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Original Contribution

Intravenous subdissociative-dose ketamine versus morphine for acute geriatric pain in the Emergency Department: A randomized controlled trial

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ABSTRACT

Study objective: We compare the analgesic efficacy and safety of subdissociative intravenous-dose ketamine (SDK) versus morphine in geriatric Emergency Department (ED) patients.
Methods: This was a prospective, randomized, double-blind trial evaluating ED patients aged 65 and older experiencing moderate to severe acute abdominal, flank, musculoskeletal, or malignant pain. Patients were randomized to receive SDK at 0.3 mg/kg or morphine at 0.1 mg/kg by short intravenous infusion over 15 min. Evaluations occurred at 15, 30, 60, 90, and 120 min. Primary outcome was reduction in pain at 30 min. Secondary outcomes included overall rates of adverse effects and incidence of rescue analgesia.
Results: Thirty 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: 9.0 versus 8.4 at baseline (mean difference 0.6; 95% CI −0.30 to 1.43) and 4.2 versus 4.4 at 30 min (mean difference −0.2; 95% CI −1.93 to1.46). Patients in the SDK group reported higher rates of psychoperceptual adverse effects at 15, 30, and 60 min post drug administration. Two patients in the ketamine group and one in the morphine group experienced brief desaturation episodes. There were no statistically significant differences with respect to changes in vital signs and need for rescue medication.
Conclusion: SDK administered at 0.3 mg/kg over 15 min provides analgesic efficacy comparable to morphine for short-term treatment of acute pain in the geriatric ED patients but results in higher rates of psychoperceptual adverse effects. ClinicalTrials.gov Registration #: NCT02673372.

1. Introduction

1.1. Background

Management of acute pain in elderly patients in the Emergency Department is associated with a set of unique challenges that complicate care of these patients and at times lead to suboptimal pain relief [1-6]. Age-related changes in drug absorption, metabolism and clearance as well as polypharmacy leading to dangerous drug-drug interactions place elderly patients at significant risks of drug-related side effects and even treatment failures related to frequent use of opioids and NSAID's [1,6-8]. To complicate the issue of geriatric pain management even further, data shows that elderly patients are less likely to receive opioid analgesia or receive an appropriate dose of opioids both in the ED and on discharge in comparison to their younger counterparts [9-11]. Thus, in order to provide timely, effective and safe pain control for elderly patients, ED clinicians might consider exploring the utilization of non-opioid/non-NSAID-based analgesic modalities that have potential to provide comparable or even better pain relief than opioids and NSAID's but with lower rates of serious side effects. One such analgesic modality is subdissociative-dose ketamine (SDK).

1.2. Importance

Ketamine is a non-competitive *N*-methyl-D-aspartate (NMDA)/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 [12-14]. Ketamine administration in subdissociative doses

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(0.1–0.3 mg/kg) in pre-hospital settings and in the ED results in effective pain relief in patients with acute traumatic and non-traumatic pain, chronic non-cancer and cancer pain, and in patients with opioid-tolerant pain by virtue of providing anti-hyperalgesia, anti-allodynia, and anti-tolerance [15-19]. Two commonly employed strategies of SDK administration in the ED include an intravenous push (IVP) dose (over 2–5 min), which is associated with relatively high rates of minor but bothersome psychoperceptual side effects (feeling of unreality and dizziness), or short infusion (SI) given over 15 min with significantly reduced rates of unreality and preserved analgesic efficacy [20-22]. To our knowledge, there are no prospective randomized trials that evaluated SDK role in managing a variety of acute and chronic painful conditions in geriatric patients in the ED.

1.3. Goals of this investigation

In our study we hypothesize that an intravenous subdissociative-dose ketamine administered as a single agent in a dose of 0.3 mg/kg via short infusion over 15 min, will provide pain relief similar to that of intravenous morphine at 0.1 mg/kg administered over 15 min in geriatric ED patients with acute pain of moderate-to-severe intensity. The primary outcome of this trial is the comparative reduction in participant's pain scores at 30 min post medication administration.

2. Materials and methods

2.1. Study design

This was a prospective, randomized, double-blind trial comparing the analgesic efficacy and safety of intravenous SDK with intravenous morphine both administered as a short infusion (over 15 min) for acute pain in elderly ED patients. This study was approved by the Maimonides Medical Center institutional review board and registered with clinicaltrials.gov (NCT02673372). The study was conducted and is reported according to the Consolidated Standards of Reporting Trials Group [23].

