

Original Contribution

Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial^{☆,☆☆}



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ABSTRACT

Objectives: To compare the maximum change in numeric rating scale (NRS) pain scores, in patients receiving low-dose ketamine (LDK) or morphine (MOR) for acute pain in the emergency department.

Methods: We performed an institutional review board–approved, randomized, prospective, double-blinded trial at a tertiary, level 1 trauma center. A convenience sample of patients aged 18 to 59 years with acute abdominal, flank, low back, or extremity pain were enrolled. Subjects were consented and randomized to intravenous LDK (0.3 mg/kg) or intravenous MOR (0.1 mg/kg). Our primary outcome was the maximum change in NRS scores. A sample size of 20 subjects per group was calculated based on an 80% power to detect a 2-point change in NRS scores between treatment groups with estimated SDs of 2 and an α of .05, using a repeated-measures linear model.

Results: Forty-five subjects were enrolled (MOR 21, LDK 24). Demographic variables and baseline NRS scores (7.1 vs 7.1) were similar. Ketamine was not superior to MOR in the maximum change of NRS pain scores, MOR = 5 (confidence interval, 6.6–3.5) and LDK = 4.9 (confidence interval, 5.8–4). The time to achieve maximum reduction in NRS pain scores was at 5 minutes for LDK and 100 minutes for MOR. Vital signs, adverse events, provider, and nurse satisfaction scores were similar between groups.

Conclusion: Low-dose ketamine did not produce a greater reduction in NRS pain scores compared with MOR for acute pain in the emergency department. However, LDK induced a significant analgesic effect within 5 minutes and provided a moderate reduction in pain for 2 hours.

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1. Introduction

Pain is the most common complaint for emergency department (ED) visits [1]. Opioids, commonly morphine, are the standard treatment of moderate and severe, acute pain in the ED. However, many patients report inadequate pain control in the ED [2,3]. Patients with opioid dependence may present to the ED in anticipation of obtaining treatment with opioids [4]. In addition, the serious adverse effect profile of opioids can be underappreciated given their common use in the ED. In 2012, the Joint Commission released a *Sentinel Event Alert*, which stated that opioid analgesics rank among the drugs most frequently associated with adverse drug events. Of the opioid-related adverse drug events—including deaths—that occurred in hospitals and were reported to The Joint

Commission's Sentinel Event database (2004–2011), 47% were wrong dose medication errors, 29% were related to improper monitoring of the patient, and 11% were related to other factors, including excessive dosing, medication interactions, and adverse drug reactions [5].

Like opioids, ketamine has analgesic properties [6–9]. Ketamine, however, has a very large therapeutic window. Overdoses from 5 to 100 times the therapeutic dose have been reported without adverse outcomes [10]. In addition, the adverse effect profile of ketamine (elevated pulse and blood pressure, hallucinations, emergence) is much different from that of opioids (decreased pulse, blood pressure, and respiratory rate, sedation).

The predominant use of ketamine in the ED, as well as the focus of research, has been as a dissociative agent (1.5–2 mg/kg intravenous [IV]) to facilitate procedural sedation [11–14]. There were a small number of non-ED studies with low-dose ketamine (<0.55 mg/kg IV) from as early as the 1970s which reported efficacious analgesia without dissociation [15,16]. More recent studies from the ED and prehospital environment have shown that low-dose ketamine, when used alone or in combination, provides safe and efficacious analgesia [8,9,17–19]. These studies, however, are limited in that opioids or sedatives were used in conjunction with low-dose ketamine; patients were treated for chronic pain, not acute pain, or there was no comparison arm.

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Studies are needed to independently compare the safety and efficacy of opioids to other analgesics, such as ketamine, in order to ensure that patients are receiving the safest and most effective pain management possible when experiencing acute pain in the ED. Thus far, a prospective, randomized, double-blinded trial comparing low-dose ketamine alone to morphine for the treatment of acute pain in the ED has not been reported.

The goal of this study was to compare the ability of low-dose ketamine and morphine to reduce acute pain as measured by the numeric rating scale (NRS). In addition, we describe the details of ketamine analgesia over time in an ED population. Finally, we also sought to examine the reduction of pain as measured by provider and nurse satisfaction scores.

