Comparison of Nebulized Ketamine at Three Different Dosing Regimens for Treating Painful Conditions in the Emergency Department: A Prospective, Randomized, Double-Blind Clinical Trial

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Study objective: We aimed to assess and compare the analgesic efficacies and adverse effects of ketamine administered through a breath-actuated nebulizer at 3 different dosing regimens for emergency department patients presenting with acute and chronic painful conditions.

Methods: This was a prospective, randomized, double-blinded trial comparing 3 doses of nebulized ketamine (0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg) administered through breath-actuated nebulizer in adult emergency department patients aged 18 years and older with moderate to severe acute and chronic pain. The primary outcome included the difference in pain scores on an 11-point numeric rating scale between all 3 groups at 30 minutes. Secondary outcomes included the need for rescue analgesia (additional doses of nebulized ketamine or intravenous morphine) and adverse events in each group at 30 and 60 minutes.

Results: We enrolled 120 subjects (40 per group). The difference in mean pain scores at 30 minutes between the 0.75 mg/kg and 1 mg/kg groups was 0.25 (95% confidence interval [CI] 1.28 to 1.78); between the 1 mg/kg and 1.5 mg/kg groups was −0.225 (95% CI −1.76 to 1.31); and between the 0.75 mg/kg and 1.5 mg/kg groups was 0.025 (95% CI −1.51 to 1.56). No clinically concerning changes in vital signs occurred. No serious adverse events occurred in any of the groups.

Conclusion: We found no difference between all 3 doses of ketamine administered through breath-actuated nebulizer for short-term treatment of moderate to severe pain in the emergency department. [Ann Emerg Med. 2021;■:1-9.]

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INTRODUCTION

Background

Ketamine is a noncompetitive N-methyl-D-aspartate/glutamate-receptor complex antagonist that decreases pain by diminishing central sensitization, hyperalgesia, and "wind-up" phenomenon at the level of the spinal cord (dorsal ganglion) and central nervous system.[1,2] This N-methyl-D-aspartate antagonism coupled with the potentiation of opioid receptors is primarily responsible for ketamine's role in the management of a variety of acute painful conditions in the emergency department (ED).[3-10] A recent systematic review of 8 randomized trials that included 1,191 patients and compared low-dose ketamine to morphine demonstrated similar analgesic efficacy (up to 60 minutes) and comparable safety profiles between the 2 drugs in managing acute pain in the ED.[11] The commonly employed dosing regimens of subdissociative-dose ketamine in the ED include intravenous push dose, short infusion, and continuous infusion.[7-15] The use of subdissociative-dose ketamine for managing a variety of acute painful conditions in the ED has been endorsed by the American College of Emergency Physicians and the American Academy of Emergency Medicine.[16,17]

When intravenous access is not readily available or is unobtainable, subdissociative-dose ketamine can be administered through the intranasal route.[18] The unpleasant feeling of taking a medication intranasally frequently leads adult ED patients to decline this method of administration. Hence, another noninvasive route of ketamine administration, such as inhalation, might be a

Editor's Capsule Summary

What is already known on this topic

Nebulized ketamine is an effective analgesic, but its optimal dosing is unknown.

What question this study addressed

Which of the following doses is most effective: 0.75, 1.0, or 1.5 mg/kg?

What this study adds to our knowledge

In this randomized, double-blinded trial of 120 emergency department adults requiring analgesia, all three doses produced similar and clinically important reductions in pain scores. Adverse effect profiles were similar.

How this is relevant to clinical practice

When nebulized as an analgesic, ketamine dosing need not exceed 0.75 mg/kg.

viable option for treating a variety of painful conditions in the ED. Numerous randomized non-ED-based trials compared nebulized ketamine to placebo in managing postoperative sore throat and demonstrated up to 50% pain relief without the presence of major side effects.[19-22] In addition, ketamine inhalation at 3 increasing doses in healthy volunteers was associated with a bioavailability of 20% to 40% of the intravenous route, an inhalation duration of 20 to 40 minutes, and an increase in maximal concentration values in a dose-dependent manner by 77% from the lowest to the highest inhalation dose.[23]

Our own experience (2 published case series) with ketamine administration to adult ED patients in various dosing regimens through breath-actuated nebulizers that allow either a continuous aerosol generation or a breath-actuated one (in response to the patient's inspiratory flow) demonstrated good analgesic efficacy and a lack of serious adverse effects.[24-27] To our knowledge, there is no literature in emergency medicine that evaluates or compares the analgesic efficacy and safety of nebulized ketamine for managing pain in the ED through a prospective randomized trial.