2.2. Study setting and selection of participants

The study facility is a 711-bed community teaching hospital with an annual ED census of >120,000 visits. Patient screening, enrollment, and data collection were performed by a study investigator. 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 fashion. A convenience sample of patients was enrolled between April 2016 and February 2018. 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 65 and older who presented to the ED with acute abdominal, flank, back, or musculoskeletal pain with a 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 [24,25]. Acute pain was defined as having an onset within 7 days. Exclusion criteria included altered mental status, allergy to morphine or ketamine, weight <40 kg or >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 past medical history of acute head or eye injury, seizure, intracranial hypertension, severe chronic obstructive pulmonary disease, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4 h 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. When 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 100 mL of normal saline solution according to the predetermined randomization list, which was created in SPSS (version 24; IBM Corp, Armonk, NY) with block randomization of every 10 participants. We based our decision to utilize short infusion of either analgesics instead of intravenous push on the prior research (SDK) [22] and clinical experience (morphine) that demonstrated a lesser degree of psychoperceptual side effects and preserved analgesic efficacy of SDK and lesser degree of nausea and lightheadedness of morphine. The medication was delivered to the treating nurse in a blinded fashion and was administered by short intravenous infusion over 15 min via an infusion pump.

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 min. If patients reported a pain numeric rating scale score of 5 or greater and requested additional pain relief, fentanyl at 0.5 μg/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 patients sex, demographics, medical history, and vital signs, were entered into SPSS (version 24.0; 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 worked independent of any data collection.

2.3. Outcome measures

The primary outcome was a comparative reduction of pain scores on numeric rating pain scale (NRS) between recipients of SDK and morphine at 30 min. The secondary outcomes included a need for rescue analgesia at either 30 or 60 min and adverse events in each group. With respect to unique adverse effects in SDK group, we used the Side Effect Rating Scale for Dissociative Anesthetics (SERSDA) and the Richmond Agitation Sedation Scale (RASS) [26,27]. SERSDA Scale includes fatigue, dizziness, nausea, headache, feeling of unreality, changes in hearing, mood change, general discomfort, and hallucinations with severity of each graded by patients on a five-point scale, with “0” representing the absence of any adverse effects and “4” representing a severely bothersome side effect. RASS evaluates the severity of agitation and/or sedation in accordance to the nine-point scale with scores ranging from “−4” (deeply sedated) to “0” (alert and calm) to “+4” (combative).

2.4. 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 24; IBM Corp). Mixed-model linear regression (SAS, version 9.4; 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 min relative to time 0. The 95% confidence intervals for the mean difference in numeric rating scale pain score for the SDK versus morphine groups at each time point were calculated with 2 estimate methods for the pooled standard deviation (SD). One method was

Table 1
Baseline patient characteristics.

	Group	
	Ketamine	Morphine
Characteristics		
No. of subjects	30	30
Age	77.3 (8.4)[a]	77.1 (8.5)
Male sex	7 (23.3)[b]	7 (23.3)
Baseline pain score	8.97 (1.5)[a]	8.40 (1.8)
Baseline vital signs		
Heart rate	77.8 (11.9)[a]	82.2 (10.8)
Blood pressure systolic	143.8 (26.0)	143.8 (22.3)
Blood pressure diastolic	75.9 (16.1)	73.8 (10.4)
Respiratory rate	17.5 (4.1)	20.2 (4.5)
O_2 saturation	97.5 (1.6)	97.2 (2.4)
Source of pain		
Abdominal	14 (46.7)[b]	10 (33.3)
Cancer	2 (6.7)	5 (16.7)
Back	5 (16.7)	1 (3.3)
Musculoskeletal	1 (3.3)	3 (10)
Fracture	5 (16.7)	7 (23.3)
Flank	3 (10)	4 (13.3)

[a] Mean (standard deviation).
[b] Frequency (percent).

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 (e.g., complete resolution of pain), a X^2 or Fisher's exact test was used to compare rates for categorical outcomes at 30 min. Percentage differences and 95% confidence intervals between the treatment groups were calculated for all time points. $P < .05$ was used to denote statistical significance. 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 primary outcome consisting of a minimal clinically meaningful difference of 1.3 between the SDK and morphine groups at the 30-minute pain assessment [28,29].

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 min (as well as at any other interval post-baseline), with an alpha = 0.05. A pre-planned interim data analysis was to occur upon reaching a total of 60 patients (30 in each group).

3. Results

At the planned interim data analysis that included 60 patients, a decision was made to stop the recruitment of patients due to the facts that a) refusal rates to either participate in the study or to receive morphine were much higher than we anticipated as presented in patient flow diagram, and b) the interim data analysis demonstrated an attainment of sufficient power to test the study hypothesis with fewer participants.