2. Methods

2.1. Study design

Our study was a prospective, randomized, controlled, double-blinded, superiority trial comparing the efficacy of IV low-dose ketamine to IV morphine for moderate to severe acute pain in the ED setting. We hypothesized that ketamine would provide a greater maximum reduction in pain compared with morphine. The Brooke Army Medical Center Institutional Review Board in San Antonio, TX, approved the study protocol. Written and signed informed consent was obtained in accordance with institutional policy.

2.2. Setting

The study was conducted in a military, level 1 trauma center ED, where approximately 80000 ED patients are treated annually. The ED patient population consists of uniformed military personnel (20%) and civilians (80%). Enrollment occurred from February 2012 to March 2013.

2.3. Study protocol

A convenience sample of patients was obtained by a full-time, trained, research nurse coordinator using a standard enrollment protocol. Patients were screened at triage during daytime and evening hours on weekdays. Patients were eligible for inclusion if they were between the ages of 18 and 59 years and complained of abdominal, flank, low back, or extremity pain that the ED provider felt warranted IV opioid treatment. Patients were excluded if any of the following were met: oxygen saturation less than 95%, systolic blood pressure less than 90 mm Hg or greater than 180 mm Hg, pulse rate less than 50 or greater than 120 beats/min, respiratory rate less than 10 or greater than 30 respirations/min, altered mental status, intoxication, fibromyalgia or other chronic pain condition requiring the use of opioids or tramadol as an outpatient, ischemic heart disease, heart failure or unstable dysrhythmias, use of an opioid or tramadol within 4 hours prior to enrollment, an allergy to morphine or ketamine, required pain medication immediately, pregnant or breast-feeding, history of chronic oxygen-dependent pulmonary disease, hepatic cirrhosis, or dialysis dependent, presence of intracranial mass, a history of psychosis, weight less than 45 kg or greater than 115 kg, or presence of acute ocular or head trauma.

Eligible patients, in whom opioid analgesia was anticipated, gave written consent immediately after triage and the blinded study protocol was implemented: (1) if the provider prescribed opioid analgesia and (2) if the provider was agreeable after being made aware of the patient's consent to the protocol. The trial was open to all patients regardless of the provider and nurse caring for the patient. All enrolled patients gave written consent.

Once enrolled, patients were assigned a random study identification number and an opaque envelope. The envelopes were prepared by the research team and contained the study drug and dose. Upon enrollment, the research nurse would obtain the assigned opaque envelope and give

it to a trained clinical nursing specialist (CNS). The CNS would then open the envelope containing a presigned prescription with the assigned medication and weight-based dosing. The CNS would obtain the drug from the ED dispensing system in an unlabeled syringe, dilute the medication to 10 mL (a 20-mL syringe was used if the body weight precluded the medication from fitting into a 10-mL syringe) using normal saline as indicated, and infuse the medication for 5 minutes. Unused medications were disposed of using standard nursing protocols.

An initial dose of ketamine at 0.3 mg/kg of total body weight (maximum dose 25 mg) was infused intravenously for 5 minutes, or morphine at 0.1 mg/kg of total body weight (maximum dose 8 mg) was infused intravenously for 5 minutes. Completion of the initial infusion was considered time zero. A second dose could be given as early as 20 minutes after completion of the initial dose and was the same dose as the first dose. The protocol allowed for midazolam treatment of agitation or emergence reactions and naloxone treatment of evidence of opioid overdose. All other medication reactions were treated at the provider's discretion. If the patient requested a third dose of pain medication, data collection stopped, the provider was notified, and the patient was eligible for open-label pain medication of the providers choosing (Fig. 1).

There was one major protocol deviation. The CNS calculated the dose of the study medication based on the patient's weight and administered the weight-based dose to the patient. The resulting dose was greater than the maximum dose allowed by the protocol. There were no adverse events as a result of this deviation, and the deviation was reported to our institutional review board.