Goals of This Investigation

We hypothesized that the administration of ketamine through breath-actuated nebulizer at the 1.5 mg/kg dose would provide better analgesia at 30 minutes after administration in comparison to the 0.75 mg/kg and the 1 mg/kg dosing regimens for adult patients presenting to the ED with acute and chronic painful conditions.

MATERIALS AND METHODS

Study Design and Setting

We performed a randomized, double-blind superiority trial comparing the analgesic efficacy and adverse effects of ketamine administered through breath-actuated nebulizer at 3 different doses (0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg) for adult ED patients presenting with acute and chronic painful conditions. We conducted this study at a 711-bed urban community teaching hospital with an annual ED census of more than 120,000 visits. Study investigators performed patients' screening, enrollment, and data collection. The Maimonides Medical Center Institutional Review Board approved the trial. The study is registered on www.clinicaltrials.gov/ (NCT03909607). We report the findings of this study in accordance with the Consolidated Standards of Reporting Trials.[28]

Selection of Participants

We included adult patients ($\geq$18 years of age) who presented to the ED with acute pain and exacerbation of chronic painful conditions with initial pain scores of $\geq$5 on a standard 11- point (0 to 10) numeric rating scale (NRS) who warranted the use of ketamine analgesia as determined by the treating attending physician. The decision to administer ketamine by an attending physician was based on the patient's clinical presentation and departmental ketamine analgesia protocol. Emergency department staff had extensive education through didactic sessions and simulation training in our department with respect to ketamine analgesia, and the study protocol was presented and discussed in detail among the ED staff. The painful syndromes included the following: acute pain (traumatic and nontraumatic abdominal, flank, back, and musculoskeletal pain; headache) and chronic pain (chronic abdominal, musculoskeletal, back, and neuropathic pain).

We excluded patients whose painful conditions were deemed to require immediate intervention (treatment) by the treating physician; those with altered mental status, unstable vital signs (systolic blood pressure $<$90 or $>$180 mm Hg, pulse rate $<$50 or $>$150 beats/min, or respiratory rate $<$10 or $>$30 breaths/min); those with acute intoxication; those who had received opioids within 4 hours prior to enrollment; and those with an allergy to ketamine. Patients with actual body weight of more than 150 kg, patients unable to provide consent, patients with past medical history of alcohol or drug abuse, and pregnant or breastfeeding patients were excluded as well.

We commenced screening and enrollment of subjects in April 2019 and concluded in October 2020. The enrollment occurred Monday through Friday between 8 AM and 8 PM, when an ED pharmacist was available for blinded medication preparation. Study investigators identified all potentially qualifying participants. Before enrollment into the study, all participants provided written informed consent and Health Insurance Portability and Accountability Act authorization. For patients who did not speak English, we used noninvestigator, hospital-employed, trained interpreters for the acquisition of informed consent.

Interventions

The on-duty ED pharmacist prepared all medications in identical, transparent 5-mL syringes by using an injectable formulation of ketamine at a 50 mg/mL concentration. The syringes were prepared according to a randomization list generated by the research manager using SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) with block randomization of every 15 participants. The pharmacist standardized the volume to be inhaled at 5 mL for each group by adding normal saline to each syringe. We allocated study participants to 3 groups according to the predetermined randomization list: the first group received 0.75 mg/kg of nebulized ketamine; the second group received 1.0 mg/kg; and the third group received 1.5 mg/kg. All enrolled participants were eligible to receive up to 3 doses of nebulized ketamine for their pain control, with the second and third doses matching the initial dosing regimen. The blinded study investigators received a syringe with ketamine and a breath-actuated nebulizer from the pharmacist, which were then delivered to the treating nurse. We allowed the medication to be inhaled for a minimum of 5 minutes and a maximum of 15 minutes through the breath-actuated mode, which was monitored by the blinded study investigators. This time frame was established by the study investigators prior to study initiation. The on-duty pharmacist, research manager, and biostatistician were the only people with knowledge of the study arms to which the participants were randomized. The ED providers, ED nurses, study participants, and study investigators were blinded to the dosing of medication received.