Sixty patients (30 in SDK group and 30 in morphine) were enrolled in the study. The patients' mean age was 77.3 and 77.1 years, respectively (SD = 23.3 for both groups); 23.3% were men in both groups. There were no differences between the groups in terms of demographic characteristics or baseline vital signs, pain scores, or source of pain (Table 1) with the exception of having more patients with cancer pain in the morphine group. The patient flow diagram is illustrated in Fig. 1. As shown in Table 2, patients' reported pain scores at time 0

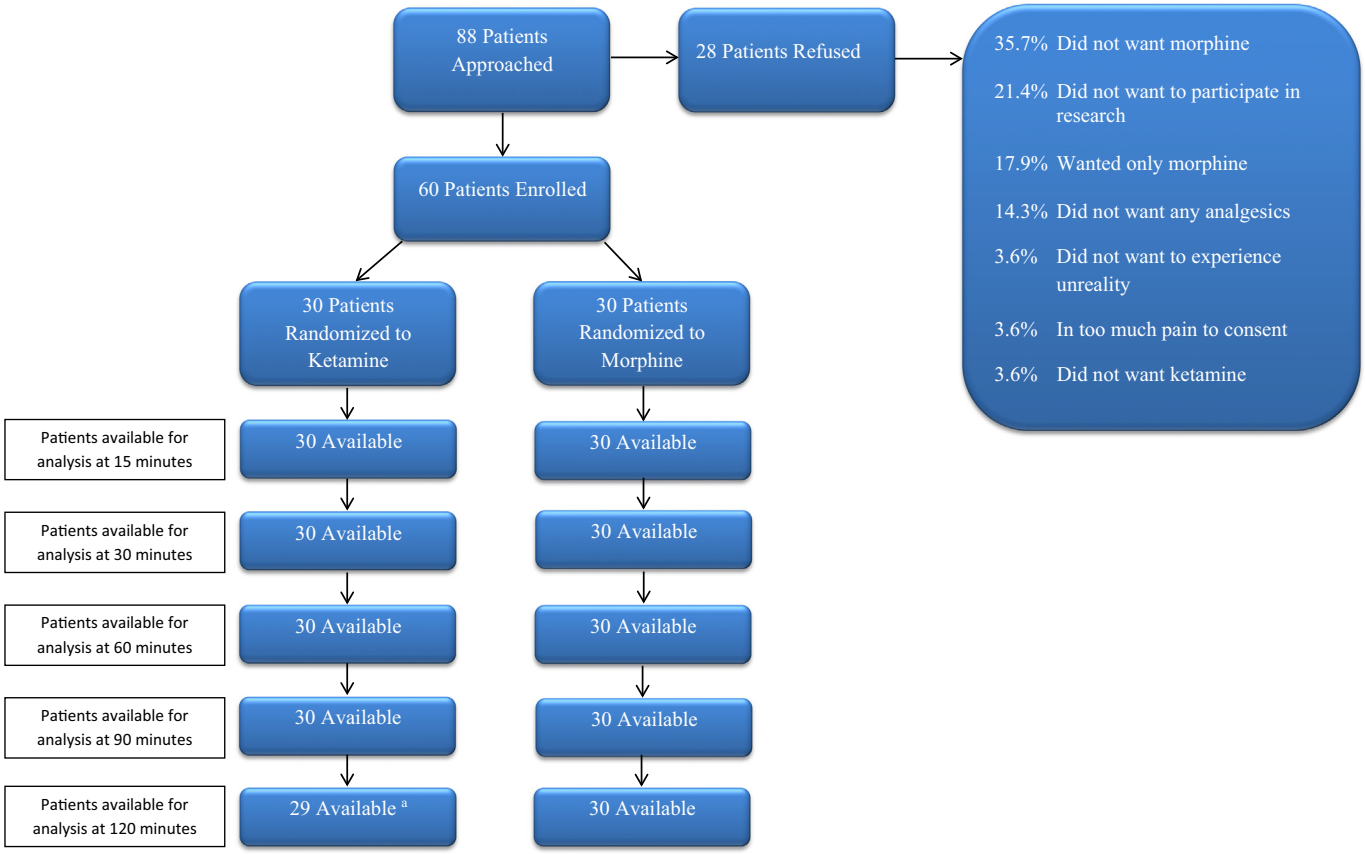

Fig. 1. Patient flow diagram.

Table 2
Pain trends.

