Intravenous Subdissociative-Dose Ketamine Versus Morphine for Analgesia in the Emergency Department: A Randomized Controlled Trial

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Study objective: We assess and compare the analgesic efficacy and safety of subdissociative intravenous-dose ketamine with morphine in emergency department (ED) patients.

Methods: This was a prospective, randomized, double-blind trial evaluating ED patients aged 18 to 55 years and experiencing moderate to severe acute abdominal, flank, or musculoskeletal pain, defined as a numeric rating scale score greater than or equal to 5. Patients were randomized to receive ketamine at 0.3 mg/kg or morphine at 0.1 mg/kg by intravenous push during 3 to 5 minutes. Evaluations occurred at 15, 30, 60, 90, and 120 minutes. Primary outcome was reduction in pain at 30 minutes. Secondary outcome was the incidence of rescue analgesia at 30 and 60 minutes.

Results: Forty-five patients per group were enrolled in the study. The primary change in mean pain scores was not significantly different in the ketamine and morphine groups: 8.6 versus 8.5 at baseline (mean difference 0.1; 95% confidence interval −0.46 to 0.77) and 3.2 versus 4.2 at 30 minutes (mean difference 0.2; 95% confidence interval −1.19 to 1.46; P=.97). There was no difference in the incidence of rescue fentanyl analgesia at 30 or 60 minutes. No statistically significant or clinically concerning changes in vital signs were observed. No serious adverse events occurred in either group. Patients in the ketamine group reported increased minor adverse effects at 15 minutes post–drug administration.

Conclusion: Subdissociative intravenous ketamine administered at 0.3 mg/kg provides analgesic effectiveness and apparent safety comparable to that of intravenous morphine for short-term treatment of acute pain in the ED. [Ann Emerg Med. 2015;■:1-8.]

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INTRODUCTION

Background

The provision of adequate, safe, and timely analgesia is a core component of patient care in the emergency department (ED). Ketamine is a noncompetitive *N*-methyl-D-aspartate and glutamate receptor antagonist that decreases central sensitization, "wind-up" phenomena, and pain memory.[1,2] As a phencyclidine-like dissociative agent, ketamine possesses a number of pharmacologic characteristics useful to the emergency physician. At doses commonly used for procedural sedation (1 to 1.5 mg/kg), ketamine produces a trancelike cataleptic state, whereas at subdissociative doses (0.1 to 0.6 mg/kg; most commonly 0.3 mg/kg) it maintains potent analgesic and amnestic effects that are accompanied by preservation of protective airway reflexes, spontaneous respiration, and cardiopulmonary stability.[3-5]

Importance

In subdissociative doses, ketamine has been shown to confer potent, opioid-sparing effects and to be effective in providing analgesia for pain that is poorly controlled by opioids in a variety of settings outside of the ED.[6-9] Emerging data on the use of subdissociative-dose ketamine as a single agent in out-of-hospital and austere settings, where it has compared favorably to morphine, support a role for ketamine in the analgesic armamentarium of emergency physicians. Two retrospective studies demonstrated that subdissociative-dose ketamine in the dosing range of 0.1 to 0.6 mg/kg, when administered as an

Editor's Capsule Summary

What is already known on this topic

Ketamine is a potent analgesic.

What question this study addressed

Is ketamine more or less effective than morphine in treating acute pain?

What this study adds to our knowledge

In this trial, 90 adults with acute pain were randomized in the emergency department in double-blind fashion to receive either ketamine at 0.3 mg/kg or morphine at 0.1 mg/kg intravenously. Pain score reductions and the proportion of patients with complete pain relief were statistically similar between groups, with reasonable power to exclude clinically important differences. There were no serious adverse events, although ketamine subjects more frequently experienced dizziness and disorientation.

