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ORIGINAL ARTICLE

Low-dose ketamine as an adjunct to morphine: A randomized controlled trial among patients with and without current opioid use

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Abstract

Background: Pain is a common complaint among patients presenting to the emergency department (ED), yet pain treatment is frequently suboptimal. The aim of this study was to determine the effectiveness of low-dose ketamine (LDK) as an adjunct to morphine versus morphine alone for treatment of acute pain among ED patients with and without current opioid use.

Methods: Adult patients presenting with acute pain of ≥5 on a numeric rating scale (0–10) who were deemed by their treating ED physician to require intravenous opioids were randomized to receive either 0.1 mg/kg ketamine (treatment group) or isotonic saline (placebo) as an adjunct to morphine. Patients with and without current opioid use were randomized separately. Pain was measured at baseline (T0) and 10, 20, 30, 45, 60, and 120 min after randomization. The primary outcome was pain reduction from T0 to T10. Secondary outcomes included pain intensity over 120 min, need of rescue opioids, side effects, and patient and provider satisfaction.

Results: A total of 116 patients were included from May 2022 to August 2023. Median (IQR) age was 51 (36.5–67) years; 58% were male and 36% had current opioid use. Pain reduction from T0 to T10 was greater in the LDK group (4 [IQR 3–6]) compared to the placebo group (1 [IQR 0–2]; $p = 0.001$). Pain intensity was lower in the LDK group at T10, T20, and T30, compared to the placebo group. There was a higher risk of nausea, vomiting, and dissociation in the LDK group during the first 10 min.

Conclusions: LDK may be effective as an adjunct analgesic to morphine for short-term pain relief in treatment of acute pain in the ED for both patients with and without current opioid use.

KEYWORDS
analgesia, ketamine, morphine

EudraCT-number 2021-005116-64. Trial Registration: ClinicalTrials.gov Identifier NCT05422001.

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INTRODUCTION

Acute pain is one of the most common presentations in the emergency department (ED),[1] yet it often remains inadequately treated,[2] particularly among patients who receive opioids on a daily basis.[3,4] Effective pain management in patients with reduced responsiveness to opioid analgesics poses a significant challenge to ED physicians since opioid tolerance is associated with increased opioid requirements, risk of hyperalgesia, and withdrawal symptoms.[5] Thus, other pharmaceutical alternatives have been investigated, notably low-dose ketamine (LDK) as a stand-alone agent or adjunct to opioid analgesics.[6]

As an antagonist of the *N*-methyl-D-aspartate receptor, LDK has been hypothesized to provide synergistic and/or additive effects to opioids,[7,8] which could result in lower opioid requirements while effectively reducing pain, thus favoring a more acceptable side effect profile than ketamine or opioids as stand-alone agents. Relatively few studies have investigated LDK as an adjunct to morphine and there is considerable between-study heterogeneity among existing studies in terms of outcome, dosage, and routes of administration.[9] In addition, most existing studies have methodological limitations that make it difficult to assess the clinical effectiveness of LDK as an adjunct to morphine.[9] Furthermore, no studies have, to our knowledge, investigated LDK as an adjunct to morphine in patients with a current opioid use presenting in the ED with acute pain. However, some studies in pre- and postoperative settings have demonstrated positive results concerning pain reduction and reduced need for rescue opioids among opioid tolerant patients.[10–12]

In the context of the current opioid epidemic, there is a demand to explore adjuvant nonopioid treatments as alternatives to conventional opioid-centric approaches. Therefore, the objective of this study was to investigate the effect of LDK as an adjunct to morphine, compared to morphine alone, in patients with and without current opioid use. We hypothesized that LDK as an adjunct to morphine would result in greater pain relief pain control for up to 2 h following administration, increased patient and provider satisfaction with treatment and no increased risk of serious side effects in both patients with and without current opioid use.