	Group		Difference (95% CI)
	Ketamine	Morphine	
Pain at each time point			
Baseline	9.0 (1.5)[a]	8.4 (1.8)	0.6 (−0.30 to 1.43)
15 min	3.0 (3.6)	5.0 (3.5)	−2.0 (−3.82 to −0.11)
30 min	4.2 (3.4)	4.4 (3.1)	−0.2 (−1.93 to 1.46)
60 min	3.9 (3.2)	4.0 (2.9)	−0.1 (−1.68 to 1.48)
90 min	3.8 (2.8)	3.6 (3.1)	0.2 (−1.34 to 1.68)
120 min	3.2 (2.5)	3.3 (3.0)	−0.2 (−1.60 to 1.28)
Full resolution of pain			
15 min	15 (52)[b]	5 (17)	35 (12.6 to 57.6)
30 min	7 (23)	4 (13)	10 (−9.4 to 29.4)
60 min	7 (23)	5 (17)	7 (−13.5 to 26.8)
90 min	5 (17)	6 (20)	−3 (−22.9 to 16.2)
120 min	6 (21)	7 (23)	−3(−23.8 to 18.5)
Reduction of NRS 3+			
15 min	22 (73)[c]	16 (53)	20 (−3.8 to 43.9)
30 min	21 (70)	21 (70)	0 (−23.2 to 23.2)
60 min	24 (80)	22 (73)	7 (−14.7 to 28.0)
90 min	25 (83)	24 (80)	3 (−16.2 to 22.9)
120 min	25 (83)	23 (77)	7 (−13.5 to 26.8)
Rescue analgesia given			
15 min	0 (0)[d]	0 (0)	–
30 min	2 (7)	1 (3)	3 (−7.6 to 14.3)
60 min	1 (3)	2 (7)	−3 (−14.3 to 7.9)
90 min	1 (3)	2 (7)	3 (7.7 to 14.3)
120 min	0 (0)	3 (10)	−10 (−20.7 to 0.01)

[a] Mean (standard deviation).
[b] Frequency (%).
[c] Frequency (%).
[d] Frequency (%).

were similar in both groups: the mean difference in pain numeric rating scale score for SDK versus morphine was 0.6 (95% CI −0.30 to 1.43). Participants received an average dose of either 21.9 mg (SD = 6.2) of ketamine or 6.8 mg (SD = 1.5) of morphine. All patients showed significant reductions in mean pain NRS score at 15 and 30 min compared with baseline. However, at 15-minute interval, SDK group had significantly greater reduction in pain from the baseline with a mean difference in pain score of −2.0 (95% CI −3.82 to −0.11). At 30 min, the primary outcome comparison, the mean difference between two groups was −0.2 (95% CI −1.93 to 1.46). The 95% CI for the mean difference at 30 min according to the mixed-model regression SD was −0.20 to 1.33 (mean difference = 0.56) The parallel line plots (Fig. 2) presenting the changes in pain numeric rating scale show an almost a similar pattern of pain decrease for each group from baseline to 30 min. The box plots of the difference show a similar pattern of central tendency and dispersion. As shown in Fig. 3, comparison of the pain scores over time points demonstrates similar mean pain numeric rating scale scores in the study groups with exception of 15-minute interval where SDK group had a greater change in mean pain score.

At the 15-minute interval, more patients reported complete resolution of pain (numeric rating scale = 0) in the SDK group (percentage difference = 35%; 95% CI 12.6 to 57.6). This difference was also noted at 30 min (percentage difference = 10%; 95% CI −9.4 to 29.4) and at 60 min (percentage difference = 7%; 95% CI −13.5 to 26.8). All 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. 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 at 30–120 min. However, at 15-minute time interval SDK group had a greater number of patients with change in pain score of 3-points or greater (percentage difference = 20; CI −3.8 to 43.9). There was also no significant difference between the 2 groups with respect to use of rescue analgesia at 30 min (percentage difference = 3%; 95% CI −7.6 to 14.3) or at 60 min (percentage difference = −3%; 95% CI −14.3 to 7.9). At 120 min, the morphine group required significantly more rescue analgesia (percentage difference −10%; 95% CI −20.7 to 0.01) (Table 2).

A statistically significant difference was observed in the number of patients in the SDK group who reported any adverse effects at 15 min and 30 min in comparison to morphine group (percentage difference = 40% 95% CI 18.4% to 61.6% and percentage difference = 36.67% 95% CI −13.26% to 60.7%, respectively). This difference in adverse effects