The research manager and biostatistician, who were independent of data collection, performed the programming of the randomization list, confirmed the acquisition of written informed consent, and conducted statistical analyses. The ED pharmacists maintained the randomization list, prepared the medication, and distributed it to the study investigators in a blinded manner.

The blinded study investigators were responsible for subjects' enrollment and data collection. They recorded each participant's demographics; chief complaint; weight; baseline vital signs; initial and subsequent pain scores on a standard 0 to 10 NRS (with "no pain" being 0 and "the worst pain imaginable" being 10); rescue medication administration; and adverse effects at baseline and 15, 30, 60, 90, and 120 minutes. Study investigators verbally administered the NRS pain scale to all study participants after they were triaged and had their pain score documented by a triage nurse. They monitored study participants for the entire duration of the study (120 minutes). For participants who still desired pain medication at 30 minutes, the investigators offered a second dose (equivalent to the first) of nebulized ketamine or intravenous morphine at 0.1 mg/kg (if patient did not desire additional nebulized ketamine). In addition, study investigators measured the residual volume of the ketamine remaining in the breath-actuated nebulizer after each treatment and documented it on a wastage sheet designed by the pharmacy staff. This sheet was delivered to the pharmacist, who then calculated the actual dose received by each study participant based on their initial randomization group. The residual amount of ketamine in the breath-actuated nebulizer was discarded by a treating nurse according to the departmental policy on the wastage of controlled substances.

Outcome Measures

The primary outcome was a between-group difference in pain scores on the NRS at 30 minutes after ketamine administration. The secondary outcomes included the need for a second or third dose of nebulized ketamine, the need for rescue analgesia (morphine) at 30 and 60 minutes, and the number of adverse events in each group.

Based on the validation of a verbally administered rating scale of acute pain in the ED and the comparison of verbal and visual pain scales, we used a minimal clinically significant difference in pain score of 1.3 between the 3 groups at 30 minutes as the primary outcome.[29,30] Assuming a standard deviation of 3.0, a power analysis determined that a repeated-measures analysis of variance with a sample size of 34 patients per group (102 total) would provide at least 80% power to detect a difference of at least 1.3 at 30 minutes (as well as at any other interval after baseline) with an alpha of 0.05. We enrolled 40 patients per group (120 total) to account for possible missing data caused by patient drop-out (refusal to take nebulized ketamine treatment after enrollment).

With respect to the unique adverse effects of ketamine, we used the Side Effect Rating Scale for Dissociative

Anesthetics (SERSDA) and the Richmond Agitation Sedation Scale (RASS) (Table E1 and Table E2, available at http://www.annemergmed.com/). The SERSDA scale includes fatigue, dizziness, nausea, headache, feelings of unreality, changes in hearing, mood changes, general discomfort, and hallucinations, with severity of each graded by patients on a 5-point scale, with "0" representing the absence of any adverse effects and "4" representing severely bothersome side effects.[31] The RASS evaluates the severity of agitation and/or sedation in accordance with a 10-point scale, with scores ranging from "−5" (unarousable) to "0" (alert and calm) to "+4" (combative).[32]

Primary Data Analysis

We described data in terms of means, standard deviations, or 95% confidence intervals for continuous variables and frequencies (percentages) for categorical variables. Data analyses of the pain scores were based on the principle of intention to treat. We used frequency distributions, chi-square tests, and paired Student's *t* tests to assess a difference in pain scores within each group. Analysis of variance was used to assess differences in pain scores between the 3 groups at each of the time intervals. For the primary outcome at the 30-minute interval, we performed an analysis of covariance in order to control for the 15-minute pain score. Tukey's confidence limits were reported for pairwise comparisons at baseline and 30 minutes.