How this is relevant to clinical practice

This small but well-designed trial suggests generally similar analgesic equivalence between ketamine at 0.3 mg/kg and morphine at 0.1 mg/kg intravenously.

adjunct to opioid analgesics, significantly reduced pain reported by patients in the ED.[10,11]

Goals of This Investigation

In our study, we hypothesize that a subdissociative dose of ketamine administered as a single agent at 0.3 mg/kg will provide relief similar to that of a standard dose of morphine at 0.1 mg/kg for acute moderate to severe pain in the ED setting. The primary outcome used to test our hypothesis is the comparative reduction in participants' pain scores at 30 minutes from medication administration.

MATERIALS AND METHODS

Study Design

This was a prospective, randomized, double-blind trial comparing the safety and efficacy of subdissociative intravenous-dose ketamine with intravenous morphine for acute pain in the ED. This study was approved by the Maimonides Medical Center institutional review board and registered with clinicaltrials.gov (NCT01835262). The study was conducted and is reported according to the Consolidated Standards of Reporting Trials Group.[12]

Study Setting and Selection of Participants

The study facility is a 711-bed community teaching hospital with an annual ED census of more than 120,000 visits. Patient screening, enrollment, and data collection were performed by a study investigator (B.R., I.P., and V.T.). ED pharmacy investigators maintained the randomization list, which was generated before commencement of the study, prepared the medication, and delivered it to the nurse caring for the study participant in a blinded manner.

A convenience sample of patients was enrolled between June 2013 and May 2014. Enrollment occurred at various times of the day when both a study investigator was available for patient enrollment and an ED pharmacist was available for medication preparation.

The study included patients aged 18 to 55 years who presented to the ED with acute abdominal, flank, back, or musculoskeletal pain score of 5 or more on a standard 11-point (0 to 10) numeric rating scale and required opioid analgesia, as determined by the treating attending physician.[13,14] Acute pain was defined as having an onset within 7 days. Exclusion criteria included pregnancy, breast-feeding, altered mental status, allergy to morphine or ketamine, weight less than 46 kg or greater than 115 kg, unstable vital signs (systolic blood pressure <90 or >180 mm Hg, pulse rate <50 or >150 beats/min, and respiration rate <10 or >30 breaths/min), and medical history of acute head or eye injury, seizure, intracranial hypertension, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4 hours before) opioid use.

Each patient was approached by a study investigator for acquisition of written informed consent and Health Insurance Portability and Accountability Act authorization after being evaluated by the treating emergency physician and determined to meet study eligibility criteria.

In situations in which English was not the participant's primary language, a staff interpreter or licensed telephone interpreter was used. Baseline pain score was determined with an 11-point numeric rating scale (0 to 10), described to the patient as "no pain" being 0 and "the worst pain imaginable" being 10. A patient was eligible for enrollment if a baseline numeric rating scale score of 5 or greater was reported. A study investigator then recorded the patient's body weight and baseline vital signs.

The on-duty ED pharmacist prepared 0.3 mg/kg of ketamine or 0.1 mg/kg of morphine in 10 mL of normal saline solution according to the predetermined randomization list, which was created in SPSS (version 19.0; IBM Corp, Armonk, NY) with block randomization every 10 participants, up to 90. The medication was delivered to the treating nurse in a blinded fashion and was

administered by intravenous push during 3 to 5 minutes. The preparing pharmacist, research manager, and statistician were the only members of the team with knowledge of the study arm to which the participant was randomized, leaving the providers, participants, and data-collecting research team blinded to the medication received. Study investigators recorded pain scores, vital signs, and adverse effects at 15, 30, 60, 90, and 120 minutes. If patients reported a pain numeric rating scale score of 5 or greater and requested additional pain relief, fentanyl 1 μ/kg was administered as a rescue analgesic. Blinding of the patient, research team, and clinical staff was strictly maintained by the on-duty ED pharmacist.

All data recorded on data collection sheets, including sex, demographics, medical history, and vital signs, were entered into SPSS (version 19.0; IBM Corp) by the research manager. Development of the randomization list, confirmation of written consent acquisition for all participants, and statistical analyses were conducted by the research manager and statistician, who were independent of any data collection.

