Comparison of Nebulized Ketamine to Intravenous Subdissociative Dose Ketamine for Treating Acute Painful Conditions in the Emergency Department: A Prospective, Randomized, Double-Blind, Double-Dummy Controlled Trial

Tommy Nguyen, MD; Mo Mai, MD; Amulya Choudhary, MD; Slavic Gitelman, DO; Jefferson Drapkin, MPH*; Antonios Likourezos, MA, MPH; Sarah Kabariti, MPH; Rukhsana Hossain, MPH; Karina Kun, PharmD; Ankit Gohel, PharmD; Patrizia Niceforo, PharmD; Michael Silver, MS; Sergey Motov, MD

*Corresponding Author. E-mail: jdrapkin@maimonidesmed.org.

Study objective: We aimed to assess and compare the analgesic efficacy and adverse effects of intravenous subdissociative-dose ketamine to nebulized ketamine in emergency department (ED) patients with acute painful conditions.

Methods: We conducted a prospective, randomized, double-blind, double-dummy clinical trial in adult patients (ages 18 and older) with a numerical rating scale pain score of $\geq$5. We randomized subjects to receive either a single dose of 0.3 mg/kg of intravenous (IV) ketamine or 0.75 mg/kg of nebulized ketamine through a breath-actuated nebulizer. Primary outcome was the difference in pain scores on the numerical rating scale between groups at 30 minutes postmedication administration. The secondary outcomes included the need for rescue analgesia, occurrences of adverse events in each group, and the difference in pain scores at 15, 30, 60, 90, and 120 minutes. We calculated a 95% confidence interval (CI) for a mean difference at 30 minutes, with a minimum clinically important difference set at 1.3 points.

Results: We enrolled 150 subjects (75 per group). Mean pain scores through numerical rating scale were 8.2 for both groups at baseline, which decreased to 3.6 and 3.8 at 30 minutes, yielding a mean difference of 0.23 (95% CI −1.32 to 0.857). We observed no clinically concerning changes in vital signs. No serious adverse events occurred in any of the groups throughout the study period.

Conclusion: We found no difference between the administration of IV and nebulized ketamine for the short-term treatment of moderate to severe acute pain in the ED, with both treatments providing a clinically meaningful reduction in pain scores at 30 minutes. [Ann Emerg Med. 2024;■:1-9.]

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INTRODUCTION

Background

Administration of ketamine in subdissociative doses of 0.1 to 0.3 mg/kg, either as a single agent or as an adjunct to opioids, has demonstrated effective analgesia for a variety of acute painful syndromes in the emergency department (ED) and the out-of-hospital setting.[1-5]

Several systematic reviews and meta-analyses demonstrated that subdissociative-dose ketamine has similar or superior analgesia and comparable safety profiles to opioids for the short-term management of acute pain in ED.[6-9] The traditional routes of subdissociative-dose ketamine administration in the ED include intravenous (IV) push dose and short and continuous intravenous infusion.[10-12]

In addition to IV ketamine administration, intranasal (IN) ketamine has proven to be safe and effective in managing acute pain in the ED and out-of-hospital settings.[13-16] It has gained a great deal of attention and popularity due to its relative noninvasiveness, ease of use, and obviation of the need for IV/intramuscular routes of administration in patients without intravenous access and in cases where obtaining intravenous lines is difficult and time-intensive. When considering IN ketamine analgesia,

Editor's Capsule Summary

What is already known on this topic

Ketamine has multiple effective routes of administration.

What question this study addressed

Which ketamine regimen is superior for treating moderate to severe acute pain: 0.75 mg/kg nebulized or 0.3 mg/kg intravenously?

What this study adds to our knowledge

In this randomized, double-blind, controlled trial of 150 adults, both groups achieved substantial analgesia with similar pain scores at 30 minutes. Adverse effect profiles were also similar.

How this is relevant to clinical practice

When administering ketamine to treat moderate to severe acute pain, similar analgesia is observed with either 0.75 mg/kg nebulized or 0.3 mg/kg intravenously.