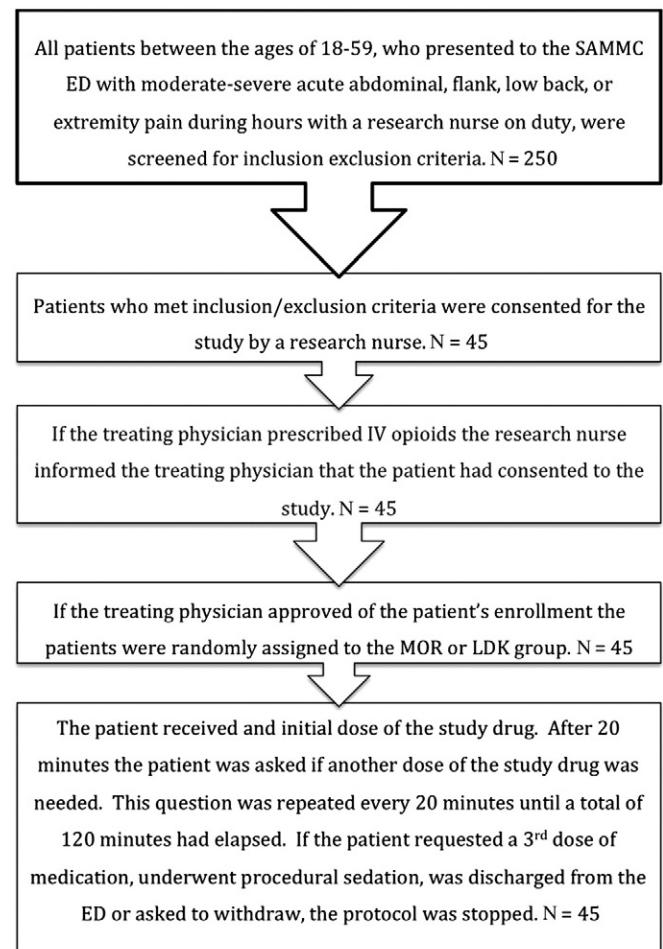


Fig. 1. CONSORT diagram. SAMMC, San Antonio Military Medical Center; MOR, morphine; LDK, low-dose ketamine.

2.4. Measures

Our primary outcome measurement was the maximum change on the verbal NRS pain scale compared with their initial score (baseline). The NRS was used to measure a patient's subjective level of pain on a scale from 0 (representing no pain at all) to 10 (the worst pain imaginable) using whole numbers. This scoring system is commonly used in the ED and correlates well with the visual analog scale [20] and has been used in clinical trials [20–24]. The NRS score was documented just prior to the administration of the study drug (time zero). After infusion of the study drug was complete, NRS scores were documented at 5, 10, 20, and then every 20 minutes thereafter up to 120 minutes. We stopped recording NRS scores prior to 120 minutes if the patient was discharged from the ED, underwent procedural sedation, or requested a third dose of the study drug.

The secondary outcomes included levels of agitation or sedation measured by the Richmond Agitation-Sedation Scale (RASS), vital signs, adverse events, and the need for repeating dosing [25,26]. Providers and nurses were surveyed after the patient encounter ended to rate their satisfaction with the study medication. They scored the medication as “very dissatisfied” (1), “somewhat dissatisfied” (2), “neither satisfied nor dissatisfied” (3), “somewhat satisfied” (4), or “very satisfied” (5).

All data were collected by our research nurse and stored in a locked, password encrypted, electronic database (Microsoft Excel, v14; Microsoft, Redmond, WA)

2.5. Data analysis

Power analysis determined that a sample size of at least 20 subjects per group would achieve 80% power to detect a 2-point change in NRS scores between treatment groups, with estimated group SDs of 2 for a 2-sided test with a significance level α of .05 (PASS-NCCS, 2011, Kaysville, UT). We used a repeated-measures linear model with adjustments for treatment group, time, and the group by time interaction with an autoregressive covariance structure (SAS Version 9.3 for Windows; SAS Institute, Cary, NC). Differences between drug groups were tested at each time point with the Sidak method of adjustment applied for multiple testing. All analyses were performed with intention to treat.

3. Results

A total of 45 patients were enrolled from March to November 2012; 21 in the morphine arm and 24 in the low-dose ketamine arm. Demographic characteristics were similar between the 2 groups including mean age, sex, baseline vital signs, chief complaint, and baseline NRS scores (Table 1).

Table 1
Patient characteristics by treatment group

	Morphine	Low-dose ketamine	Both treatment groups
Age (y), mean (SD)	29 (10)	31 (12)	30 (11)
Male sex	9 (43)	14 (58)	23 (51)
Vital signs, mean (SD)			
Systolic blood pressure (mm Hg)	121 (11)	126 (14)	124 (13)
Pulse rate (BPM)	74 (11)	76 (11)	75 (11)
Respiratory rate (RPM)	18 (3)	18 (3)	18 (3)
Oxygen saturations (%)	98 (1)	98 (2)	98 (2)
Baseline NRS pain score, mean (SD)	7.14 (1.5)	7.13 (1.7)	7.14 (1.6)
Pain location			
Abdomen	15 (71)	15 (65)	30 (68)
Back	4 (19)	8 (35)	12 (27)
Extremity	2 (10)	0 (0)	2 (5)

All results reported as no. (%) unless otherwise indicated. BPM, beats per minutes; RPM, respirations per minutes.