METHODS

Trial design and approvals

This study was a single-center, investigator-initiated randomized, double-blind controlled trial. The study was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice (GCP), approved by the Danish Health and Medicines Agency (ID 2021100973), the Regional Ethics Committee (ID 1-10-72-334-21) and registered (May 27, 2022) at ClinicalTrial.gov (NCT05422001; EudraCT-number 2021-005116-64). All participants provided written informed consent following an initial consultation with the attending ED physician where morphine was indicated and prior to participation in the study.

Setting and patients

The study was carried out in the ED of Aarhus University Hospital from May 31, 2022, to August 15, 2023. Adult patients aged 18 years and older presenting with an acute pain condition with pain intensity of ≥5 on a numeric rating scale (NRS; 0-10) who were deemed by their treating ED physician to require intravenous (IV) opioids were eligible for inclusion in the study. Exclusion criteria included systolic blood pressure ≥ 180 mm Hg, severe untreated arrhythmia, unstable angina, recent myocardial infarction (<30 days), severe heart failure (EF < 40%), symptoms of untreated hyperthyroidism, cirrhosis with ascites, pregnancy or breastfeeding, previous enrollment in the trial, severe psychiatric illness prior to admission (psychosis, schizophrenia), untreated glaucoma, known hypersensitivity to ketamine, or prior negative experience with ketamine (i.e., hallucinations). Patients who were clearly influenced by drugs/alcohol, unable to provide informed consent, or underwent initial management by the trauma team were also excluded. In this study, current opioid use was defined as daily consumption of any type of opioid for a minimum of 7 days, with no specified minimum or maximum dose. Doses were confirmed in the electronic patient record (EPJ) and in the shared medication record (FMK), a nationwide register containing all individual medical prescriptions.

Study protocol and measures

Stratified randomization was used to separately allocate patients with and without current opioid use. The hospital pharmacy prepared the randomization lists and patients were assigned to a 1:1 ratio to either receive a single low dose of ketamine or receive saline with block sizes of 2, 4, or 6. The allocation key was kept concealed until unblinding of the study. The hospital pharmacy delivered the study medication in sealed blinded boxes, marked with the randomization number 101–190 (current opioid use) and 201–290 (no current opioid use). Each box contained either ketamine (esketamine 10 mL × 5 mg/mL, Orifarm) or isotonic saline (NaCl 10 mL × 9 mg/mL, Fres.Kabi). A nurse not otherwise involved in the study or treatment of the patient, prepared the study medication according to randomization, and was not blinded to the treatment allocation. The nurse prepared a syringe for each patient containing either ketamine (0.1 mg/kg bolus) or saline. The syringe was labeled with a unique identifier and given to the primary investigator (PI). Patients, health care providers, PI, data collectors, and outcome assessors were blinded to treatment allocation.

Patients without current opioid use received IV morphine 0.05–0.1 mg/kg according to previous studies and practice guidelines[9,10] and patients with current opioid use either received 15% of their daily dose of opioids or received a minimum of 0.05–0.1 mg/kg if 15% of their daily dose resulted in a dose lower than 0.05–0.1 mg/kg. This was followed by immediate administration of a single bolus dose of ketamine. After 10 min (T10), the use of rescue morphine was permitted with a minimum time interval of 10 min. The rescue dose and

route of administration were not standardized and were left to the discretion of the attending ED physician to ensure timely and adequate pain relief. Rescue morphine doses were converted into oral morphine equivalents.[11] Peripheral nerve blocks were also permitted for use as rescue analgesia after T10. Paracetamol and NSAIDs were also administered after T10 in alignment with standard of care.

The following patient characteristics were collected upon study enrolment: age, sex, body mass index, reason for admission, daily opioid dose (OME) and baseline vital parameters. Pain intensity (NRS 0–10) and sedation level (Ramsey sedation score [RASS] +4 to −5) were assessed at T0, T10, T20, T30, T45, T45, T60, and T120. Side effects were assessed at each time point beginning at T10. Vital parameters (blood pressure, pulse, and peripheral oxygen saturation) were measured at each time point. Provider and patient satisfaction (4-point Likert scale, 0–3 where 0 = "completely unsatisfied" and 3 = "very satisfied") were recorded at T120. The surveyed providers included the treating nurse or physician not involved in ordering or administering the study medication. The study period ended at T120. All data were collected by the PI and trained research staff in the ED. All data were entered directly in eCRF in REDcap.