ED clinicians should consider minimizing the volume of ketamine by maximizing its concentration and using a delivery system that would increase ketamine dispersion and decrease the drug runoff to optimize ketamine bioavailability and resultant pain relief.[16] Furthermore, numerous case reports and case series that assessed the analgesic efficacy and safety of nebulized ketamine through a breath-actuated nebulizer in the ED and out-of-hospital settings have demonstrated clinically meaningful pain relief (average pain reduction of 30% or higher) without serious adverse effects.[17-20] The breath-actuated nebulizer allows medication delivery in response to the patient's inspiratory effort, allowing patients to control their pain relief.[21] The systemic bioavailability of inhaled ketamine is between 20% and 40% of the intravenous route, with an inhalation duration of 20 to 40 minutes based on a dose-ranging study of healthy volunteers.[22]

Our group has recently published a randomized, double-blind clinical trial that evaluated the analgesic efficacy and safety of nebulized ketamine administered at 3 different doses (0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg) in 120 adult ED pain patients. The results showed that all 3 doses were equally effective in relieving pain for up to 120 minutes in the ED.[23]

To our knowledge, there is no literature in emergency medicine comparing the analgesic efficacy and adverse effects of nebulized ketamine to intravenous subdissociative-dose ketamine for managing pain in the ED.

Goals of This Investigation

We hypothesized that an intravenous subdissociative dose of ketamine (IV-SDK) at 0.3 mg/kg would provide better analgesia at 30 minutes postmedication administration compared with nebulized ketamine at 0.75 mg/kg administered through a breath-actuated nebulizer (K-BAN).

MATERIALS AND METHODS

Study Design and Setting

We performed a randomized, double-blind, double-dummy superiority trial comparing the analgesic efficacy and adverse effects of a single dose of IV-SDK at 0.3 mg/kg to nebulized ketamine at 0.75 mg/kg administered through breath-actuated nebulizer (K-BAN) in adult ED patients presenting with acute painful conditions. We conducted this study in an urban community teaching hospital with a capacity of 711 beds and an annual ED census of more than 120,000 visits.

The Maimonides Medical Center Institutional Review Board approved the trial. The trial registration number is NCT04947085 and is listed on www.clinicaltrials.gov. We report the findings of this study following the Consolidated Standards of Reporting Trials.[24]

Selection of Participants

We included adult patients (≥18 years of age) who presented to the ED with acute painful conditions, with an initial pain score of 5 or more on a standard 11-point (0 to 10) numeric rating scale who were deemed appropriate (based on presenting chief complaint) to receive ketamine analgesia by the treating attending physician. The attending physicians' primary responsibility was to confirm that the ED patients with chief complaints of pain under their care would benefit from ketamine analgesia. Eligible participants had to be awake, alert, and oriented to person, place, and time. They had to demonstrate understanding of the informed consent process and its content. Study participants also had to demonstrate their ability to verbalize the nature of any adverse effects they might experience and express their pain severity using the numerical rating scale.

The decision to administer ketamine by an attending physician was based on the patient's clinical presentation and the departmental ketamine analgesia protocol (Appendix E1, available at http://www.annemergmed.com). Three virtual educational sessions and one simulation training session were conducted for 54 emergency medicine residents and for over 50 emergency medicine attendings, which included the following: review

of the departmental ketamine analgesia protocol, an in-depth overview of ketamine administration for pain management through the IV route and by inhalation through breath-actuated nebulizer, and discussion of the study protocol. No formal evaluation of knowledge retention was performed.

We included subjects who complained of the following acute painful syndromes that were traumatic and nontraumatic at presentation: abdominal pain, flank pain, back pain, musculoskeletal pain, and headache.

We excluded patients whose painful conditions required immediate intervention (treatment) by the treating physician, patients with altered mental status, and those with 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). In addition, we excluded patients with acute intoxication, an allergy to ketamine, an actual body weight of more than 150 kg, those unable to provide consent, those with a past medical history of alcohol or drug abuse, and pregnant or breastfeeding women.