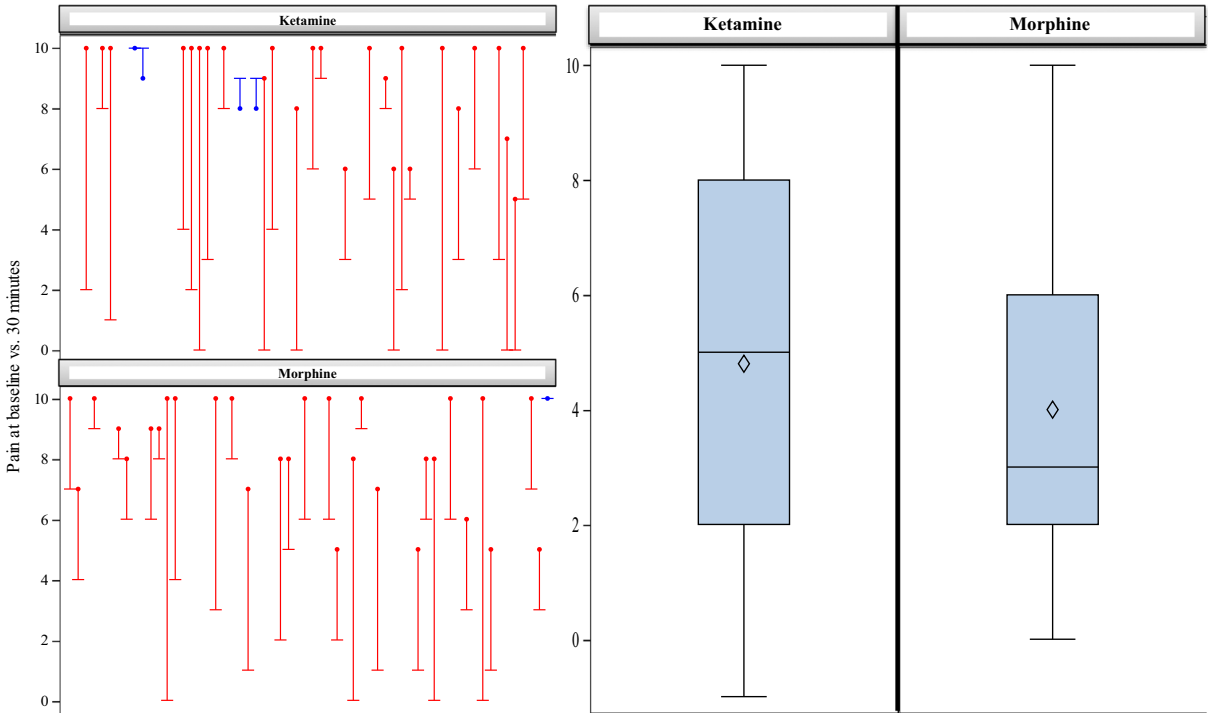

Fig. 2. Parallel line and box plots of pain scores: baseline versus 30 min.

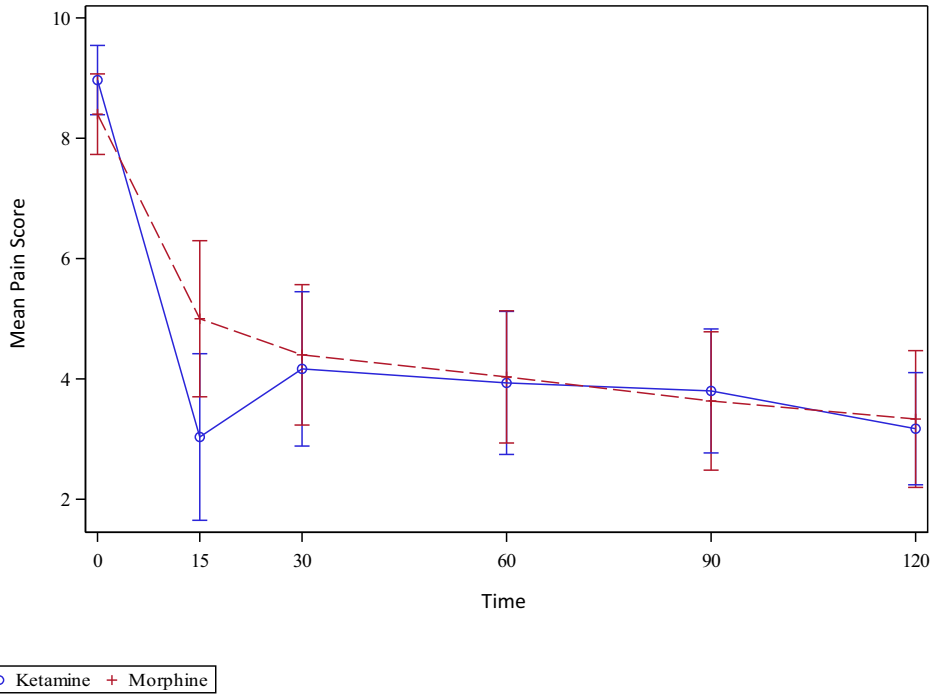

Fig. 3. Reported pain numeric rating score with 95% CI bars.