Outcomes

The primary outcome was pain reduction from T0 to T10 measured by NRS. Secondary outcomes included pain intensity scores at T10, T20, T30, T45, T60, and T120; need for rescue opioids; adverse effects; and patient and provider satisfaction.

Sample size and statistical analysis

Sample size calculations were based on a clinically meaningful reduction in patient-reported pain intensity on an 11-point NRS.[12] Assuming a mean (±standard deviation [SD]) decrease of 2.5 (±2) points on the NRS in the treatment group[12] and an alpha value of 0.05, a study sample of 74 patients (37 in each treatment arm) would be required to detect a mean difference of 1.5 points on the NRS with 90% power for the primary outcome using a two-sample *t*-test (assuming that pain reduction is normally distributed). To account for possible dropout, we added an additional five patients, bringing the total sample size to 78 patients. To analyze treatment effects between patients with and without current opioid use, we assumed equal sized treatment groups would be required since there are no previous studies that have examined effects of LDK in this patient group. Therefore, we aimed to include 78 patients with current opioid use and 78 patients without current opioid use (156 total patients). Due to feasibility and resource constraints, including slow recruitment of patients with current opioid use, the study was terminated prematurely prior to achieving the desired sample size for stratified analysis.

Patient characteristics and outcome measures were reported as means with SDs, medians with interquartile ranges (IQRs), and percentages, as appropriate. Normality was assessed using Q-Q plots and Shapiro–Wilk test. The primary outcome (pain reduction from T0 to T10 in the two treatment groups) was analyzed using the Mann–Whitney *U*-test. Moods median test was performed to test for difference in NRS change at T10 between patients with and without current opioid use. Pain intensity scores at T10 through T120 were reported as medians with IQR and compared between groups at each time point using the Mann–Whitney *U* test. Categorical data (number of patients with Ramsay Sedation Scale > 2 and side effects) were reported as numbers (%) with 95% confidence intervals (CIs) and compared using the chi-square test. A sensitivity analysis was conducted removing all patients who received at least one rescue opioid dose or rescue block to examine whether treatment effects differed from the primary analysis. All *p*-values were two-sided and those below 0.05 considered significant. Data were analyzed before unblinding using an A and B list. All analyses were performed with STATA/SE version 17 (StataCorp LP).

RESULTS

During the trial period 900 patients were assessed for eligibility; of these 116 patients were included: 31 with current opioid use and 85 without current opioid use. The main reasons for exclusion were NRS < 5 or the ED physician deemed that opioid treatment was not necessary. All 116 patients received the study drug and completed follow-up (Figure 1). Baseline characteristics are presented in Table 1.

Primary outcome

Reduction of pain intensity from T0 to T10 was greater in patients who received LDK than in the placebo group; median (IQR) reduction was 4 (3–6) versus 1 (0–2) in the two groups, respectively. Patients with current opioid use ($n = 31$) had a mean reduction in NRS pain intensity of 5 (IQR 3–6) in the LDK group ($n = 15$) versus 1 (IQR 0–2) in the placebo group ($n = 16$). For patients without current opioid use, results were similar: 4.0 (IQR 3–6) in the LDK group versus 1.5 (IQR 0–3) in the placebo group. We found no significant difference in mean pain reduction between patients with current opioid use (median difference 4) and those without (median difference 2.5, $p = 0.8412$).