We commenced screening and enrollment of subjects in October 2021 and concluded in September 2023. We enrolled participants Monday through Friday between 8 AM and 8 PM, when an ED pharmacist was available for blinded medication preparation. After the treating emergency physician evaluated patients, study investigators approached study participants who met the eligibility criteria for the acquisition of written informed consent and Health Insurance Portability and Accountability Act authorization. For subjects who did not speak English, we used noninvestigator, hospital-employed, trained interpreters, or licensed telephone interpreters for the acquisition of language-appropriate informed consent. Study investigators consisted of research staff members (research fellows and research associates) who were separate from the treating team. Their training included the following: 2 didactic lectures on ketamine analgesia in the ED; 2 educational sessions on the study protocol, pain and adverse effect scales, and data collection procedures; 2 educational sessions on properly obtaining informed consent and its documentation procedure. Study investigators were responsible for screening the ED dashboard, identifying eligible subjects, ensuring appropriateness of inclusion/exclusion criteria, consenting the subjects, delivering study medications to an ED nurse who was treating the patients, collecting study data, and observing research subjects throughout the entire study period.

Interventions

The on-duty clinical ED pharmacist prepared K-BAN (50 mg/mL concentration) at a dose of 0.75 mg/kg and IV-SDK (10 mg/mL concentration) at 0.3 mg/kg in a 100-mL normal saline solution bag. The study drugs were prepared according to the predetermined randomization list created by the research administration director using SPSS (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) with block randomization of every 10 participants.

The pharmacist standardized the inhaled volume at 5 mL for the K-BAN group by adding normal saline solution to the nebulizer. In addition, the ED pharmacist prepared corresponding placebos (a 100-mL normal saline solution bag and a breath-actuated nebulizer with normal saline solution) in order to maintain the double-dummy study design. The study investigators received both an unmarked infusion bag and an unmarked, prefilled, breath-actuated nebulizer from the pharmacist and delivered them to the treating ED nurse.

We allocated study participants to 2 groups according to the predetermined randomization list: the first group received 0.3 mg/kg of IV-SDK and a breath-actuated nebulizer with normal saline solution; the second group received K-BAN at 0.75 mg/kg and a corresponding IV normal saline solution bag. We determined these dosing regimens for each group based on our own prior published research and several systematic reviews and meta-analyses.[1,8,9,23]

We allowed the intravenous ketamine and intravenous placebo to be delivered through infusion pump with a run time of 15 minutes and the nebulized ketamine and nebulized placebo to be inhaled for a minimum of 5 minutes and a maximum of 15 minutes through the breath-actuated mode. We established these times for both infusion and inhalation prior to study initiation according to our recently conducted and published clinical trials.[11,23]

The on-duty pharmacist, research administration director, and biostatistician were the only individuals with knowledge of the study arms to which the participants were randomized. The ED clinicians, ED nurses, study participants, and study investigators were blinded to the groups in which the participants were randomized and the medications they received. The research administration director and/or 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 study investigators were responsible for the subjects' enrollment and data collection. They recorded each participant's demographics, chief complaint, weight, vital signs, initial and subsequent pain scores on a standard 0 to