RESULTS

We enrolled 120 subjects (40 in each group) into our study, with 120 patients available at 30 minutes and 109 subjects available at 120 minutes for data analysis. The patient flow diagram is illustrated in Figure 1. At 60 minutes, 4 patients were missing data due to radiological testing; at 90 minutes, 8 were missing data due to radiological testing and 2 were missing data due to being discharged; at 120 minutes, 7 were missing data due to radiological testing and 4 were missing data due to being discharged (Figure 1). Baseline characteristics with respect to age, sex, vital signs, and initial pain scores were similar between all 3 groups (Table 1). Additionally, all 3 groups were relatively similar with respect to chief complaints and final diagnoses. However, the 0.75 mg/kg nebulized ketamine group had more subjects complaining of flank pain and exacerbation of chronic pain, and the 1.5 mg/kg nebulized ketamine group had more subjects with abdominal pain (Table 1).

We demonstrated that at 30 minutes after drug administration, the change in pain score was similar among the 3 groups, with a mean value of 4.1 (Table 2). Reductions in pain scores from baseline to 30 minutes were clinically important for all study subjects (greater than 1.3-point differences). However, we observed no differences in the mean NRS pain scores between the 3 dose groups at 30 minutes (Table 2).

Furthermore, we observed a decrease in mean NRS pain scores relative to baseline at all subsequent time points (15 to 120 minutes) in all subjects. However, the reported pain scores at each time point were similar in all 3 groups (Table 2). In addition, pain ratings across the 3 groups were similar at each time point (Figure 2).

A total of 15 subjects received rescue analgesia during the entire study period, with 5 subjects receiving an additional dose of nebulized ketamine and 10 subjects receiving intravenous morphine (Table 3).

There were no clinically concerning changes in vital signs and no clinically significant adverse effects related to the study medication at any dose or at any time point throughout the study.

The dizziness and fatigue experienced at 30 minutes after treatment were predominantly of mild severity (Table E1). The full depiction of frequency and severity of SERSDA adverse effects across all groups for each time period are presented in Table E1, and a visual depiction of the scale is shown in Table E2. The values for sedation/agitation on the RASS were congruent with a mild level of drowsiness and were similar across all groups at the 15- and 30-minute marks (Table E3, available at http://www.annemergmed.com/). Lastly, we calculated the mean residual values of nebulized ketamine based on the volume of the drug left in the nebulizer after treatment. We demonstrated that the 0.75 mg/kg nebulized ketamine group had the highest consumption amount of the administered dose (Table 3).

LIMITATIONS

This was a single-center study in which study participants were enrolled as a convenience sample according to the availability of members of both the research and pharmacy teams, which may have led to sampling bias caused by underrepresentation of patients who may have presented to the ED late at night. While we aspired to enroll subjects with a variety of acute and chronic painful conditions, only 3 out of 120 participants had chronic pain as a chief complaint, and the majority of participants across all 3 groups suffered from acute musculoskeletal pain of traumatic and nontraumatic origins. These facts skew the results toward acute pain and limit the generalizability of our findings.