Secondary outcomes

Median [IQR] pain intensity was significantly lower in the LDK group than in the placebo group at T10 (3.5 [2–5] vs. 7 [5–8]; $p = 0.01$), T20 (4 [2–6] vs. 6 [4–7]; $p = 0.01$), and T30 (4 [2–6] vs. 5 [3–7]; $p = 0.03$). At T45, T60, and T120 no significant differences were observed between treatment groups (Figure 2). Thirty patients in each treatment group received rescue opioids; the LDK group received a total of 43

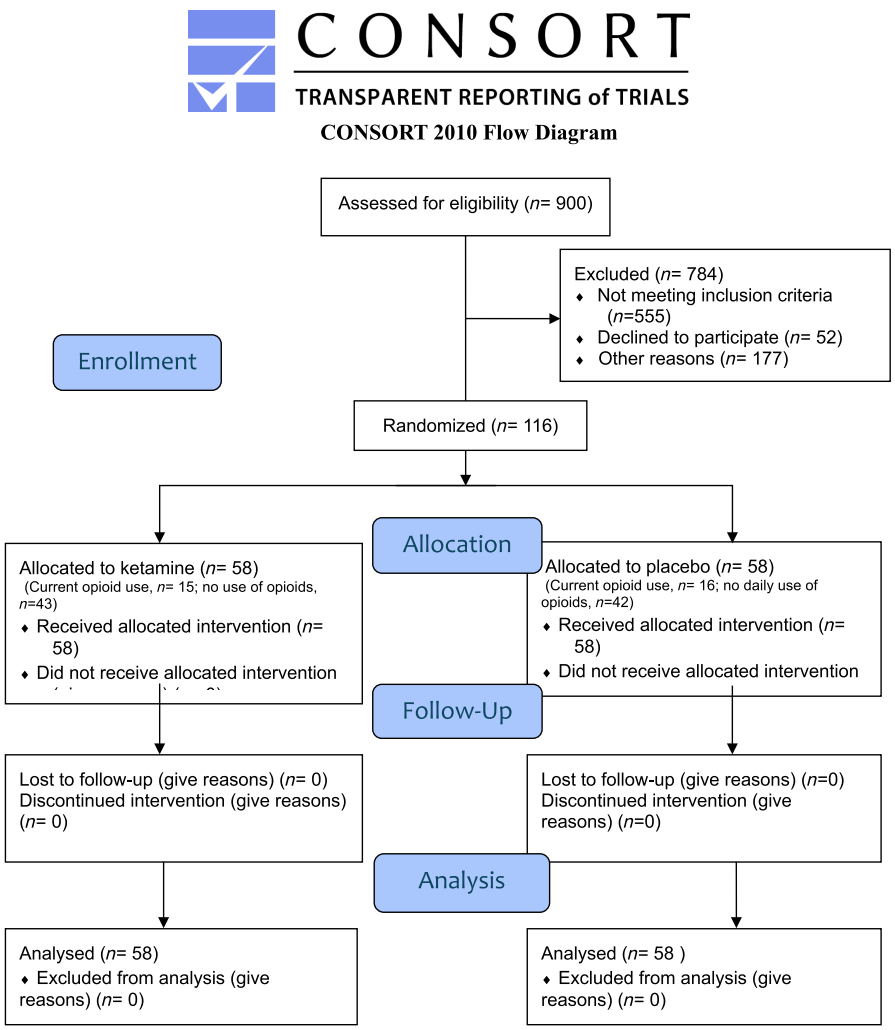

FIGURE 1 CONSORT 2010 flow diagram.

doses (total 573 mg OME), compared to 50 (total 716 mg OME) in the placebo group (Table 2).

Nausea, vomiting, and dissociation (dreamlike experiences, hallucinations, or out-of-body experiences) were more common in the LDK group overall (Table 2) and at T10, but no differences were observed between T20 and T120 (Table S1). Patient and provider satisfaction were similar in the two groups.

Sensitivity analysis on primary outcome

A sensitivity analysis was conducted on 54 patients ($n=14$ current opioid use, $n=40$ without current opioid use) after patients who received at least one rescue opioid dose or rescue block were removed. Results were similar to the primary analysis in both treatment groups among each stratum (Figure S1).