Outcome Measures

The primary outcome was comparative reduction of numeric rating scale pain scores between recipients of ketamine and morphine at 30 minutes. The secondary outcome was need for rescue analgesia at either 30 or 60 minutes. Vital sign changes and adverse events were also analyzed.

Primary Data Analysis

Data analyses included frequency distributions, paired *t* test to assess a difference in pain scores within each group, and independent-sample *t* test to assess differences in pain scores between the 2 groups at the various intervals (SPSS, version 19.0; IBM Corp). Mixed-model linear regression (SAS, version 9.1; SAS Institute, Inc., Cary, NC) was used to compare changes in pain numeric rating scale across time points. This compensated for participants lost to follow-up and allowed all patients' data to be analyzed on an intention-to-treat principle. A mean contrast test based on the mixed-model linear regression results compared the primary outcome difference at 30 minutes relative to time 0. The 95% confidence limits for the mean difference in numeric rating scale pain score for the ketamine versus morphine groups at each time point were calculated with 2 estimate methods for the pooled SD. One method was based on the pooled SD from the bivariate *t* test comparison at each specific time point, whereas the other method was based on the pooled SD from the repeated-measures ANOVA. The latter method uses data at all time points and provides a more reliable estimate of the SD. For categorical outcomes (eg, complete resolution of pain), a χ^2 or Fisher's exact test was used to compare rates for categorical outcomes at 30 minutes. Percentage differences and 95% confidence limits between the treatment groups were calculated for all time points. $P<.05$ was used to denote statistical significance.

In accordance with the validation by Bijur et al[15] of a verbally administered rating scale of acute pain in the ED and the comparison by Holdgate et al[16] of verbal and visual pain scales, we assumed a primary outcome consisting of a minimal clinically meaningful difference of 1.3 between the ketamine and morphine groups at the 30-minute pain assessment. Assuming an SD of 3.0, a power analysis determined that a repeated-measures ANOVA with a sample size of 90 (45 in each group) provided at least 83% power to detect a difference of at least 1.3 at 30 minutes (as well as at any other interval postbaseline), with an $\alpha=.05$.

RESULTS

Ninety patients (45 ketamine and 45 morphine) were enrolled in the study. The patients' mean age was 35 and 36 years, respectively (SD=10 for both groups); 67% and 62% were women, respectively. There were no differences between the groups in terms of demographic characteristics or baseline vital signs, pain scores, or chief complaint (Table 1). The patient flow diagram is illustrated in Figure 1.

As shown in Table 2, patients' reported pain scores at time 0 were similar in the 2 groups: the mean difference in pain numeric rating scale score for ketamine versus morphine was 0.1 (95% confidence interval [CI] –0.46 to 0.77). Participants received an average dose of either

Table 1. Demographics and clinical characteristics of patients at enrollment.

Characteristics	Group		Difference (95% CI)
	Ketamine	Morphine	
No. of patients	45	45	
Age, mean (SD), y	35 (9.5)	36 (10.5)	−1 (−5.1 to 3.3)
Sex			
Female, No. (%)	30 (67)	28 (62)	5 (−16 to 25)
Weight, mean (SD), kg	74 (15.9)	78 (16.6)	−4 (−11.4 to 2.2)
Blood pressure, mean (SD), mm Hg			
Systolic	125 (18.2)	127 (16.1)	−2 (−8.8 to 5.6)
Diastolic	76 (13.2)	74 (12.7)	2 (−3.6 to 7.3)
Pulse rate, beats/min	79 (14.8)	79 (15.0)	0 (−6.8 to 5.6)
Source of pain, No. (%)			
Abdominal	33 (73)	31 (69)	4 (−15 to 24)
Flank	7 (16)	9 (20)	−4 (−21 to 12)
Other*	5 (11)	5 (11)	0 (−13 to 13)

*Other pain sources include back and musculoskeletal pain.