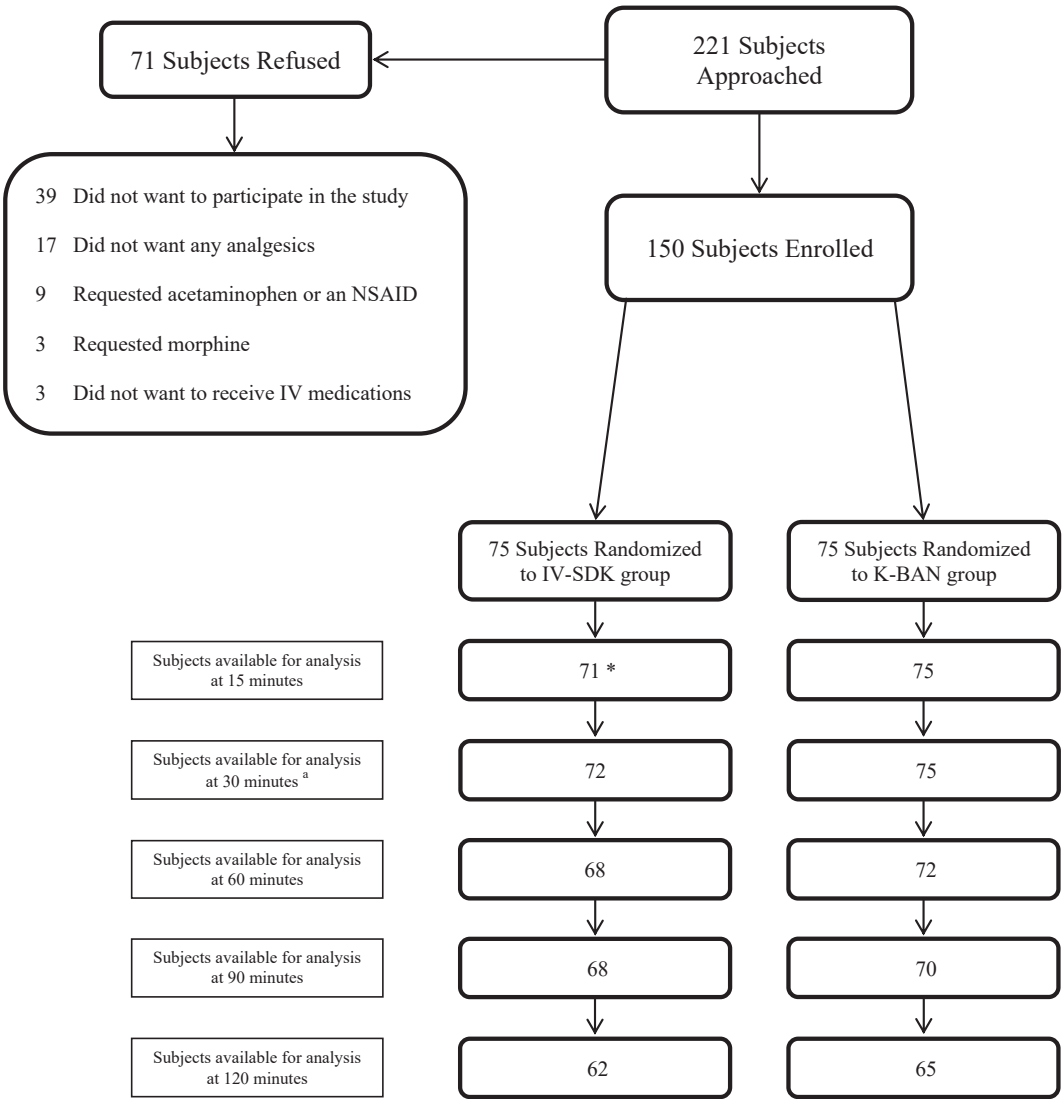

Figure 1. *NSAID* indicates non-steroidal anti-inflammatory drug. Subject flow diagram. *Subjects were missing data due to either intolerable adverse effects, discharge, transfer from the ED, or radiological testing. [a]Primary outcome.

10 numerical rating scale (with 0 being "no pain" and 10 being "the worst pain imaginable"), rescue medication administration, and adverse effects at baseline and 15, 30, 60, 90, and 120 minutes postmedication administration. Study investigators verbally administered the numerical rating scale pain scale to all study participants after they were triaged and had their pain score documented by a triage nurse. Study investigators monitored subjects for the entire study duration (120 minutes). For participants requiring rescue analgesia at any time during the study period, the investigators offered IV morphine at 0.1 mg/kg.

