 7 ketamine) due to participant treatment needs or study team error. Participants could report more than 1 side effect.
†"Generalized discomfort" was not considered a side effect due to the nature of the trial.
‡Arrival RASS was not recorded in 1 participant receiving placebo. RASS at 3 hours was not recorded for 9 participants receiving placebo and 9 receiving ketamine.

able to be studied and therefore the conclusions able to be drawn from this trial. Withholding treatment until after consent would not be clinically appropriate or morally acceptable, but standardizing the initial fentanyl dose would be considered a research activity requiring consent (and possible Food and Drug Administration Investigational New Drug determination); as a result, we have necessary clinical variability in dose and route of fentanyl administered by paramedics. The requirement for consent likely contributed to a wellness bias and excluded those with the most potential benefit as multisystem trauma, high Injury Severity Scale scores, and pain severe enough to prevent meaningful conversation led to the inability to obtain consent. Indeed, paramedics excluded some participants based on perceived inability to provide consent, and many participants declined consent, possibly due to more severe pain or trauma. We note that our experience and the subsequent limitations informed the recent approval of exception from informed consent for the Prehospital Analgesia INtervention Trial, which compares intravenous fentanyl to intravenous ketamine in patients with suspected hemorrhagic shock (NCT05437575).

Our inability to enroll females is unfortunate because sex differences in pain perception exist and all patients need data-informed care.[37] Ketamine is Food and Drug Administration pregnancy category N (not classified) and animal studies show potential negative impact on brain development.[38] We could not identify a point-of-care test with rapid enough time to results to objectively rule out pregnancy to facilitate enrollment in this trial. These non-modifiable factors will continue to impair out-of-hospital and hyperacute care research until solutions are developed.

In summary, although appearing safe, in this trial of adult males receiving out-of-hospital fentanyl after injury, we could not detect the minimum clinically important

difference in analgesia sought after the addition of 50 mg intranasal ketamine.

We posthumously acknowledge the significant contributions of USAF CMSgt (Ret.) Dario Rodriquez Jr, MSc, RRT, who guided the conception, design, funding, and implementation of this work. We thank Heidi Sucharew, PhD, for assistance in the graphical presentation of our results.

Supervising editor: Steven M. Green, MD. Specific detailed information about possible conflicts of interest for individual editors is available at https://www.annemergmed.com/editors.

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Author contributions: JTM, EJO, and CJL conceived the study. All authors contributed to trial design. JTM and RJS obtained research funding. CJL and KWH provided statistical advice on study design and analyzed the data. JTM drafted the manuscript, and all authors contributed substantially to its revision. JTM takes responsibility for the paper as a whole.

Data sharing statement: Data can be made available, on a case by case basis, through the contact author; because of the regulatory and consent process of this trial, data can only be released after institutional review board approval.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals*' policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist. This trial was funded by the United States Air Force (grant number FA8650-16-2-6G02, issued May 2, 2016).

Publication dates: Received for publication October 4, 2023. Revisions received February 2, 2024, and March 22, 2024. Accepted for publication April 12, 2024.

Trial registration number: ClinicalTrials.gov NCT02866071

Presentation information: We have presented our primary outcome as an abstract at the 2023 National Association of EMS Physicians annual meeting (Tampa, FL; January 26-28, 2023).

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