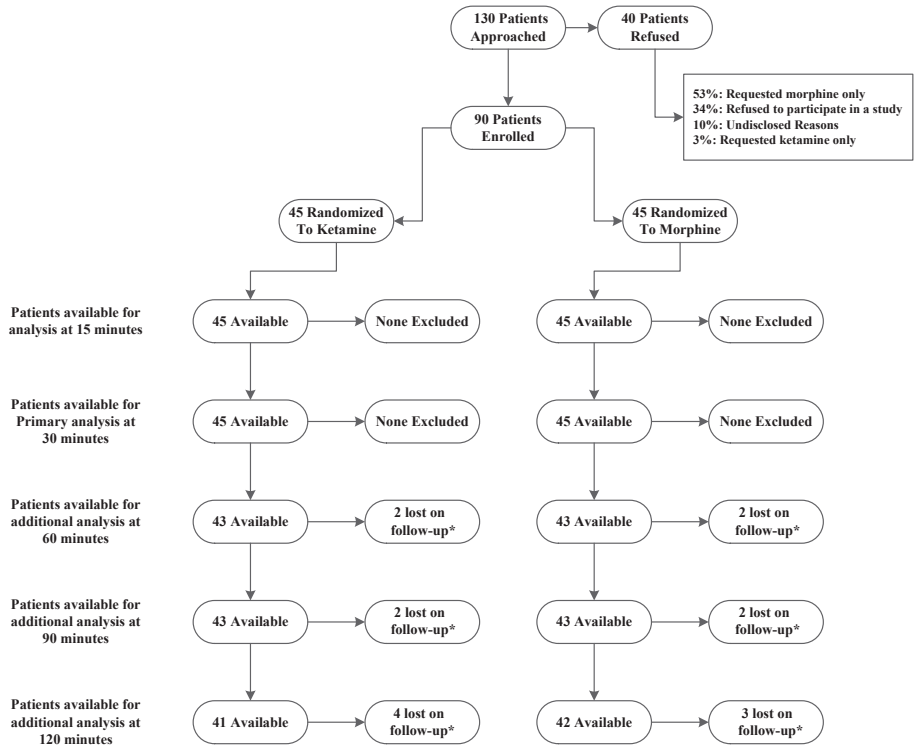

Figure 1. Participant flow diagram. *Patients were lost to follow-up because of either discharge or transfer from the ED.

21.8 mg (SD=4.9) of ketamine or 7.7 mg (SD=1.6) of morphine. All patients showed significant reductions in mean pain numeric rating scale score at 15 and 30 minutes compared with baseline. However, there were no statistically significant differences between the 2 groups at either point. At 15 minutes, the mean difference in pain numeric rating scale score was –1.0 (95% CI –2.40 to 0.31). At 30 minutes, the primary outcome comparison, the mean difference, was 0.2 (95% CI –1.19 to 1.46; *P*=.97). The 95% CI for the mean difference at 30 minutes according to the mixed-model regression SD was –0.77 to 1.05. The parallel line plots (Figure 2) presenting the changes in pain numeric rating scale score for each group from baseline to 30 minutes show almost the same pattern of decrease, with the exception of 1 patient in the ketamine group who showed an increase from 9 to 10. The box plots of the difference likewise show a similar pattern of central tendency and dispersion. As shown in Figure 3, comparison of the pain scores over all time points demonstrates similar mean pain numeric rating scale scores in the 2 study groups.

At 15 minutes, more patients reported complete resolution of pain (numeric rating scale=0) in the ketamine group (percentage difference=31%; 95% CI 13% to 49%). However, this difference was no longer present at 30 minutes (percentage difference=3%; 95% CI –16% to 21%). All of the patients who reported complete resolution of pain did so with the analgesic benefit of the study medication and without the use of a rescue analgesic dose of fentanyl during these measurement intervals. There were no statistically significant differences between the groups in the proportion of patients reporting a 3-point or more reduction in pain numeric rating scale score. There was also no significant difference between the 2 groups with respect to use of rescue fentanyl analgesia at 30 minutes (percentage difference=7%; 95% CI –3% to 16%) or at 60 minutes (percentage difference=–5%; 95% CI –18% to 9%). At 120 minutes, the ketamine group required significantly more rescue fentanyl (percentage difference=17%; 95% CI 1% to 34%) (Table2).