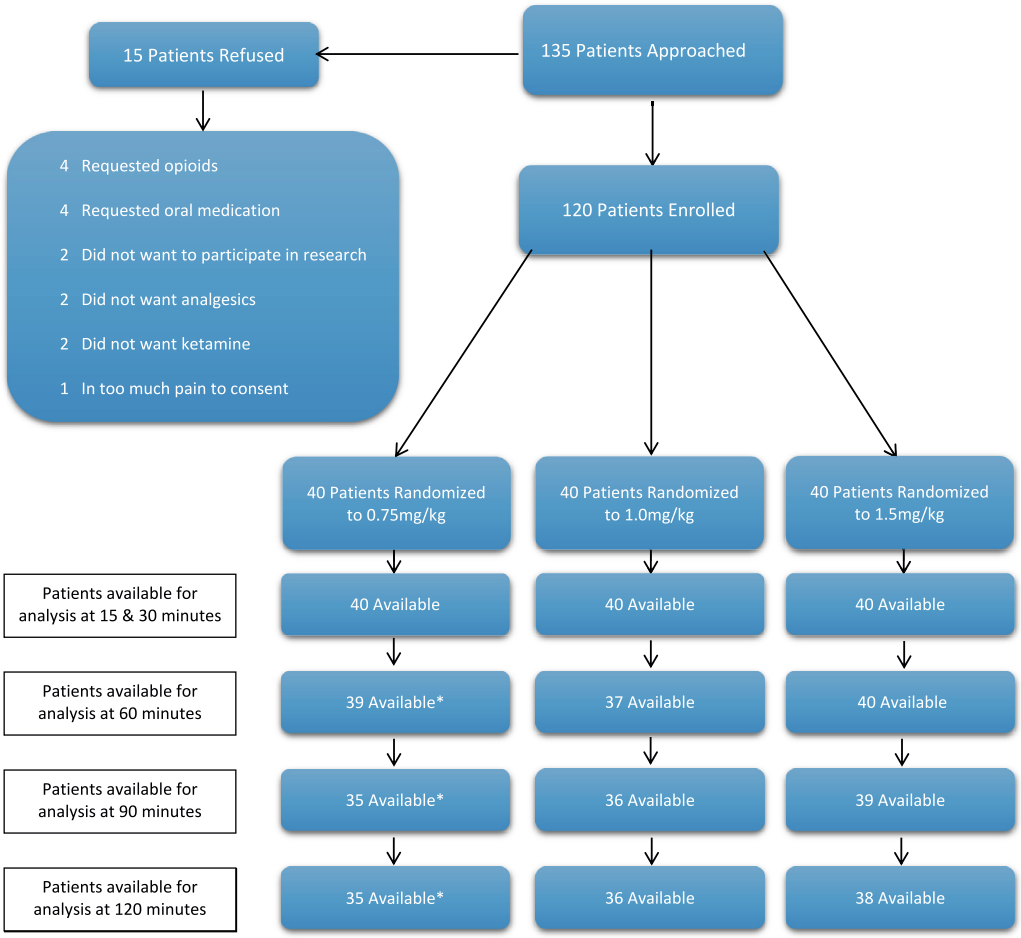

Figure 1. Patient flow diagram. *Subjects were missing data because of either discharge or radiological testing.

The sample size of 120 subjects and the short duration (120 minutes) of this study were inadequate to assess the variance in safety of the 3 different nebulized ketamine doses. We did not assess whether higher doses of nebulized ketamine may have resulted in greater pain relief beyond 120 minutes. The lack of standardization of an inhalation time (rather than the range) could have resulted in variability in the onset of analgesia among the subjects. Similarly, we did not record the actual treatment time (nebulization) for each patient, an important parameter to consider when it comes to assessing an overall compliance with the device and the inhalation mode of drug delivery. We used breath-actuated nebulizers in our study, but these devices may not be readily available for use in other EDs across the country.

While the between-group difference in mean pain score did not achieve the predetermined difference of 1.3, the confidence intervals did include a clinically important difference of 1.3 that made treatment with each dose clinically effective. The CIs did contain the minimum clinically important difference within the true population, but a larger sample size is warranted.

We did not evaluate participants' satisfaction (or lack thereof) with respect to the usability of the breath-actuated nebulizer (use of the breath-actuated mode), ketamine as an analgesic, overall pain relief, or willingness to use an inhalation route in the future. Lastly, we did not use a placebo arm in our study.

DISCUSSION

We compared the analgesic efficacy and safety of 3 different dosing regimens of inhaled ketamine through breath-actuated nebulizer in adult ED patients presenting with a variety of acute and exacerbation of chronic painful conditions. To our knowledge, this is the first trial that evaluated the feasibility and analgesic efficacy of nebulized ketamine in managing pain within the ED. We were able to demonstrate that the administration of inhaled ketamine resulted in a significant reduction in pain across all 3 dosing groups and provided short-term pain relief (up to 120 minutes). However, we were not able to show that nebulized ketamine administered at 1.5 mg/kg provided

Table 1. Patient characteristics.