Table 2
NRS pain score: raw change from baseline by treatment group

Time	Morphine (95% CI)	Low-dose ketamine (95% CI)
T5	−3 (−3.9, −2.1)	−4.9 (−5.8, −4)
T10	−3.4 (−4.4, −2.5)	−4.3 (−5.5, −3.1)
T20	−3.3 (−4.4, −2.2)	−3.2 (−4.4, −2.1)
T40	−4.5 (−5.6, −3.5)	−3.7 (−5.2, −2.3)
T60	−4.8 (−5.8, −3.8)	−3.5 (−5.4, −1.6)
T80	−4.4 (−5.9, −2.9)	−3.9 (−6.1, −1.6)
T100	−5 (−6.6, −3.5)	−4.1 (−6.8, −1.5)
T120	−5 (−7.1, −2.9)	−3.6 (−6.1, −1)

T5 was 5 minutes after drug administration. T120 was 120 minutes after drug administration and end of our observation period. Bolded texts emphasize time of maximum change in NRS pain score from baseline for each group: morphine (T100) and low-dose ketamine (T5).

The primary outcome measurement was the maximum reduction in NRS score from baseline between the 2 groups (Table 2). The maximum change in NRS pain score, from baseline, in the low-dose ketamine group was 4.9 (95% confidence interval [CI], 5.8–4). The maximum change in NRS pain score, from baseline, in the morphine group was 5 (95% CI, 6.6–3.5). The maximum change in NRS pain score took place at 5 minutes (T5) in the low-dose ketamine group and at 100 minutes (T100) in the morphine group.

We reported the NRS scores as a percentage change from baseline over time. In the morphine group, there was a steady trend of reduced pain over time. In the ketamine group, there was an initial decrease in pain scores followed by a rapid increase in pain scores within the first 20 minutes. However, after the 20-minute mark, the pain decreased by greater than 50% from baseline in the low-dose ketamine group (Fig. 2).

A second dose was administered in 38% of the morphine group vs 54% of the ketamine group ($P = .37$; Table 3). A third dose was requested for 14% of the morphine arm and 25% of the ketamine arm ($P = .47$).

Richmond Agitation-Sedation Scale scores varied within the first 20 minutes after drug administration in both groups. There was minimal variation from baseline after T20 (Fig. 3).

Significant treatment group differences (mean, 95% CI) in systolic blood pressure (mm Hg) were observed at T5 (23, 9–38) and T10 (14, 0–29; Fig. 4). No differences were found in diastolic blood pressure, heart rate, respiratory rate, or oxygen saturations (Figs. 5–8).

Fourteen patients (58%) in the low-dose ketamine group and 12 (57%) patients in the morphine group described adverse effects (Table 4). One patient in the morphine arm had a transient oxygen desaturation to 88%, which resolved after 5 minutes of oxygen via nasal cannula at 4 L/min. Two patients in the morphine arm and 3 patients in the ketamine arm were treated for nausea. One patient in each group

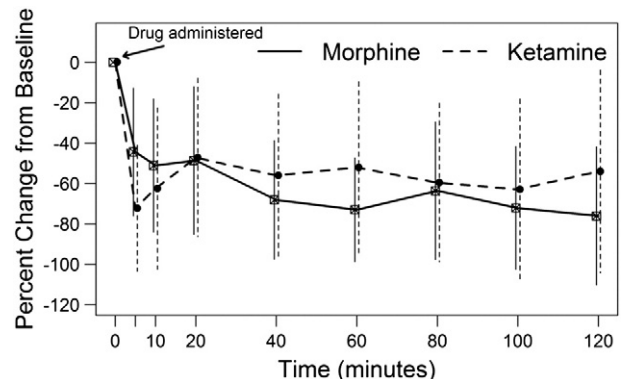


Fig. 2. Numeric rating scale pain score (mean, SD) as percent change from baseline over time by treatment group. There were no significant differences at any time point.

