Original Article

Low-dose ketamine as an analgesic agent in the emergency department: Efficacy and safety

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Abstract

Introduction: Interest in using low-dose ketamine (LDK) as an alternative analgesic to manage acute pain in the emergency department (ED) has increased. The aim of this systematic review was to compare and evaluate the analgesic effect and safety of LDK for the management of acute pain in the ED. **Method:** Databases were searched and all published articles that met the inclusion criteria were used. Electronic research was conducted on a total of 85 articles, and 13 articles that were relevant in terms of content, topic, and aim were selected for further review. The studies were analyzed and categorized after review. **Results:** The results demonstrated that in 53.84% (7 of 13) of articles, a significant reduction or more than 50% reduction in pain in the group of patients treated with ketamine (alone or combined with other analgesics) was reported. However, in 46.15% (6 out of 13) of the reviewed articles, no significant difference was observed between the pain reduction in the groups treated with ketamine alone and ketamine with other analgesics. The highest decrease in numerical rating scale (NRS) score was 6 and the lowest was 1. There was also a 100% reduction in NRS score in 14 of 30 patients treated with 0.15 mg/kg ketamine and 0.5 mg/kg hydromorphone. **Conclusion:** According to the results of the present study, the use of LDK as an analgesic with low side effects can be suggested. However, further research is needed to determine the appropriate concentration with fewer side effects.

Keywords: Analgesic agent, efficacy, emergency department, ketamine, safety low-dose ketamine

Introduction

Ketamine was first synthesized in the early 1960s as a safer alternative to phencyclidine.[1] The anesthetic properties of ketamine were identified in 1965 and its clinical use was approved by the US Food and Drug Administration (FDA) in 1970.[2] With the introduction of newer anesthetics with more limited side effects, this drug that was derived from phencyclidine and cyclohexylamine rapidly lost its popularity.[3,4] However, ketamine has a unique ability to induce catalepsy, and while providing analgesia, sedation, and forgetfulness at the same time, it can also maintain airway reflexes and hemodynamic stability.[4] Ketamine, which is used intramuscularly, intravenously, intranasally, and rectally,[5] is an anesthetic drug that also causes severe analgesia, stimulates the sympathetic nervous system, and increases blood pressure and heart rate[6]: It also increases breathing rate and can dilate the bronchi.[7] Ketamine acts as an N-methyl-D-aspartate (NMDA) receptor antagonist and binds to opioid receptors and sigma receptors.[7] NMDA receptors play an essential role in pain perception; in various studies on NMDA receptors, it has been shown that the blockers of this receptor stimulate opioid receptors and enhance opioid effects.[8] Ketamine also increases the opioid effects in C-fiber synapses and subsequently causes analgesia even in opioid-tolerant patients.[9] Pain management is a fundamental and challenging component in the field of emergency medicine. There is a constant search to find an ideal agent that acts quickly and provides pain relief with minimal side effects.[4]

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However, there is limited evidence on the clinical use of low-dose ketamine (LDK) in the emergency department (ED), and most emergency physicians are unfamiliar with its use in low doses.[9] Therefore, the present systematic review aimed to evaluate the efficacy and safety of the use of LDK as an analgesic agent in the ED.

Materials and Methods

The present study systematically investigated the efficacy and safety of the use of LDK as an analgesic agent in the ED. A comprehensive search of the databases of PubMed/MEDLINE, EMBASE, CINAHL, and AMED was performed. In the present systematic clinical review, various types of studies were assessed including open pilot trials, case reports, case series, retrospective, quasi-experimental trials, randomized clinical trials, and split-face comparative studies.

Inclusion criteria were articles that used LDK (any dosage), articles that compared ketamine to any other analgesic agent, articles published between 2000 and 2020, and articles that were written in English. Exclusion criteria included articles not written in English, articles in which ketamine was used as procedural sedation, articles in which ketamine was used in a ward other than the ED (inpatients, prehospital, and emergency services), and articles in which ketamine was used for purposes other than analgesia. Also, data related to review studies and non-original articles were not extracted.