Outcome Measures

The primary outcome was a between-group difference in pain scores on the numerical rating scale 30 minutes after ketamine administration. We used a minimal clinically significant difference in pain score of 1.3 between the 2 groups at 30 minutes as the primary outcome, based on a validated, verbally administered rating scale of acute pain in the ED and comparing verbal and visual pain scales.[25-27]

Assuming a greater improvement in pain score in the IV-SDK group of 1.3 points over the K-BAN group, with an SD of 3.0 in both groups, we needed to enroll 67 subjects per group (134 total) to have 80% power at an alpha of 0.0465 for a one-sided z-test. To account for possible missing data caused by subjects' attrition (early withdrawals, discharge prior to the study completion, absence from the ED due to imaging), we increased the total sample size to 150 subjects (75 per group). A

Table 1. Patient characteristics.

Baseline Characteristics	Group	
	IV-SDK, mean (SD)	K-BAN, mean (SD)
Age	46 (13)	47 (16)
Pain score	8.2 (1.6)	8.2 (1.5)
Pulse rate	76 (14)	80 (16)
Blood pressure—systolic	132 (19)	131 (19)
Blood pressure—diastolic	82 (13)	81 (14)
Respiratory rate	17 (3)	18 (3)
Oxygen saturation	99 (1)	99 (1)
	IV-SDK, n (%)	**K-BAN, n (%)**
Male sex	34 (45)	36 (48)
Chief complaint		
Musculoskeletal nontraumatic pain	14 (19)	10 (13)
Musculoskeletal traumatic pain	9 (12)	7 (9)
Abdominal pain	34 (45)	35 (47)
Flank pain	15 (20)	18 (24)
Genitourinary pain	0 (0)	2 (3)
Other pain	3 (4)	3 (4)
Primary diagnosis*		
Musculoskeletal nontraumatic pain	13 (17)	10 (13)
Musculoskeletal traumatic pain	14 (19)	9 (12)
Abdominal pain	27 (36)	26 (35)
Flank pain	13 (17)	16 (21)
Genitourinary pain	2 (3)	8 (11)
Other pain	6 (8)	6 (8)

IV-SDK, intravenous subdissociative dose of ketamine; *K-BAN*, nebulized ketamine through a breath-actuated nebulizer.
*Diagnosis of musculoskeletal traumatic pain includes trauma related: fractures, dislocations, strains/sprains, back pain. Diagnosis of musculoskeletal nontraumatic pain include: generalized acute back pain and myalgia. Diagnosis of abdominal pain includes diverticulitis, gastritis, colitis, biliary colic, pancreatitis, appendicitis, small bowel obstruction. Diagnosis of flank pain includes renal colic, pyelonephritis. Diagnosis of genitourinary pain includes urinary tract infection, pelvic inflammatory disease, dysuria, testicular pain, polycystic ovaries. Diagnosis of other pain includes: soft tissue, sickle cell crisis, sciatica, headache, acute herpetic neuralgia.

preplanned interim data analysis occurred on reaching 60 subjects (30 subjects per group), and an alpha of 0.0035 was used to maintain overall power, making the overall alpha of the study 0.05.

The post hoc secondary outcomes included the need for rescue analgesia (IV morphine), occurrences of adverse events in each group, and the difference in pain scores at 15, 30, 60, 90, and 120 minutes. We used the Side Effect Rating Scale for Dissociative Anesthetics and the Richmond Agitation Sedation Scale to assess adverse effects related to ketamine administration. The Side Effect Rating Scale for Dissociative Anesthetics scale includes fatigue, dizziness, nausea, headaches, feelings of unreality, changes in hearing, mood changes, general discomfort, and hallucinations, with the 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.[28] The Richmond Agitation Sedation Scale evaluates the severity of agitation and/or sedation per a 10-point scale, with scores ranging from "−5" (unarousable) to "0" (alert and calm) to "+4" (combative).[29]

Primary Data Analysis

The data analyses of the pain scores were based on the intention-to-treat principle. Percentage differences and 95% confidence intervals (CI) between the treatment groups were calculated for all time points, with $P<.05$ to denote statistical significance.

RESULTS

We enrolled a total of 150 subjects (75 in each group) in our study, with 147 subjects available at 30 minutes and 127 subjects available at 120 minutes for data analyses. The subject flow diagram describing the total number of participants and the reasons for missing data at each time point is presented in Figure 1.