Table 3
Repeat dosing of analgesia reported by treatment group

	Morphine	Low-dose ketamine	P	Total
Second dose, n (%)			.37 ^a	
Yes	8 (38)	13 (54)		21 (47)
No	13 (62)	11 (46)		24 (53)
Total	21	24		45
Third dose, n (%)			.47 ^b	
Yes	3 (14)	6 (25)		9 (20)
No	18 (86)	18 (75)		36 (80)
Total	21	24		45

^a χ^2 Test.
^b Fisher exact test.

vomited. One patient in the morphine arm was treated for pruritus. Three patients in the ketamine group experienced hallucinations. No dissociation or emergency reactions were detected. Neither midazolam nor naloxone was given during the study.

The median provider satisfaction score was 4 (interquartile range [IQR], 3-5) for the low-dose ketamine group and 4 (IQR, 4-5) for the morphine group (Table 5). The average nursing score was 4 (IQR, 3-5) for the low-dose ketamine group and 5 (IQR, 4-5) for the morphine group (Table 6).

4. Discussion

Low-dose ketamine was not superior to morphine in the maximum change of NRS pain scores from baseline. However, if alternatives to opioids are going to be prescribed for acute pain in the ED, the analgesic potential of the alternatives must be comparable to opioids. Our study demonstrates that ketamine may have comparable analgesic effects; however, more studies are needed.

The maximum reduction in pain scores for low-dose ketamine was seen immediately after the infusion was complete and was sustained for only 5 to 10 minutes. In the morphine group, a similar maximum reduction in pain scores was reached 100 minutes after the infusion was complete. The rapid decrease in pain provided by low-dose ketamine is an advantage compared with morphine for the treatment of acute pain in the ED. However, the inability to sustain this degree of pain relief over the normal course of an ED stay may require higher doses of low-dose ketamine infused over a longer duration or the use of adjunctive medications.

The short duration of maximum analgesia likely contributed to the increased rate of repeat dosing in the ketamine arm (54%) vs the morphine arm (38%), although the difference was not statistically significant.

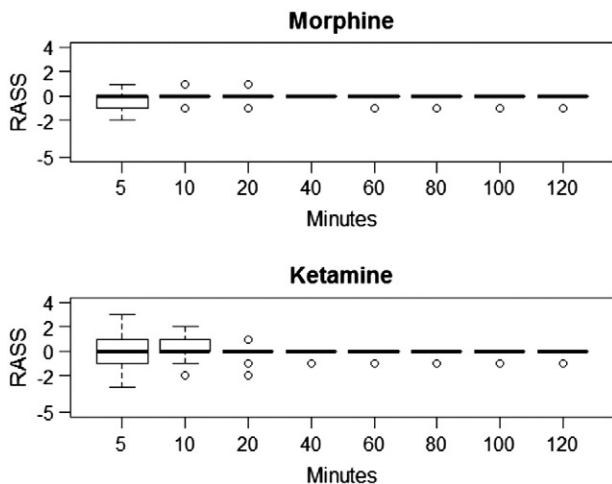


Fig. 3. Box-and-whisker plot of RASS for morphine and low-dose ketamine over time. The x-axis shows time after the initial infusion of medication was complete.

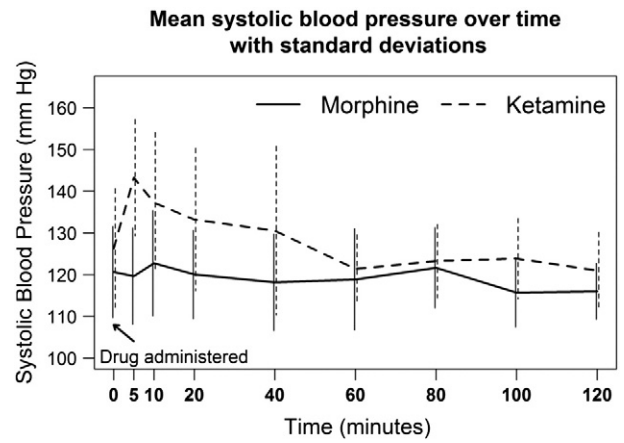


Fig. 4. Mean systolic blood pressure over time with SD. Significant differences in systolic blood pressure were observed at T5 (23 mm Hg; 95% CI, 9-38) and T10 (14 mm Hg; 95% CI, 0-29).