DISCUSSION

In this RCT of 116 adult patients with acute pain, we found 0.1 mg/kg ketamine as an adjunct to morphine was superior to morphine alone in achieving a clinically meaningful reduction in pain intensity scores for short-term (up to 30 min) pain relief. Reductions in pain intensity were similar in both patients with and without current opioid use.

Previous studies that investigated LDK as an adjunct to morphine in the ED have used ketamine doses between 0.1 and 0.3 mg/kg.[9] In the largest previous study by Hosseininejad et al.,[13] the authors investigated the effect of a 0.2 mg/kg adjuvant dose of ketamine among 200 patients presenting to the ED with renal colic pain. They found a small, but significant reduction in NRS pain intensity scores in favor of LDK. Beaudoin et al.[14] compared different doses of adjuvant LDK (0.15 and 0.3 mg/kg) and found a greater reduction in NRS pain intensity and need for rescue opioids in the 0.3 mg/kg group. Only two previous studies have used ketamine doses of 0.1 mg/kg.[15,16] In both studies, small significant decreases in pain intensity were found over 120-min study periods and fewer requests/lower cumulative doses for rescue analgesia were observed. However, Mohammadshahi et al.[16] used intranasal ketamine and in the study by Bowers et al.,[16] a provider determined dose of morphine or equivalent was administered up to 30 min prior to LDK administration.

We found significantly lower NRS pain intensity scores in the LDK group after 10, 20, and 30 min, compared to morphine alone.

TABLE 1 Patient characteristics and clinical data at inclusion.

	All included		Current opioid use		No current opioid use	
Patients ($n=116$)	**Placebo ($n=58$)**	**LDK($n=58$)**	**Placebo ($n=16$)**	**LDK ($n=15$)**	**Placebo ($n=42$)**	**LDK ($n=43$)**
Age (years)[a]	64 (38–73)	46.5 (32–57)	67 (47.5–76.5)	51 (34–61)	59.5 (37–70)	46 (30–57)
Sex, male	29 (50)	21 (36)	3 (18.8)	6 (40.0)	26 (61.9)	15 (34.8)
Reason for admission						
Abdominal pain	27 (46.4)	24 (41.4)	4 (25.0)	6 (40.0)	23 (54.7)	18 (41.9)
Extremity pain	16 (27.6)	10 (17.2)	6 (37.5)	1 (6.7)	10 (23.8)	9 (20.9)
Back pain	10 (17.2)	11 (18.9)	5 (31.3)	3 (20)	5 (11.9)	8 (18.6)
Renal pain/colic	0	8 (13.8)	0	2 (13.3)	0	6 (13.9)
Traumatic pain	4 (6.9)	4 (6.9)	1 (6.3)	2 (13.6)	3 (7.1)	2 (4.6)
Acute in chronic pain	0	1 (1.7)	0	1 (6.3)	0	0
Other	1 (1.7)	0	0	0	1 (2.4)	0
Weight (kg)	80.3 (±18.4)	78.2 (±16.7)	79.7 (±22.8)	77.1 (±18.5)	80.5 (±16.7)	78.7 (±16.2)
Blood pressure, systolic, T0	141 (±20)	142 (±20)	144 (±23)	139 (±17)	140 (±19)	144 (±22)
Blood pressure, diastolic, T0	86 (±15)	87 (±13)	83 (±13)	87 (±15)	87 (±16)	87 (±12)
Pulse T0	75 (63–85)	74 (64–89)	74 (66–83)	72 (62–87)	77 (63–85)	77 (64–90)
RASS score T0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Opioid 6 h pre inclusion (mg)	15 (10–30)	18.5 (10–30)	25 (12–36)	17 (10–29)	15 (10–20)	20 (10–30)
Respiratory frequency	17 (16–18)	18 (15–20)	17 (16–19)	18 (16–19)	17 (16–18)	18 (15–20)
NRS at inclusion, T0	8 (7–9)	8 (7–10)	9 (8–10)	8 (7–10)	8 (7–9)	8 (7–10)
Dose of study medication (mL)[b]	1.4 (±0.2)	1.4 (±0.2)	1.3 (±0.3)	1.3 (±0.2)	1.5 (±0.2)	1.4 (±0.2)
Dose of morphine, at inclusion (mg)	5 (5–7)	6 (5–7)	7 (5–10)	7 (7–10)	5 (5–6.5)	6 (5–7)
Daily dose of morphine (mg)	—	—	22.5 (13–117.5)	50 (30–60)	—	—

Note: Data are presented as median (IQR), *n* (%), or mean (±SD).