diminished to equivalence with morphine at the 60-minute interval (Table 3). In addition, SDK group had greater number of patients reporting dizziness at 15, 30, 60 and −90 min and nausea at 15 and 60 min in comparison to morphine group (Table 3). With respect to rates and severity of adverse effects in the SDK group on the SERSDA scale, dizziness, feeling of unreality, and general discomfort were reported more frequently and with greater severity at 15 min (30%, 26.7%, and 13.3% of patients, respectively) (Table 4). Similarly, drowsiness, light and/or moderate levels of sedation via RASS were more prominent at 15-minute interval (16.7%, 13.3%, and 16.7% respectively) (Table 5). Of note, one patient in SDK group exhibited combativeness at the 15 minute mark that did not required any intervention. Dizziness and fatigue were the most commonly reported adverse effects in morphine group at 15, 30 and 60 min (Table 3). 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

Table 3
Rates of adverse effects & interventions.

Report of any adverse effect[b]

Time point	Ketamine	Morphine	Difference (95% CI)
15 min	26 (86.7)[a]	14 (46.7)	40.00 (18.40 to 61.60)
30 min	22 (73.3)	11 (36.7)	36.67 (13.26 to 60.07)
60 min	16 (53.3)	12 (40.0)	13.33 (−11.69 to 38.35)
90 min	10 (33.3)	11 (36.7)	−3.33 (−27.46 to 20.79)
120 min	9 (30.0)	10 (33.3)	−3.33 (−26.86 to 20.19)

Most common adverse effects

Time point	Ketamine	Morphine	Difference (95% CI)	Ketamine	Morphine	Difference (95% CI)	Ketamine	Morphine	Difference (95% CI)
	Dizziness			Nausea			Fatigue		
15 min	18 (62.7)[a]	9 (30.0)	32.1 (8.0 to 56.2)	4 (13.8)	1 (3.3)	10.5 (−3.6 to 24.6)	8 (26.7)	5 (16.7)	10.0 (=10.7 to 30.7)
30 min	16 (53.3)	7 (23.3)	30.0 (6.6 to 53.4)	2 (6.7)	2 (6.7)	0.0 (−12.6 to 12.6)	4 (13.3)	6 (20.0)	−6.7 (−25.4 to 12.1)
60 min	10 (34.8)	6 (20.0)	14.5 (−8.0 to 36.9)	6 (20.7)	2 (6.7)	14.0 (−3.2 to 31.3)	5 (17.2)	5 (16.7)	0.5 (−18.6 to 19.7)
90 min	6 (20.0)	2 (6.7)	13.3 (−3.5 to 30.2)	4 (13.3)	2 (6.7)	6.7 (−8.4 to 21.7)	2 (6.7)	5 (16.7)	−10.0 (−26.5 to 6.0)
120 min	5 (17.9)	5 (16.7)	1.2 (−18.3 to 20.7)	3 (10.7)	2 (6.7)	4.0 (−10.5 to 18.6)	3 (10.7)	6 (20.0)	−9.3 (−27.6 to 9.0)

Report of any intervention

Time point	**Ketamine group**	Ondansetron given	Oxygen given	**Morphine group**	Ondansetron given	Oxygen given
15 min	4 (13.3)[a]	2 (6.7)	2 (6.7)	2 (6.7)	2 (6.7)	–
30 min	–	–	–	1 (3.3)	–	1 (3.3)
60 min	2 (6.7)	2 (6.7)	–	–	–	–
90 min	1 (3.3)	1 (3.3)	–	1 (3.3)	1 (3.3)	–
120 min	–	–	–	–	–	–

[a] Frequency (%).
[b] Patients experiencing multiple adverse effects at one time point were grouped together.

Table 4
Severity of SERSDA.