In the ketamine group, 25% of the patients did not complete the entire 120 minutes of data collection (assessments were stopped for inadequate pain control if the patients requested a third dose of the study drug). These 2 outcomes highlight the poor sustained maximum analgesia of low-dose ketamine. However, as mentioned above, the safest and most effective dose for low-dose ketamine has yet to be established. In addition, because most patients in the ketamine arm received a total of 0.6 mg/kg (0.3 mg/kg \times 2 separated by at least 20 minutes), a higher initial dose infused over a longer period of time could lengthen the duration of maximum analgesia. Additional prospective studies to evaluate this approach are needed.

Despite the inability of low-dose ketamine to sustain its maximum analgesic effect, there was greater than 50% reduction in pain scores for 2 hours at all intervals, after T20. As stated above, 25% of the patients did not complete the entire 120-minute observation period, and the majority needed a repeat dose of ketamine. However, an alternate medication to opioids that can provide a greater than a 50% decrease in acute pain for 2 hours is valuable for clinical use.

We also collected provider and nurse satisfaction scores after completion of the patient's observation period. Both drugs scored similar and well with both the providers and the nurses. The nursing group was slightly more satisfied with morphine; however, this trend was not clinically significant. Future studies should further evaluate this trend.

In addition to the similarities in pain control between low-dose ketamine and morphine, low-dose ketamine was comparable to

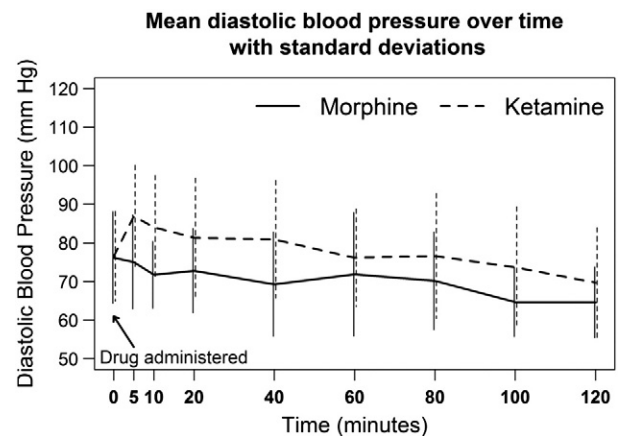


Fig. 5. Mean diastolic blood pressure over time with SD. There were no significant differences at any time point.

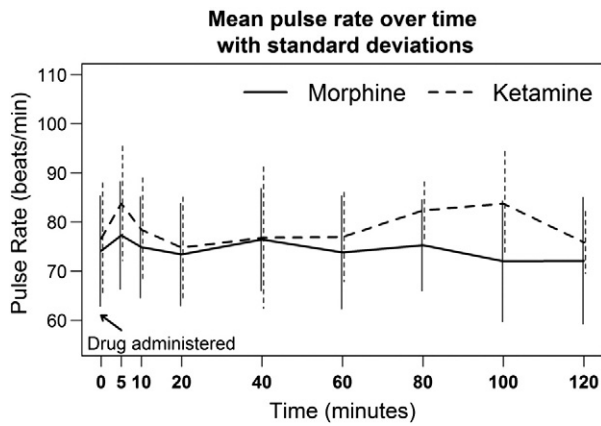


Fig. 6. Mean pulse rate over time with SD. There were no significant differences at any time point.

morphine regarding adverse effects as well. We detected a similar adverse effect rate (57% vs 58%) and RASS scores in both arms. Vital signs were similar as well, although there were statistically significant differences in systolic and diastolic blood pressure between the groups. These differences were secondary to both decreases in blood pressure in the morphine group and increases in blood pressure in the low-dose ketamine group. These findings are established effects of these medications and should be anticipated, but are of minimal clinical significance. We did observe dysphoria (4) and hallucinations (3) only in the ketamine arm. These effects should be anticipated with low-dose ketamine. However, no episodes of dissociation or emergence reactions were detected. We specifically did not detect more hypoxia, bradycardia, or sedation in the morphine group.

Our results are similar to prior studies that evaluated low-dose ketamine alone for the treatment of pain. Hirlinger and Pfenninger [27] demonstrated a decrease in pain scores with 5 minutes of infusion in ED patients receiving IV low-dose ketamine (0.25 or 0.5 mg/kg) for acute musculoskeletal injuries. However, this study lacked a control arm. The 0.3-mg/kg dose in the study by Persson et al [28] decreased pain scores immediately, with the effect starting to decrease at 20 minutes after infusion, which was similar to our results. In addition, the patients in this study, although they had chronic and not acute pain, experienced a greater than 50% decrease in pain scores for 1 hour after infusion, just as in our study. Persson et al also compared low-dose ketamine to morphine and showed a similar delayed but prolonged analgesic effect.