Baseline characteristics related to age, sex, vital signs, and initial pain scores were similar between the 2 groups (Table 1). All participants in the 2 groups were relatively similar with respect to chief complaints and final diagnoses, with the IV-SDK group having slightly more subjects with nontraumatic musculoskeletal pain (Table 1).

The change in mean pain score between the 2 groups is presented in Table 2. We demonstrated that at 30 minutes poststudy drug administration, the mean pain score in the IV-SDK group was 3.6, and in the K-BAN group was 3.8, with a mean difference of 0.23 (95% CI −1.32 to 0.857) (Table 2). Similarly, we observed no statistically significant difference in the change in pain score between the 2 groups at 60 to 120 minutes poststudy drug administration.

The 95% CIs for the pain reduction from baseline to 30 minutes in both groups are presented in Figure 2.

A total of 31 participants (10 in the IV-SDK group and 21 in the K-BAN group) received rescue analgesia throughout the entire study period, with only 12 subjects receiving rescue morphine analgesia according to the protocol (Table 3). Treating attending physicians ordered rescue medications for the remaining 19 participants outside of the study-proposed opioid analgesia.

Due to the unexpectedly large number of participants receiving rescue analgesia outside of the protocol, we

Table 2. Pain scores for both groups over time.

	Group					
Time	IV-SDK Mean (SD)	N	K-BAN Mean (SD)	N	Difference	95% CI
Baseline	8.2 (1.6)	75	8.2 (1.5)	75	0.03	−0.53 to 0.47
15 min	2.6 (3.1)	71	3.8 (3.4)	75	1.18	−2.24 to −0.12
30 min	3.6 (3.3)	72	3.8 (3.3)	75	0.23	−1.32 to 0.857
60 min	3.3 (2.8)	68	4.1 (3.4)	72	0.79	−1.83 to 0.245
90 min	3.7 (3.2)	68	3.6 (3.3)	70	0.06	−1.02 to 1.15
120 min	3.3 (3.0)	62	3.4 (3.1)	65	0.12	−1.17 to 0.95

IV-SDK, intravenous subdissociative dose of ketamine; *K-BAN*, nebulized ketamine through a breath-actuated nebulizer; *CI*, confidence interval; *SD*, standard deviation.

conducted an additional sensitivity analysis on the "per protocol" subjects only (those not receiving rescue analgesia or receiving morphine only) to assess the robustness of our findings in the primary analysis. We found no difference in the change in pain scores between the 2 groups for the primary outcome of 30 minutes and for the additional time points up to 120 minutes (Table 4).

We observed no clinically concerning changes in vital signs and no clinically significant adverse effects requiring intervention related to the study medication at any dose or at any time point throughout the study period. More subjects in the IV-SDK group experienced sedation, restlessness, dizziness, and feelings of unreality up to 30 minutes post medication administration (Appendices E2 and E3, available online at http://www.annemergmed.com).

LIMITATIONS

We performed a single-center study in which we enrolled study participants 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 the underrepresentation of patients presenting to the ED throughout the night.

The sample size of 150 subjects and the short duration (120 minutes) of our study were inadequate to assess the full extent of the safety and analgesic efficacy of the IV-SDK and K-BAN regimens beyond 120 minutes. We did not standardize an inhalation time as we used a time range of 5 to 15 minutes, which could have led to variability in the onset of analgesia among the subjects receiving K-BAN. Similarly, we did not record the actual treatment time for each patient in the K-BAN group,