Abbreviations: LDK, low-dose ketamine; NRS, Numeric Rating Scale; RASS, Richmond Agitation Sedation Score.

[a]Significant difference ($p=0.002$).

[b]Esketamine 5 mg/mL.

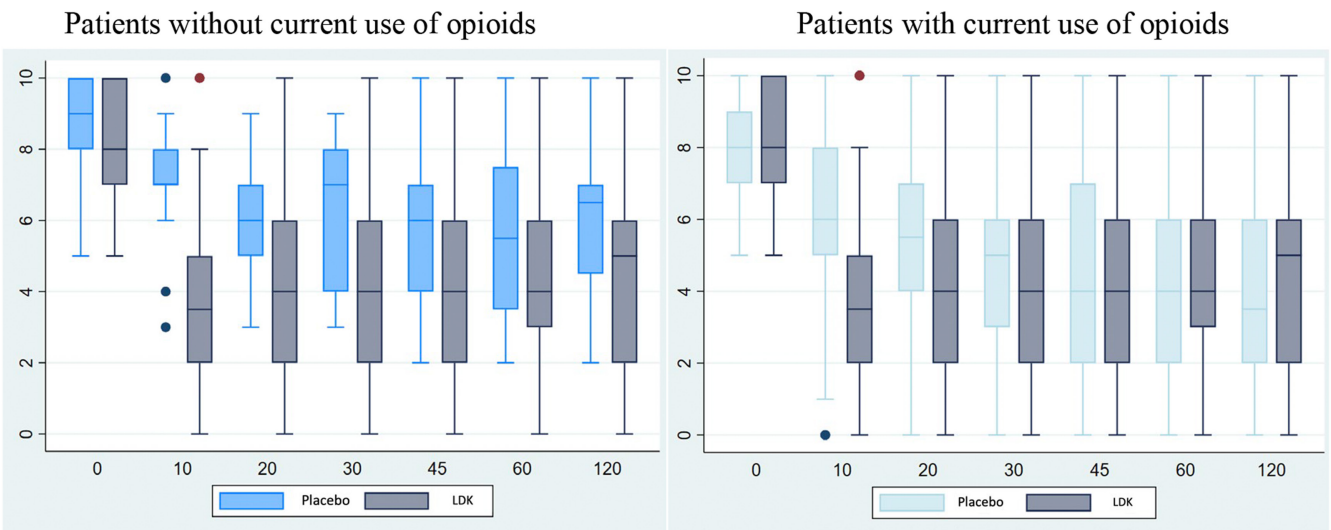

FIGURE 2 Pain intensity scores during the study period. The median is represented by the bold horizontal line within the box. The box defines the IQR. LDK, low-dose ketamine; NRS, Numeric Rating Scale.

This could support findings concerning the synergistic or additive effects of LDK when added to morphine.[7,8] To our knowledge, this is the first study to compare adjuvant LDK use in patients with and without current opioid use. Although previous studies have included patients with chronic pain and long-term and current opioid use,[9] it has not been determined whether treatment effects differ

TABLE 2 Rescue opioids, side effects, and patient and provider satisfaction during the study period.