No serious or life-threatening adverse events occurred in either medication group; these included, but were not limited to, respiratory distress, seizures, and cardiac arrest. There were no changes in vital signs that were clinically concerning or required intervention (Table E1, available online at http://www.annemergmed.com). All adverse effects were transient and did not require treatment.

A statistically significant difference was observed in the number of ketamine patients who reported any adverse effects immediately after the medication injection and at 15 minutes (percentage difference=38%; 95% CI 18% to 57%). This difference in adverse effects diminished to

Table 2. Pain trends.

Time Interval*	Group		
	Ketamine	Morphine	Difference (95% CI)
Pain NRS, mean (SD)			
Baseline	8.6 (1.5)	8.5 (1.5)	0.1 (−0.46 to 0.77)
15	3.2 (3.5)	4.2 (2.9)	−1.0 (−2.40 to 0.31)
30	4.1 (3.2)	3.9 (3.1)	0.2 (−1.19 to 1.46)†
60	4.8 (3.2)	3.4 (3.0)	1.4 (0.13 to 2.75)
90	4.8 (3.1)	3.9 (3.1)	0.9 (−0.37 to 2.28)
120	3.9 (2.9)	3.7 (2.9)	0.2 (−1.09 to 1.46)
Complete resolution of pain, No. (%)			
15	20 (44)	6 (13)	31 (13.1 to 49.2)
30	12 (27)	11 (24)	3 (−16.3 to 20.7)
60	9 (21)	12 (27)	−6 (−25.6 to 11.6)
90	7 (16)	9 (21)	−5 (−21.5 to 12.2)
120	9 (22)	9 (21)	1 (−17.7 to 18.8)
Reduction of 3+ NRS, No. (%)			
15	34 (75)	31 (69)	6 (−12.3 to 25.6)
30	33 (73)	31 (69)	4 (−14.7 to 23.6)
60	25 (58)	33 (77)	−19 (−38.5 to 1.3)
90	23 (54)	33 (77)	−23 (−43.3 to -3.2)
120	29 (71)	33 (79)	−8 (−27.0 to 11.3)
Fentanyl rescue incidence, No. (%)			
15	0	0	0
30	4 (9)	1 (2)	7 (−2.9 to 16.3)
60	4 (9)	6 (14)	−5 (−18.1 to 9.0)
90	5 (11)	5 (12)	−1 (−13.1 to 14.1)
120	12 (29)	5 (12)	17 (0.8 to 34.2)

NRS, Numeric rating scale.
*Minutes from time of medication injection.
†95% CI −0.77 to 1.05 is based on the SD from the mixed-model regression.

equivalence with morphine at the 30-minute interval (Table 3). The most common adverse effects reported by ketamine patients were dizziness, disorientation, mood changes, and nausea. Dizziness and nausea were also reported by morphine patients.

LIMITATIONS

This was a single-center study in which patients were enrolled as a convenience sample according to predetermined inclusion and exclusion criteria. Sample size was near minimum for adequate power (80%). There was a potential for unblinding because some participants exhibited ketamine-specific reactions such as nystagmus. Patient enrollment was restricted to time frames in which both a member of the research team and pharmacy team were available.