	Group		
Baseline Characteristics	**0.75 mg/kg N=40**	**1.0 mg/kg N=40**	**1.5 mg/kg N=40**
Age, mean (SD)	52 (20)	51 (16)	50 (18)
Male sex, N (%)	17 (43)	18 (45)	17 (43)
Pain, mean (SD)	8.7 (1)	8.6 (1)	8.7 (1)
PR, mean (SD)	71 (13)	74 (11)	73 (10)
BP, systolic, mean (SD)	136 (20)	132.7 (21)	132 (24)
BP, diastolic, mean (SD)	78 (14)	79 (12)	79 (17)
RR, mean (SD)	17 (5)	19 (10)	17 (3)
O_2, mean (SD)	99 (2)	99 (2)	99 (1)
Chief Complaint	**N (%)**	**N (%)**	**N (%)**
Musculoskeletal nontraumatic pain	10 (25.0)	12 (30.0)	14 (35.0)
Musculoskeletal traumatic pain	12 (30.0)	14 (35.0)	11 (27.5)
Abdominal pain	5 (12.5)	5 (12.5)	9 (22.5)
Flank pain	8 (20.0)	5 (12.5)	4 (10.0)
Soft tissue pain	1 (2.5)	2 (5.0)	0 (0)
Genitourinary pain	0 (0)	1 (2.5)	1 (2.5)
Chronic pain	3 (7.5)	0 (0)	1 (2.5)
Headache	1 (2.5)	1 (2.5)	0 (0)
Diagnosis	**N (%)**	**N (%)**	**N (%)**
Musculoskeletal nontraumatic pain	9 (22.5)	13 (32.5)	14 (35.0)
Musculoskeletal traumatic pain*	12 (30.0)	14 (35.0)	8 (20.0)
Abdominal pain†	4 (10.0)	4 (10.0)	7 (17.5)
Flank pain‡	7 (17.5)	4 (10.0)	0 (0)
Soft tissue pain§	2 (5.0)	2 (5.0)	5 (12.5)
Genitourinary pain‖	0 (0)	2 (5.0)	3 (7.5)
Sciatica	2 (5.0)	0 (0)	2 (5.0)
Chronic pain	3 (7.5)	0 (0)	1 (2.5)
Headache	1 (2.5)	1 (2.5)	0 (0)

BP, blood pressure; O_2, oxygen saturation; *PR*, pulse rate; *RR*, respiratory rate; *SD*, standard deviation.
*Diagnosis of musculoskeletal traumatic pain includes fractures, dislocations, motor vehicle accidents, falls, strains/sprains.
†Diagnosis of abdominal pain includes diverticulitis, biliary colic/cholelithiasis.
‡Diagnosis of flank pain includes renal colic, hydronephrosis, nephrolithiasis.
§Diagnosis of soft tissue pain includes contusion, effusion, swelling, cellulitis.
‖Diagnosis of genitourinary pain includes fibroids, endometriosis, urinary tract infection.

better pain relief in comparison to the 0.75 mg/kg and 1 mg/kg doses for short-term pain management in the ED.

All 3 dosing regimens resulted in similar changes in pain scores at 30 minutes and up to 120 minutes. Additionally, we showed that a mean change in pain score of 4 points in each group at 30 minutes and 5 points at 120 minutes was larger than the minimum clinically important cutoff of 1.3 points. From a clinical perspective, these changes in pain scores translate to reductions in pain intensity of 45% and 56% at the 30-minute and 120-minute time points, respectively.

Of note, this 4-point change in pain score in each nebulized ketamine group is similar to the difference in pain score from our prior clinical trial in which we compared intravenous subdissociative-dose ketamine to intravenous morphine with resultant changes in pain scores of 4.1 points and 3.9 points, respectively.[9] Similarly, the difference in pain from baseline to 30 minutes demonstrated in our trial closely resembled the difference in pain score in 2 clinical trials in which intranasal ketamine was used for ED patients with headache (2.9 points) and renal colic.[33,34]

Table 2. Pain scores for all groups over time and difference in mean pain score between groups at baseline and primary outcome of 30 minutes.