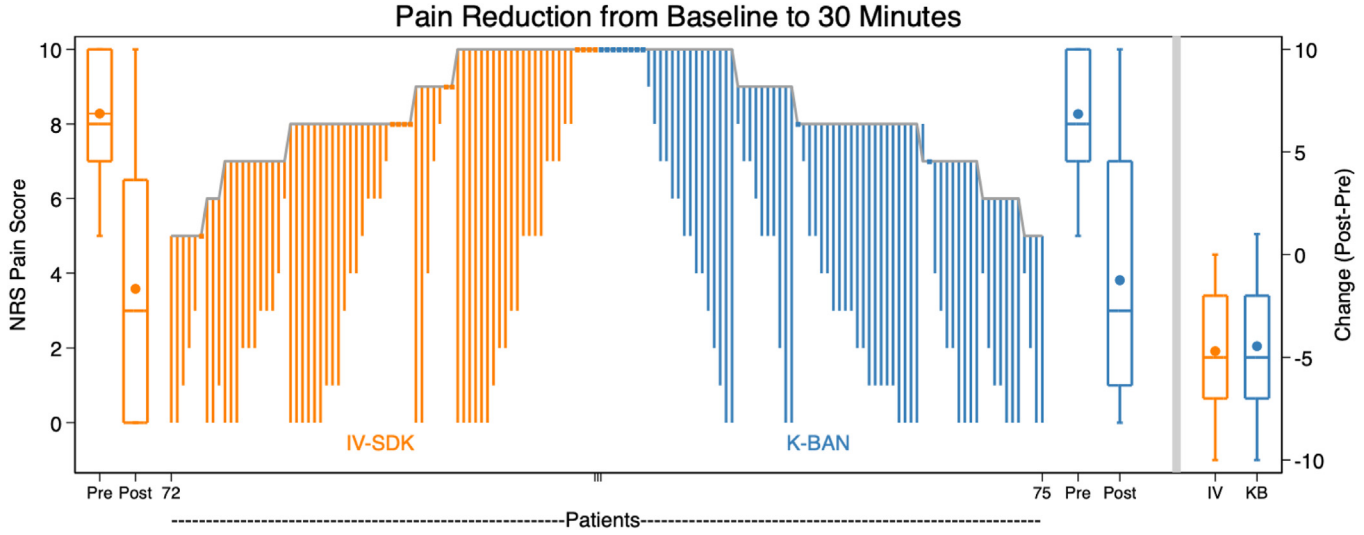

Figure 2. Parallel line plot of NRS pain scores and 95% CI from baseline to 30 minutes. *Horizontal line on boxplot represents median, circle represents mean, and vertical lines represent data above and below percentiles. *NRS*, numeric rating scale; *CI*, confidence interval.

Table 3. Use of any rescue medication over time.

	Group			
Rescue Medication Time of Administration	**IV-SDK (n)**	**IV-SDK (n), name of rescue medication**	**K-BAN (n)**	**K-BAN (n), name of rescue medication**
15 min	0	0	1	(1) Ketorolac 15 mg
30 min	1	(1) Ketorolac 15 mg	2	(1) Morphine 4 mg (1) Ketorolac 15 mg
60 min	4	(3) Morphine 4 mg (1) Ketorolac 15 mg	4	(1) Morphine 4 mg (2) Ketorolac 15 mg (1) Acetaminophen 650 mg
90 min	5	(1) Morphine 4 mg (1) Ketorolac 15 mg (2) Ketorolac 30 mg (1) Acetaminophen 650 mg	8	(4) Morphine 4 mg (1) Tramadol 10 mg (1) Ketorolac 15 mg (1) Ketorolac 30 mg (1) Acetaminophen 650 mg
120 min	0	0	6	(2) Morphine 4 mg (2) Ketorolac 15 mg (2) Ketorolac 30 mg

which would help us assess the participants' compliance with device use.

We observed a large number of rescue analgesics that were administered outside of the study protocol, which could have diluted the treatment effect even though our additional sensitivity analysis supported the robustness of the primary outcome. A difference in the administration of rescue analgesia was noted between the groups, as the IV-SDK group received less rescue analgesia compared with the K-BAN group. This may be explained by the lack of a standardized inhalation time (variation in the onset and duration of analgesia), as well as not measuring the residual amount of ketamine remaining in the breath-actuated nebulizer (variability in the amount of ketamine inhaled).

We did not blind research associates to the clinical manifestation of nystagmus, a unique reaction to ketamine, especially after intravenous administration, which could have had the potential to un-blind. Additionally, we did not measure the efficacy of blinding.