DISCUSSION

Subdissociative ketamine has been shown to mitigate pain and reduce opioid consumption in patients with chronic pain (neuropathic pain), cancer pain, and acute postoperative pain, as demonstrated in the anesthesia and surgical literature.[17-20] There have been several published retrospective studies and prospective trials examining ketamine used for analgesia in ED patients. Lester et al[10] evaluated 35 patients who received subdissociative ketamine for analgesia and reported that 19 patients (54%) experienced pain relief after opioid analgesics had failed. Richards and Rockford[11] evaluated 24 patients who received subdissociative ketamine and reported an overall reduction in pain score of 5 points (8.9 [SD=2.1] to 3.9 [SD=3.4]); however, 18 patients (75%) had received opioid analgesics before ketamine. In addition, 55% of patients reported satisfaction with subdissociative ketamine analgesia and 67% stated that they would choose ketamine analgesia again.[11] Neither study reported significant adverse effects in the ketamine recipients. Several prospective randomized trials examined the analgesic effect of subdissociative ketamine and morphine combination on patients with traumatic and nontraumatic pain. An out-of-hospital study by Johansson et al[21] demonstrated statistical improvement in pain reduction by 4.4 points with the use of morphine-ketamine combination in comparison to 3.1 points with morphine alone. The 3-arm trial by Beaudoin et al[22] that evaluated 2 different doses of subdissociative ketamine-morphine combinations compared with morphine alone for ED analgesia showed a clinically significant decrease in pain intensity for more than 50% of patients who received morphine (0.1 mg/kg) and ketamine (0.15 or 0.3 mg/kg) combination compared with the morphine-only group. In addition, the authors concluded that morphine combined with ketamine at a dose of 0.3 mg/kg had more efficacious analgesic effect than a combination using a ketamine dose of 0.15 mg/kg.[22] Last, Miller et al[23] conducted the first randomized controlled superiority trial directly comparing subdissociative ketamine to morphine for acute pain in the ED. The results showed that ketamine administered at a dose of 0.3 mg/kg ketamine did not provide a superior maximum reduction in numeric rating scale pain scores compared with morphine at 0.1 mg/kg.

In our prospective, randomized, double-blind trial, we compared single subdissociative-dose ketamine with single-dose morphine for ED patients experiencing acute severe pain. Our study suggests that subdissociative ketamine is as effective as morphine in relieving pain at 15 and 30 minutes. The subdissociative ketamine group had a larger proportion of patients who reported complete resolution of pain (numeric rating scale score=0), without the use of analgesic fentanyl rescue, at 15 minutes (44% versus 13%); however, there was no difference between the groups in pain resolution or change in pain scores at 30 minutes. There was