		Ketamine Dose					
		0.75 mg/kg	1.0 mg/kg	1.5 mg/kg			
Time	N	Mean (SD)	Mean (SD)	Mean (SD)	Time	Between-Group Comparison	Difference (95% CI)
Baseline	120	8.7 (1.4)	8.6 (1.4)	8.7 (1.4)	Baseline	0.75 mg/kg to 1 mg/kg	0.1 (−0.6 to 0.9)
15 min	120	5.8 (3)	5.2 (3.4)	6 (2.7)		1 mg/kg to 1.5 mg/kg	−0.1 (−0.9 to 0.6)
30 min	120	4.7 (2.7)	4.4 (3.2)	4.6 (2.8)		0.75 mg/kg to 1.5 mg/kg	0 (−0.7 to 0.7)
60 min	116	4.7 (2.9)	4.4 (3.1)	4.2 (2.8)	30 Minutes	0.75 mg/kg to 1 mg/kg	0.3 (−1.3 to 1.8)
90 min	110	4 (2.8)	4.4 (3.1)	3.7 (2.9)		1 mg/kg to 1.5 mg/kg	−0.2 (−1.8 to 1.3)
120 min	109	3.7 (3)	3.4 (2.7)	3.6 (3.2)		0.75 mg/kg to 1.5 mg/kg	0.0 (−1.5 to 1.6)

SD, standard deviation.