Level of severity						
Adverse effect	Time point	0 – No change	1 – Weak	2 – Modest	3 – Bothersome	4 – Very bothersome
Dizziness	15 min	12 (40.0)[a]	–	9 (30.0)	2 (6.7)	7 (23.3)
	30 min	14 (46.7)	8 (26.7)	5 (16.7)	2 (6.7)	1 (3.3)
	60 min	20 (66.7)	4 (13.3)	5 (16.7)	–	1 (3.3)
	90 min	24 (80.0)	4 (13.3)	2 (6.7)	–	–
	120 min	25 (83.3)	4 (13.3)	1 (3.3)	–	–
Feeling unreality	15 min	15 (50.0)	2 (6.7)	5 (16.7)	2 (6.7)	6 (20.0)
	30 min	24 (80.0)	3 (10.0)	1 (3.3)	2 (6.7)	–
	60 min	27 (90.0)	2 (6.7)	–	1	–
	90 min	28 (93.3)	1 (3.3)	1 (3.3)	–	–
	120 min	29 (96.7)	1 (3.3)	–	–	–
Fatigue	15 min	22 (73.3)	1 (3.3)	7 (23.3)	–	–
	30 min	26 (86.7)	2 (6.7)	1 (3.3)	1 (3.3)	–
	60 min	26 (86.7)	3 (10.0)	1 (3.3)	–	–
	90 min	28 (93.3)	2 (6.7)	–	–	–
	120 min	27 (90.0)	3 (10.0)	–	–	–
Change in hearing	15 min	29 (96.7)	–	1 (3.3)	–	–
	30 min	–	–	–	–	–
	60 min	–	–	–	–	–
	90 min	–	–	–	–	–
	120 min	–	–	–	–	–
Headache	15 min	24 (80.0)	2 (6.7)	1 (3.3)	–	3 (10.0)
	30 min	24 (80.0)	4 (13.3)	–	1 (3.3)	1 (3.3)
	60 min	25 (83.3)	2 (6.7)	2 (6.7)	–	1 (3.3)
	90 min	27 (90.0)	1 (3.3)	1 (3.3)	1 (3.3)	–
	120 min	28 (93.3)	–	1 (3.3)	1 (3.3)	–
Change in vision	15 min	24 (80.0)	1 (3.3)	2 (6.7)	1 (3.3)	2 (6.7)
	30 min	25 (83.3)	3 (10.0)	1 (3.3)	1 (3.3)	–
	60 min	26 (86.7)	3 (10.0)	–	1 (3.3)	–
	90 min	29 (96.7)	–	–	1 (3.3)	–
	120 min	–	–	–	–	–
General discomfort	15 min	20 (66.7)	2 (6.7)	4 (13.3)	–	4 (13.3)
	30 min	23 (76.7)	3 (10.0)	3 (10.0)	1 (3.3)	–
	60 min	25 (83.3)	3 (10.0)	–	1 (3.3)	1 (3.3)
	90 min	26 (86.7)	2 (6.7)	2 (6.7)	–	–
	120 min	28 (93.3)	1 (3.3)	1 (3.3)	–	–
Mood change	15 min	25 (83.3)	2 (6.7)	1 (3.3)	1 (3.3)	1 (3.3)
	30 min	27 (90.0)	1 (3.3)	–	2 (6.7)	–
	60 min	27 (90.0)	1 (3.3)	2 (6.7)	–	–
	90 min	26 (86.7)	3 (10.0)	–	1 (3.3)	–
	120 min	–	–	–	–	–
Hallucination	15 min	28 (93.3)	–	1 (3.3)	–	1 (3.3)
	30 min	–	–	–	–	–
	60 min	–	–	–	–	–
	90 min	–	–	–	–	–
	120 min	–	–	–	–	–
Nausea	15 min	26 (86.7)	1 (3.3)	1 (3.3)	2 (6.7)	–
	30 min	28 (93.3)	–	2 (6.7)	–	–
	60 min	25 (83.3)	2 (6.7)	2 (6.7)	1 (3.3)	–
	90 min	26 (86.7)	2 (6.7)	–	1 (3.3)	1 (3.3)
	120 min	27 (90.0)	1 (3.3)	–	1 (3.3)	1 (3.3)

[a] Frequency (%).

signs that were clinically concerning or required intervention. Most adverse effects were transient and did not require treatment, however 7 patients in SDK group and 4 patients in Morphine group required ondansetron for nausea and/or supplemental oxygen for correction of brief hypoxic events (Table 3).

4. Limitations

This was a single-center study with patients who may not reflect the rest of the population in the country. Both medications were administered via short infusion that is not a generally accepted route of such

Table 5
Patients reporting agitation or sedation according to RASS.

Time point	Level of sedation					No effect	Level of agitation			
	−5 Unarousable	−4 Deep sedation	−3 Moderate sedation	−2 Light sedation	−1 Drowsy	0 Alert & calm	+1 Restless	+2 Agitated	+3 Very agitated	+4 Combative
15 min	–	–	5 (16.7)[a]	4 (13.3)	5 (16.7)	11 (36.7)	2 (6.7)	2 (6.7)	–	1 (3.3)
30 min	–	–	–	1 (3.3)	4 (13.3)	22 (73.3)	3 (10.0)	–	–	–
60 min	–	–	–	–	3 (10.0)	26 (86.7)	1 (3.3)	–	–	–
90 min	–	–	–	–	1 (3.3)	26 (86.7)	2 (6.7)	1 (3.3)	–	–
120 min	–	–	–	–	1 (3.3)	29 (96.7)	–	–	–	–