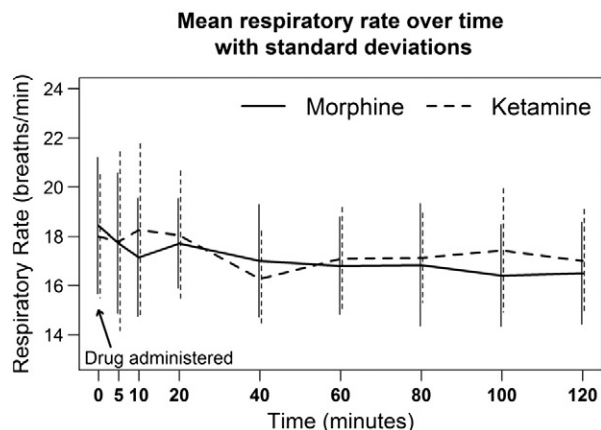


Fig. 7. Mean respiratory rate over time with SD. There were no significant differences at any time point.

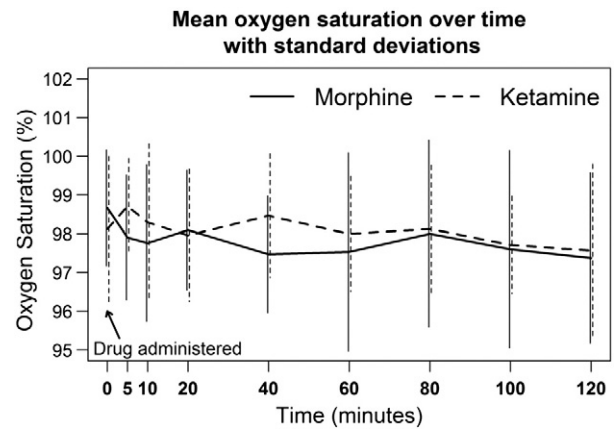


Fig. 8. Mean oxygen saturation over time with SD. There were no significant differences at any time point.

Our study was not the first to evaluate low-dose ketamine in the ED, but it is unique [8,27,29,30]. Although other ED studies have evaluated low-dose ketamine as an adjunct to opioid therapy [29,30], as the sole agent without comparison [27], and in a retrospective case series [8], to our knowledge, this is the first randomized, double-blinded study to compare low-dose ketamine to morphine for acute pain in the ED. In addition, we evaluated low-dose ketamine for the treatment of multiple types of pain (trauma, medical) and at multiple anatomical sites (abdomen, back, extremity). Most studies with low-dose ketamine in the ED and prehospital setting have evaluated its use in acute traumatic or musculoskeletal pain [18,27,30,31]. Another unique aspect of this study was the use of the RASS score to capture the cognitive and behavioral effects of the study drugs, although we saw no difference between groups.

4.1. Limitations

There were several limitations to our study. Our study was conducted at a military medical center, which has the potential to limit the generalizability of its results. However, only $\approx 20\%$ of the ED patients are uniformed active military service members. Most of the patients are civilians who have similar demographic characteristics compared with other civilian EDs at a level 1 trauma and tertiary care centers. In addition, the generalizability of our results may be limited, as our data were collected from a single medical center.

Table 4
Adverse effects reported by total events

Adverse effects	Morphine (n = 8)	Low-dose ketamine (n = 12)	Total
Nausea	2	3	5
Dysphoria	0	4	4
Hallucinations	0	3	3
Dizziness	1	2	3
Headache	3	0	3
Drowsiness	2	0	2
Vomiting	1	1	2
Lightheaded	1	0	1
Decreased oxygen saturation	1	0	1
Numbness	0	1	1
Pruritus	1	0	1
Total	12	14	26

n = number of patients experiencing an adverse effect. Some patients reported multiple adverse effects.

Table 5

Provider Satisfaction Score as assessed by survey after drug administration to evaluate provider's clinical experience with the analgesic

Satisfaction category (value)	Morphine, n (%)	Low-dose ketamine, n (%)
Very dissatisfied (1)	0 (0)	2 (8)
Somewhat dissatisfied (2)	5 (24)	3 (13)
Neither (3)	0 (0)	2 (8)
Somewhat satisfied (4)	9 (43)	7 (29)
Very satisfied (5)	7 (33)	10 (42)
Median value (IQR)	4 (4-5)	4 (3-5)

Results are reported as number of responses and percent of group total.