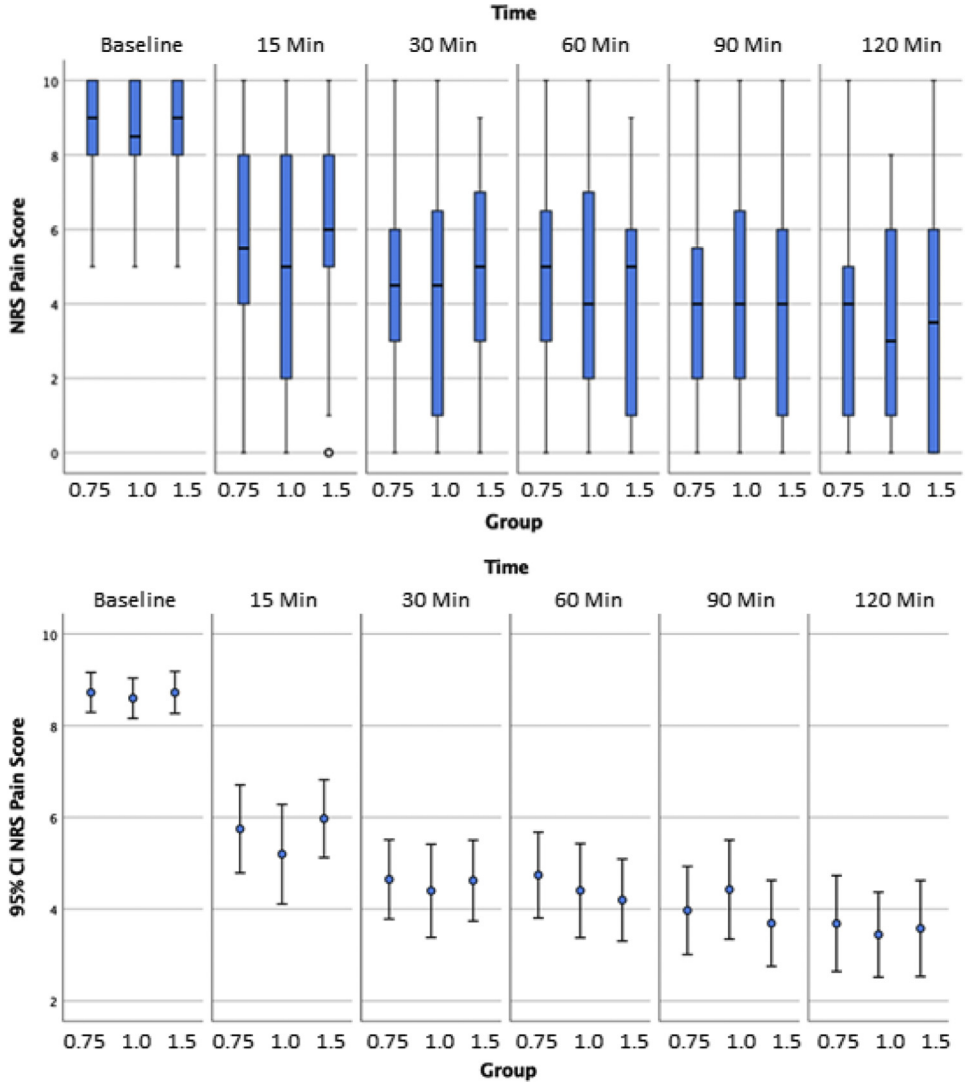

Figure 2. Box plot of median (top) and mean (bottom) NRS pain scores and 95% CI over time. Baseline N=120, 15 minutes N=120, 30 minutes N=120, 60 minutes N=116, 90 minutes N=109, 120 minutes N=109. Whiskers on box plot represent the minimum and maximum values with the exception of the outlier (more than 1.5 times the interquartile range) at 15 minutes.

Table 3. Dosing regimens, analgesic consumption, rescue analgesia, proportions, and 95% CI.

Dosing Regimens, Analgesic Consumption, and Rescue Analgesia	Ketamine Dose		
	0.75 mg/kg	1.0 mg/kg	1.5 mg/kg
Mean Dose Administered, mg	56.7	80.8	110.0
Mean Dose Consumed, mg	43.3	48.5	78.5
Difference Between Consumed and Administered, mg (95% CI)	13.4 (10.9-15.8)	32.3 (31.4-33.3)	31.5 (29.9-33.2)
Received a Second Dose of Ketamine N, (Time)	2 (30 min) 2 (60 min)	0	1(30 min)
Proportion Receiving Second Dose N, (95% CI)	4/40 (2.8-23.7)	0/40 (0.0-8.9)	1/40 (0.06-13.2)
Received Rescue Morphine N, (Time)	1 (60 min)	3 (30 min) 1 (60 min) 2 (120 min)	2 (60 min) 1 (120 min)
Proportion Receiving Rescue Morphine N, (95% CI)	1/40 (0.06-13.2)	6/40 (5.7-29.8)	3/40 (1.6-20.4)

Overall occurrences of adverse effects were close to 25% at 30 minutes after nebulized ketamine administration. The proportions of subjects experiencing dizziness and fatigue were similar across all 3 groups. In contrast, these occurrences of adverse effects were lower than in our prior trial comparing intravenous subdissociative-dose ketamine to intravenous morphine.[9,35] As these psycho-perceptual side effects often serve as a limiting factor in ketamine administration in the ED, their reduced rates through the inhalation route may lead to wider acceptance of ketamine analgesia in the ED.

Out of 15 recipients of rescue analgesia, 10 subjects needed an opioid analgesic. This number is much lower than the total number of subjects needing an opioid rescue in our previous trial evaluating intravenous subdissociative-dose ketamine (25 subjects) and intravenous morphine (17 subjects).[9] These results might set the stage for a comparative nebulized ketamine versus intravenous subdissociative-dose ketamine clinical trial assessing rates of adverse effects and analgesic efficacy.

The utilization of the breath-actuated nebulizer for our study allowed patients to be in control of their pain management by self-administering analgesic in a breath-triggered fashion. This self-control, in addition to noninvasiveness, rapidity, and titratability, could have led to improved pain management. Lastly, we hope that the results of our trial will enrich the analgesic armamentarium of ED clinicians and set the ground for utilization of nebulized ketamine for pain management in the ED. We believe that our results might pave the way for further clinical trials to assess and compare the analgesic efficacy and safety of inhaled ketamine through different routes of administration (intravenously) and/or different analgesics (opioids, nonopioids).

In summary, we found no difference between all 3 doses of ketamine administered through breath-actuated nebulizer for the short-term treatment of moderate to severe pain in the ED.

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Author contributions: DD and SM conceived the study, designed the trial, and obtained research funding. SM, AL, and JM supervised the conduct of the trial and data collection. SM, DD, JD, CF, AD, RH, SK, and MB undertook recruitment of participating subjects and managed the data, including quality control. AL and MS provided statistical advice on study design and analyzed the data. JD, DD, and SM drafted the manuscript, and all authors contributed substantially to its revision. SM takes responsibility for the paper as a whole.

All authors attest to meeting the 4 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.

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