	All included		Current opioid use		No current opioid use	
	Placebo ($n=58$)	LDK ($n=58$)	Placebo ($n=16$)	LDK ($n=15$)	Placebo ($n=42$)	LDK ($n=43$)
Rescue morphine						
T10	0	0	0	0	0	0
T20	8 (13.8)	5 (8.6)	2 (12.5)	0	6 (14.3)	5 (11.6)
95% CI	7.0–25.4	3.6–19.2	2.9–40		6.5–28.6	4.9–25.3
T30	9 (15.5)	6 (10.3)	3 (18.8)	1 (6.7)	6 (14.3)	5 (11.6)
95% CI	8.2–27.4	4.7–21.3	5.9–46.1	0.8–37.2	6.5–28.6	4.9–25.3
T45	7 (12.1)	10 (17.2)	4 (25)	1 (6.7)	3 (7.1)	9 (20.9)
95% CI	5.8–23.4	9.4–29.3	9.2–52.0	0.9–37.2	2.2–20.2	11.2–35.8
T60	7 (12.1)	6 (10.3)	0	2 (13.3)	7 (16.6)	4 (9.3)
95% CI	5.8–23.4	4.7–21.3		3.2–42.1	8.1–31.3	3.5–22.6
T120	19 (32.8)	16 (27.6)	7 (43.8)	2 (13.3)	12 (28.6)	14 (32.6)
95% CI	21.9–45.9	17.6–40.3	21.7–68.5	3.1–42.1	16.9–44.1	20.2–48.0
At least one rescue dose overall	30 (51.7)	30 (51.7)	10 (62.5)	6 (40.0)	20 (47.6)	24 (55.8)
95% CI	38.9–64.3	38.9–64.3	37.7–82.7	18.5–66.3	33.0–62.7	40.7–69.9
Total rescue dose (OME)	12.3 (±19.3)	9.8 (±13.7)	14.4 (±13.5)	5.9 (±9.0)	11.6 (±21.2)	11.1 (±14.9)
Rescue nerve block						
T10	0	0	0	0	0	0
95% CI						
T20	1 (1.7)	1 (1.7)	0	0	1 (2.4)	1 (2.3)
95% CI	0.2–11.4	0.2–11.4			0.32–15.4	0.3–15.1
T30	1 (1.7)	1 (1.7)	1 (6.3)	1 (6.7)	0	0
95% CI	0.2–11.4	0.2–11.4	0.8–37.1	0.8–37.1		
T45	0	0	0	0	0	0
95% CI						
T60	0	0	0	0	0	0
95% CI						
T120	0	1 (1.7)	0	0	0	1 (2.3)
95% CI		0.2–11.4				0.3–15.1
Overall	2 (3.4)	3 (5.2)	1 (6.3)	1 (6.7)	1 (2.4)	2 (4.6)
95% CI	0.9–12.9	1.7–15.0	0.8–37.1	0.8–37.1	0.32–15.4	1.1–17.1
Adverse events overall	27 (46.6)*	41 (70.7)*	6 (37.5)*	13 (86.7)*	21 (50.0)	28 (65.1)
95% CI	34.1–59.5	57.7–81.0	17.2–63.3	57.9–96.8	35.2–64.9	49.7–77.9
Nausea	21 (36.2)	20 (34.5)	4 (25.0)	5 (33.3)	17 (40.5)	15 (34.9)
95% CI	24.8–49.4	23.3–47.6	9.3–52.0	14.0–60.5	26.7–55.9	22.1–50.3
Vomiting	4 (6.9)	8 (13.8)	2 (12.5)	1 (6.7)	2 (4.8)*	7 (16.3)*
95% CI	2.6–17.1	7.0–25.4	3.0–40.1	0.9–37.2	1.2–17.4	7.9–30.7
Dissociation	4 (6.9)*	16 (27.6)*	0	5 (33.3)	4 (9.5)	11 (25.6)
95% CI	2.5–17.1	17.5–40.3		14.0–60.5	3.6–23.0	14.6–40.8
Dizziness	19 (32.8)*	30 (51.7)*	3 (18.8)*	10 (66.7)*	16 (38.1)	20 (46.5)
95% CI	21.9–45.9	38.9–64.3	5.9–46.1	39.5–85.9	24.6–53.7	32.1–61.5
Anxiety	2 (3.5)	2 (3.5)	0	1 (6.7)	2 (4.8)	1 (2.3)
95% CI	0.8–12.9	0.8–12.9		0.9–37.2	1.2–17.4	0.3–15.1
Patient satisfaction	4 (4–4)	4 (4–5)	4 (2–4)	4 (4–5)	5 (4–5)	5 (4–5)
Provider satisfaction	4 (3–4)	4 (4–4)	4 (2–4)	4 (4–4)	4 (4–5)	4 (4–5)

Note: Data are presented as *n* (%), mean (±SD), or median (IQR).