To collect information in this field, in terms of content, keywords of LDK, analgesic agent, ED, efficacy, and safety were searched in the desired databases. The articles were evaluated in terms of different aspects of methodology including sampling methods, reliability of the tools used, and the objectives of the study; finally, a set of articles that were appropriate in terms of subject coverage and content structure was included in the study. An electronic search was conducted on a total of 85 articles, and 13 articles that were relevant in terms of content, topic, and aim were selected for further review.

Results

In the present study, a total of 13 articles were reviewed; of these, 6 articles were randomized, double-blind (46.15%), one article was a randomized, double-blind, placebo-controlled trial (7.69%), one was a prospective, nonrandomized, nonblinded observational study (7.69%), one was a prospective randomized, double-dummy trial (7.69%), one was a randomized controlled trial (7.69%), one was a randomized placebo-controlled trial (7.69%), one was a prospective, randomized, double-blind trial (7.69%), and one was a single-center, randomized, prospective, parallel clinical trial (7.69%). A summary of the results of the reviewed articles is given in Table 1.

In the reviewed articles, a total of 1,195 patients were treated with ketamine to reduce pain in the ED, of which 744 were male and 336 were female. One article did not report the number of male and female patients. The mean age of these patients was 36.14 years. The patients are referred to the ED with pain such as acute abdominal, lateral or lumbar pain, renal colic, and acute migraine. According to the results of the present study [Table 1], the minimum amount of ketamine used was 0.1 mg/kg and the maximum amount was 0.15 mg/kg. In nine articles (69.23%) ketamine was evaluated in comparison with other analgesic drugs such as morphine, propofol, midazolam, fentanyl, and hydromorphone, and in four other articles (30.76%) the effect of ketamine alone was evaluated in comparison with placebo or it was used with other analgesic drugs. The results demonstrated that in 53.84% (7 of 13) of articles, a significant reduction of more than 50% reduction in pain in the group of patients treated with ketamine (alone or combined with other analgesics) was reported. However, in 46.15% (6 out of 13) of the reviewed articles, no significant difference was observed between the pain reduction in the groups treated with ketamine alone and ketamine with other analgesics. The highest decrease in numerical rating scale (NRS) score was 6 and the lowest was 1. There was also a 100% reduction in NRS score in 14 of 30 patients treated with 0.15 mg/kg ketamine and 0.5 mg/kg hydromorphone. However, an 88.89% reduction in pain was reported in the group of patients treated with ketamine. Although side effects were reported in 100% of the articles, none of them reported persistent or severe side effects. The most commonly reported side effects were dizziness, blurred vision, nausea, and vomiting. A comparison of the side effects demonstrated that in four articles (30.76%), the side effects of the groups treated with ketamine were lower, and in four articles, the side effects in this treatment group were higher compared to those in patients treated with other analgesics.

In the study of severe complications (hypotension, severe hypersensitivity reaction, decreased arterial oxygen saturation, cardiac arrhythmia, and seizures) in the methods used [Table 2], the results showed that in six of the reviewed articles, severe complications either did not exist or were not reported. In other articles, increased systolic blood pressure (15.38%, in 2 of 13), decreased blood pressure (30.76%, in 4 of 13), hypoxia (7.69%, 1 of 13), transient respiratory depression (15.38%, in 2 of 13), and sinus tachycardia (7.69%, 1 of 13) were reported. Observed complications included hypertension in patients treated with ketamine, hypotension in patients treated with ketamine and morphine, hypoxia in patients treated with ketamine and morphine, transient respiratory depression in the standard care group, and patients treated with morphine, and sinus tachycardia in patients treated with ketamine and morphine. Also, based on the data extracted from the table, a comparison of the duration of analgesia after drug administration showed that the lowest duration of analgesia was 5 min (hydromorphone and ketamine were used together) and the maximum was 240 min (which was observed in both morphine and ketamine groups). The mean duration of analgesia for ketamine was 62.54 min.