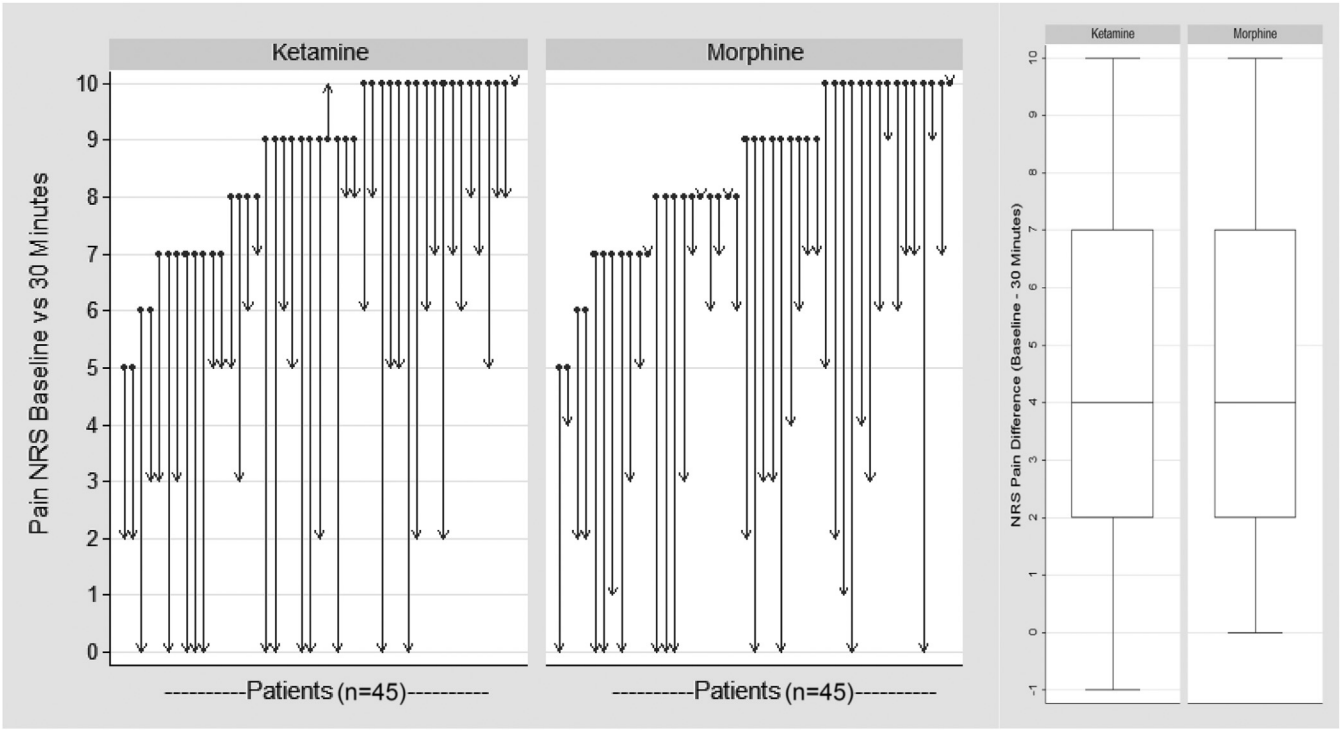

Figure 2. Parallel line and box plots of pain scores: baseline versus 30 minutes. The parallel line plots contrast the change in each patient's pain numeric rating scale score from baseline to 30 minutes in the ketamine versus the morphine group, whereas the box plots show the overall group changes in pain numeric rating scale score between the ketamine and morphine groups.

also no difference in the proportion of patients who reported a 3-point or more reduction in pain numeric rating scale score at either interval. These findings suggest that subdissociative ketamine is as effective as morphine in the reduction of acute pain within 15 minutes of administration.

No participants in either group experienced clinically concerning adverse events or changes in vital signs. However, the subdissociative ketamine recipients did experience a statistically significant increase in adverse effects immediately postinjection and at the 15-minute interval, with high percentages of participants experiencing dizziness and disorientation compared with the morphine recipients

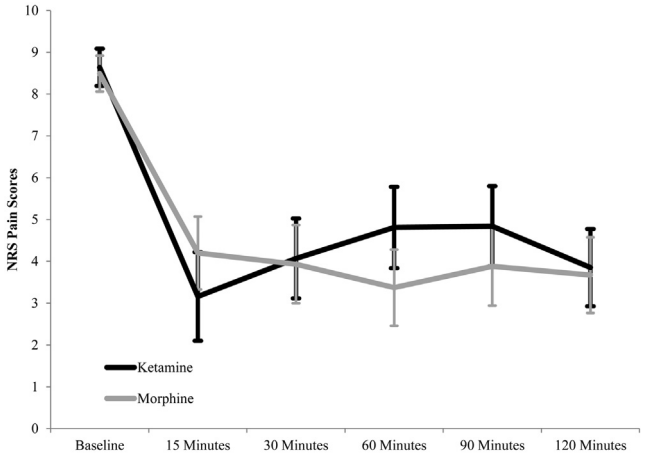

Figure 3. Reported pain numeric rating scale score with 95% CI bars.

Table 3. Adverse effects.