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

We used breath-actuated nebulizers in our study, but these devices may not be readily available for use in other EDs across the country. We did not evaluate participants' satisfaction (or lack thereof) with respect to the usability of the breath-actuated nebulizer (in the breath-actuated

Table 4. Sensitivity analysis of pain scores of those not receiving rescue analgesia or receiving morphine only.

		Group			
Time	**n**	**IV-SDK Mean (SD)**	**K-BAN Mean (SD)**	**Difference**	**95% CI**
Baseline	150	8.1 (1.6)	8.1 (1.5)	0.0	−0.564 to 0.549
15 min	145	2.4 (2.9)	2.7 (2.7)	0.3	−1.314 to 0.722
30 min	145	3.0 (3.1)	2.7 (2.7)	0.3	−0.674 to 1.429
60 min	136	2.9 (2.6)	2.9 (2.8)	0.0	−1.039 to 0.948
90 min	130	3.2 (3.0)	2.7 (2.7)	0.5	−0.486 to 1.625
120 min	123	3.0 (2.9)	2.8 (2.7)	0.2	−0.91 to 1.31

mode), ketamine as an analgesic, overall pain relief, or willingness to use either the inhalation route or the intravenous route in the future. Lastly, we did not use a placebo arm in our study.

DISCUSSION

We compared the analgesic efficacy and adverse effect profile of IV-SDK administered at 0.3 mg/kg as a short infusion over 15 minutes with a K-BAN administered at 0.75 mg/kg through a breath-actuated nebulizer in adult ED patients presenting with acute painful syndromes. To our knowledge, this is the first trial comparing the IV route to the nebulized route for ketamine analgesia in the ED. We demonstrated that both delivery methods led to a significant and clinically important reduction in pain throughout the study duration. However, we showed a lack of analgesic superiority of IV-SDK over the K-BAN for short-term pain relief in the ED. Both routes resulted in similar changes in pain scores at 30 minutes and up to 120 minutes postmedication administration.

In addition, we demonstrated that a mean change in pain score of nearly 4.5 points in each group from baseline to 30 minutes and a mean change in pain score of nearly 5 points in each group from baseline to 120 minutes was larger than the minimum clinically important cutoff of 1.3 points (Table 2). From a clinical perspective, these changes in pain scores translate to reductions in pain intensity of nearly 55% and 60% at the 30-minute and 120-minute time points, respectively.

Our findings of pain reduction are similar to those from our earlier published clinical trials, in which we compared IV-SDK with intravenous morphine and K-BAN given at 3 different dosing regimens. The pain scores changed by 4.2 points and 4.0 points, respectively.[1,23]

Out of 31 recipients of rescue analgesia, 12 subjects received an opioid rescue, with only 4 of these subjects being in the IV-SDK group. This number is much lower than the total number of subjects needing opioid rescue analgesia in our previous trial evaluating IV-SDK (25 subjects) and IV morphine (17 subjects).[3] Of the 8 participants in the K-BAN group who received rescue opioids, only 2 subjects received the rescue medications prior to the 60-minute mark, which is similar to the results of our nebulized ketamine trial.[23]

None of our subjects in the K-BAN group experienced difficulties initiating breath-actuated mode, even though this issue is frequently seen in the out-of-hospital setting with the use of nitrous oxide.[30,31]

In conclusion, we found no difference between ketamine administered IV or through nebulization through a breath-actuated nebulizer for the short-term treatment of moderate to severe acute pain in adult ED patients, with both treatments providing a clinically meaningful reduction in pain scores at 30 minutes.

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Author affiliations: From the Department of Emergency Medicine (Nguyen, Mai, Choudhary, Gitelman, Drapkin, Likourezos, Kabariti, Hossain, Silver, Motov) Maimonides Medical Center, Brooklyn, NY; and Department of Pharmacy (Kun, Gohel, Niceforo), Maimonides Medical Center, Brooklyn, NY.

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

Data sharing statement: The entire deidentified dataset, data dictionary and analytic code for this investigation are available upon request, from the date of article publication by contacting Sergey Motov, MD, at SMotov@maimo.org.

Authorship: 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.

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