[a] Frequency (%).

analgesic administrations in the ED's across the country. An enrollment via a convenience sampling according to specific time frames in which both a member of the research team and pharmacy team were available could have introduced a selection bias. Sample size due to significant refusal rates of participation in the study and administration of morphine was small and below the near minimum for adequate power (83%) to detect true analgesic difference between two groups. Extensive exclusion criteria that may not be generalizable to the rest of the population severely limited the enrollment process. The study was not powered to detect the difference in adverse effects between two groups. Lastly, there could have been a potential for unblinding due to the fact that some participants exhibited ketamine-specific reactions such as nystagmus and a feeling of unreality.

5. Discussion

Subdissociative-dose ketamine administration in the form of intravenous push or short infusion is gaining popularity as a viable adjunct to or substitute for opioid analgesics in order to manage a multitude of acute and chronic painful conditions in the pre-hospital setting and in the ED. Retrospective case series, prospective observational, and randomized controlled trials evaluating SDK analgesia given as an intravenous push for patients with acute pain demonstrated comparable to morphine analgesic efficacy, opioid sparing, and moderate rates of minor but bothersome side effects [15-22,30-32]. These side effects were apparent in the first few minutes of SDK administration, were short-lived and did not require any interventions [20,30]. A recently published trial by our group demonstrated greater reduction (by 40%) in the rates of psychoperceptual side effects of SDK administered via short infusion over 15 min in comparison to intravenous push dose and preserved analgesic efficacy [22]. This route has become a primary modality of SDK administration in our ED and was chosen for this trial.

In our prospective, randomized, double-blind trial, we compared a single intravenous subdissociative-dose ketamine with single intravenous dose morphine administered via short infusion for geriatric ED patients experiencing acute pain. We were able to demonstrate that SDK is as effective as morphine in relieving pain at 30 min. In addition, we showed that SDK group had a greater pain relief (by 2 points) at 15 min, had a larger proportion of patients achieving change in NRS by 3 + points or greater at 15 min (73% vs. 53%) and reporting complete resolution of pain (NRS = 0) at 15 min (52% vs 17%) and at 30 min (23% vs. 13%) in comparison to morphine group. There was no significant difference between the groups with respect to change in pain scores at 30 to −120 min and in the proportion of patients who reported a 3-point or more reduction in pain numeric rating scale score at the 30 to 120 minute intervals. These findings suggest that sub-dissociative ketamine is more effective than morphine in the reduction of acute pain within 15 min of administration.

The SDK recipients experienced statistically significant higher rates in overall adverse effects at 15 min post-administration (86.7% vs. 46.7%) and at 30 min (73.3% vs 36.7%). (Table 3). The SDK group, in addition, had higher rates of dizziness at 15–60 min in comparison to the morphine recipients (Table 3). Furthermore, the SDK group had a high percentage of patients experiencing adverse effects via SERSDA scale and RASS scale that were moderate in severity with high 60% of participants experiencing dizziness, 40% of feeling of unreality (40%), and 30% of participants experiencing light-to-moderate sedation at 15 min. (Tables 4 and 5). These findings are consistent with those of previous trials of SDK administered via short infusion. Galinski et al. compared intravenous SDK at 0.2 mg/kg given over 10 min to 0.1 mg/kg of IVP morphine for severe acute traumatic pain and demonstrated that 36% of patients receiving SDK experienced neuropsychological adverse effects (dizziness, feeling of unreality, and dizziness) [33]. A trial by Motov et al. that compared safety and efficacy of SDK give via IVP vs. short infusion showed that 57% and 75% of patients receiving SDK via short infusion reported feeling of unreality and dizziness with moderate severity [22].

Lastly, 2 patients (at 15 min) in SDK group and one patient (at 30 min) in morphine group required supplemental oxygen due to brief episodes of desaturation (Table 3).

Based on our results, we believe that further prospective randomized trial comparing different SDK dosing regimens and different durations of infusion are warranted to determine the optimal strategy of SDK administration that will significantly reduce psychoperceptual adverse effects while maintaining analgesic efficacy similar to that of morphine.

In conclusion, our trial demonstrated that subdissociative-dose intravenous ketamine administered at 0.3 mg/kg over 15 min provides analgesic efficacy comparable to intravenous morphine for short-term treatment of acute moderate-to- severe pain in geriatric ED patients but results in higher rates of overall and specific psychoperceptual adverse effects.

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Conflicts of interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors have no independent disclosures or conflicts of interest.

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