Abbreviations: LDK, low-dose ketamine; OME, oral morphine equivalents.

*Significant difference, $p<0.05$.

within this patient population. Ketamine has been hypothesized to counteract opioid tolerance and NMDA receptor–mediated central sensitization.[17] Both American[18] and European[19] guidelines recommend LDK could be used in the ED for opioid tolerant patients presenting with acute pain. However, these recommendations are based on perioperative studies[20,21] on spine surgery patients that may not be comparable to the ED setting. In our study, we did not find a difference in treatment effects between patients with and without current opioid use. The lack of difference between these groups could indicate that positive findings from perioperative studies may not generalize to ED settings. It could also be that our sample was more heterogeneous compared to perioperative studies based on specific spine surgeries. Another explanation could be that our study was underpowered to identify a significant difference in treatment effect between these groups.

Consideration should be given to possible side effects of adjuvant LDK to morphine in the ED. As in previous studies, we found a higher proportion of minor side effects in the LDK group. However, this proportion was only higher in the LDK group within the first 10 min after study drug administration. Two retrospective studies[22,23] explored patient-reported side effects following LDK administration and found 21.5%–29.2% of patients experienced psychomimetic side effects. In our study, we found 27.5% of patients in the LDK group experienced dissociation, compared to 6.9% in the placebo group. Although the risk of psychomimetic effects may be greater among patients who receive LDK, these side effects still occur among patients who receive opioids alone. We found no difference in patient satisfaction between LDK and placebo groups, and there were no complaints made by patients related to psychomimetic side effects, thus suggesting that this side effect profile was acceptable.

LIMITATIONS

Some limitations of the present study must be considered. First, due to the unexpectedly slow inclusion rate, we were unable to achieve the anticipated sample size of 156 patients. The study was terminated early for practical reasons without interim analysis. Therefore, our study may have been underpowered to detect differences in our stratified analysis comparing treatment effects in patients with and without current opioid use. While the smaller sample size of patients with current opioid use increases the risk of false-negative outcomes, our findings revealed a significant difference in pain reduction between the LDK and placebo groups within this patient population. Second, the primary outcome of 10 min postadministration was selected based on its alignment with the time frame important for patients to experience pain relief. While acknowledging this time point might be premature for the peak effect of morphine, opting for a later time point would compromise capturing the peak effect of ketamine. Third, various types of painful conditions were included, which increases the generalizability of the results. However, this likely resulted in heterogeneity of treatment effects between patients presenting with different painful conditions. Finally, NRS was used to assess pain intensity as the primary outcome, although other measures such as analgesic requirements or patient satisfaction could have been selected. Among the three validated pain scales (Visual Analog Scale, Visual Rating Scale, and NRS) for use in clinical practice, the NRS is valid, has good sensitivity, and can be easily analyzed.[24]

Despite these limitations, we believe that the results of this study will contribute to the improvement of pain treatment for ED patients presenting with acute pain. The balance between effectiveness and side effects should be carefully considered as LDK should not be recommended for all patients experiencing moderate to severe pain.[14] Instead, LDK should be particularly considered in cases where traditional opioid treatments prove ineffective or in patients where pain management is expected to be complex (i.e., opioid-tolerant patients).

CONCLUSIONS

Our study demonstrates that a single dose of 0.1 mg/kg low-dose ketamine is effective as an adjunct analgesic to morphine for the treatment of acute pain in the ED for patients both with and without current opioid use. Future research should focus on optimizing low-dose administration through bolus/continuous administrations to achieve longer lasting pain reductions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS APPROVAL

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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