Our study has a small sample size. Our study required a number of very specific inclusion and exclusion criteria as it was a prospective pain study and one of the study drugs (ketamine) was otherwise used almost exclusively for procedural sedation. In addition, the number of patients who were able to complete an adequate screening and enrollment process while experiencing moderate to severe acute pain further limited our study population.

We calculated our sample size to detect a 2-point difference in the maximum change from baseline between the 2 groups. Detecting a 2-point difference in NRS pain scores is greater than what some authors have reported as clinically significant (eg, an NRS difference of 1.3) [32]. We reported a 0.1 difference in the maximum change in NRS pain scores between the 2 groups. A larger number of patients would have provided more precise data to allow us to determine if a larger difference between NRS pain scores was detectable. However, given the small difference between the 2 groups in our study, an argument for a similar clinical effect can be made, although our study was not powered to demonstrate this.

The analgesic dose of ketamine is not standardized. We administered ketamine at a dose of 0.3 mg/kg. Several studies have reported the use of "low-dose ketamine," but there are many differences in the dose and the mode of delivery (IM vs IV) between the studies [15–18,27,28,31,33]. The studies by Hirlinger and Pfenninger [27] and Persson et al [28] provided the best data to guide our dosing. Both studies correlated IV ketamine dose with plasma levels of ketamine. Hirlinger and Pfenninger compared 0.25 and 0.5 mg/kg of ketamine in trauma patients in the ED. Persson et al compared 0.15, 0.3, and 0.45 mg/kg in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. Both studies cited impairment or adverse neurologic effects with the highest dose. Pain control was adequate, and these neurologic effects were not seen at the 0.25- and 0.3-mg/kg dosing. However, there are no large trials with data to support a specific dose that maximizes analgesia and avoids neurologic adverse effects.

Our measure of sedation and agitation has not been validated in the ED. The RASS is a validated tool used in the intensive care unit setting to evaluate for both sedation and agitation and is not routinely used in the ED [26]. The typical adverse effect profiles of ketamine and morphine are quite different. Ketamine can cause both sedation and psychomotor agitation, whereas morphine can cause sedation. Rather than just reporting a list of adverse reactions, we wanted our blinded research

Table 6

Nurse Satisfaction Score as assessed by survey after drug administration to evaluate provider's clinical experience with the analgesic

Satisfaction category (value)	Morphine, n (%)	Low-dose ketamine, n (%)
Very dissatisfied (1)	1 (5)	2 (8)
Somewhat dissatisfied (2)	2 (10)	2 (8)
Neither (3)	1 (5)	4 (17)
Somewhat satisfied (4)	4 (20)	7 (29)
Very satisfied (5)	12 (60)	9 (38)
Median value (IQR)	5 (4-5)	4 (3-5)

Results are reported as number of responses and percent of group total.

nurse to have an objective scoring system that could be used to evaluate all patients, regardless of the study drug they received. In addition, this tool allowed us to quantify and provide a time course for some of the more clinically significant adverse reactions associated with these medications (hallucinations, altered sensorium, agitation, emergence, sedation, etc). The RASS score was the best tool that we found for capturing the adverse effects of both drugs; however, its reliability and validity have not been established in the population of patients enrolled in this study.

We did not obtain serum levels for the drug administered during our study. As mentioned above, prior studies have done this [27,28]. These data would have been helpful to make more specific correlations with the study drugs and their effects on pain scores and adverse reactions.

We did not obtain long-term follow up. We do not know if there was a difference in the number of patients who returned to the ED for treatment of the same pain after their initial encounter. These outcomes should be evaluated in future ED studies involving low-dose ketamine and morphine for acute pain.

Finally, we did not include patients with chronic pain. This is a patient population that frequents the ED. However, the analgesic effects as well as adverse effects of ketamine or morphine in this population may be different.

5. Conclusions

In ED patients with acute, moderate-severe pain, low-dose ketamine did not provide a superior maximum reduction in NRS pain scores compared with morphine. However, these 2 medications produced similar adverse effects, as well as provider and nurse satisfaction scores. In addition, low-dose ketamine induced analgesic effects within 5 minutes of infusion and provided a moderate reduction in pain for 2 hours.

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