	Group*		
Time Interval	**Ketamine**	**Morphine**	**Difference (95% CI)**
Report of any adverse effect			
Postinjection	33 (73)	23 (51)	22 (2.2 to 42.2)
15 min	31 (69)	14 (31)	38 (18.2 to 57.4)
30 min	16 (36)	15 (33)	3 (−17.9 to 22.3)
Most common adverse effects			
Dizziness			
Postinjection	24 (53)	14 (31)	22 (1.8 to 42.6)
15 min	19 (42)	9 (20)	22 (3.2 to 41.3)
30 min	8 (18)	6 (13)	5 (−10.9 to 19.8)
Disorientation			
Postinjection	13(29)	1 (2)	27 (12.4 to 40.9)
15 min	5 (11)	0	11 (1.7 to 20.5)
30 min	1 (2)	0	2 (−2.2 to 6.6)
Mood changes			
Postinjection	6 (13)	1 (2)	11 (0 to 22.2)
15 min	5 (11)	0	11 (1.7 to 20.5)
30 min	1 (2)	0	2 (−2.2 to 6.6)
Nausea			
Postinjection	4 (9)	4 (9)	0 (−12.1 to 12.1)
15 min	8 (18)	5 (11)	7 (−8.2 to 21.5)
30 min	6 (13)	9 (20)	−7 (−22.4 to 9.1)

*Data are presented as No. (%).

(Table 3). These findings are consistent with those of previous trials of ketamine and opioid combination regimens. Ahern et al[24] found that 24 of 30 out-of-hospital patients (80%) receiving an intravenous combination of hydromorphone (0.5 mg) and ketamine (15 mg) experienced an adverse effect, with dizziness being the most common. These results were observed again in the study by Beaudoin et al,[22] in which 9 of 20 (45%) of the morphine (0.1 mg/kg) and ketamine (0.3 mg/kg) group reported lightheadedness or dizziness. We believe further investigation of ketamine dose ranges and duration of infusion will help to diminish the adverse effects experienced by patients while maintaining analgesic efficacy similar to that of morphine.

Subdissociative-dose intravenous ketamine administered at 0.3 mg/kg provides analgesic effectiveness and apparent safety comparable to that of intravenous morphine for short-term treatment of acute moderate to severe pain in the ED.

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Author contributions: SM, VC, IP, AL, ES-Z, and CF conceived the study, designed the trial, and obtained research funding. SM, BR, AL, and CF supervised the conduct of the trial and data collection. BR, IP, CM, and VT undertook recruitment of patients and managed the data, including quality control. AL and PH provided statistical advice on study design and data analysis. BR drafted the article, and all authors contributed substantially to its revision. SM takes responsibility for the paper as a whole.

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Table E1. Vital signs.

	Group		
Time Interval	**Ketamine**	**Morphine**	**Difference (95% CI)**
Pulse rate, mean (SD), beats/min			
Preinjection	79 (14.8)	79 (15.0)	0 (−6.8 to 5.6)
15 min	85 (18.7)	82 (14.5)	3 (−3.7 to 10.4)
30 min	78 (14.6)	82 (14.7)	−4 (−9.8 to 2.8)
Systolic blood pressure, mean (SD), mm Hg			
Preinjection	125 (18.2)	127 (16.1)	−2 (−8.8 to 5.6)
15 min	134 (18.6)	122 (17.5)	12 (3.9 to 19.4)
30 min	128 (18.5)	123 (17.3)	5 (−2.7 to 12.8)
Diastolic blood pressure, mean (SD), mm Hg			
Preinjection	76 (13.2)	74 (12.7)	2 (−3.6 to 7.3)
15 min	82 (14.1)	72 (10.6)	10 (4.4 to 15.0)
30 min	76 (12.7)	72 (9.9)	4 (−1.6 to 8.3)
Respiratory rate, mean (SD), breaths/min			
Preinjection	18 (5.7)	18 (4.4)	0 (−2.1 to 2.2)
15 min	19 (4.5)	17 (4.1)	2 (0.6 to 4.2)
30 min	18 (5.0)	18 (4.0)	0 (−1.4 to 2.5)
Oxygen saturation, mean (SD), %			
Preinjection	99 (1.3)	98 (2.0)	1 (0.3 to 1.7)
15 min	99 (2.0)	98 (2.3)	1 (0.2 to 2.0)
30 min	99 (2.0)	98 (1.9)	1 (0.1 to 1.8)