Table 1: Summary of reviewed articles

Author(s), year, type of study	Title	Number, age, and dosage	Results and conclusion
Cevik *et al*., 2013[10] A double-blind randomized trial	Comparison of low-dose ketamine with midazolam-fentanyl for orthopedic emergencies: a double-blind randomized trial	Sixty-one patients with a mean age of 28 years (between 4 and 75 years, 18 female and 43 male) were divided into two groups: KM (*n*=31) and MF (*n*=30). These patients had large joint dislocations or fractures. MF group: received midazolam 0.1 mg/kg, maximum 5 mg in 10 ml saline, and fentanyl 12 μg/kg in 10 mL of saline. KM group: ketamine 2 mg/kg in 10 mL of saline, midazolam 0.02 mg/kg in 10 mL of saline. Hypoxia, duration of hypoxia, need for oxygen, time to start sedation, recovery time, pain scores, and depth of sedation were determined as initial measures. VAS system was used.	Hypoxia and duration of hypoxia were significantly lower in the ketamine-low-dose midazolam (KM) group (45.2%) compared to the midazolam-fentanyl (MF) group (76.7%). Patients in the KM group demonstrated a significant reduction (88.89%) in the amount of pain. Also, side effects were higher in the MF group and 16 patients (48.38%) had side effects, while 2 patients in the KM group had side effects. Reported complications included nausea and vomiting, dizziness, and recovery agitation.
Ahern *et al*., 2013[9] a prospective, nonrandomized, nonblinded observational study	Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain	30 patients with severe pain with a mean age of 44.33 years (15 females and 15 males). 0/5 mg intravenous (IV) hydromorphone and 15 mg ketamine IV followed by optional 1 mg hydromorphone IV at 15 and 30 min. Pain intensity was assessed using the 10-point verbal numerical rating scale (NRS) in 12 intervals of more than 120 min. Patients were monitored for side effects.	Out of 30 patients with severe pain (with a mean initial NRS of 9), 14 had complete pain relief (NRS, 0), i.e., a 100% reduction in 5 min. The mean reduction in NRS pain score was 6.0 (33.34% reduction). At 15 min, the mean reduction in NRS pain score was 5. Most patients (80%) had only mild to moderate side effects (fatigue, headache, dizziness). Low-dose ketamine combined with a reduced dosage of hydromorphone rapidly and profoundly relieves pain in a diverse group of patients with acute pain without significant side effects.
Beaudoin *et al*., 2014[11] A randomized, double-blind, clinical trial	Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: results of a randomized, double-blind, clinical trial	60 patients with moderate to severe acute pain (aged between 18 and 65 years, 37 men and 23 women) were divided into 3 groups: Standard care group: morphine and 9% placebo saline Group 1: morphine and 0.15 mg/kg ketamine Group 2: morphine and 0.3 mg/kg ketamine In all three groups, patients first received 0.1 mg/kg to 10 mg of morphine intravenously, followed by administration of the drug (placebo or ketamine). Ten minutes were set between the morphine dose and the drug to monitor adverse reactions. The pain was not assessed during this time. The main assessment for the outcome of pain relief or reduction of pain intensity was performed using NRS. The incidence of side effects was also assessed.	During the 2-hour post-study period, the summed pain intensity (SPID) was higher for the ketamine groups than for the control group (higher pain relief). SPID was similar for the ketamine-treated groups. When compared to standard care, group 2 maintained pain relief for up to 2 h, whereas group 1 was similar to standard care for 2 h. SPID percentage was 21% for the standard care group, 39% for group 1, and 42% for group 2. There was no significant difference in terms of SPID between group 1 and group 2. More participants (45%) in the low-dose ketamine groups had dizziness.
Motov *et al*., 2015[12] prospective, randomized, double-blind trial	Intravenous sub dissociative--dose ketamine versus morphine for analgesia in the emergency department: A Randomized Controlled Trial	90 patients (58 females and 32 males) aged 18 to 55 years with acute abdominal, flank, skeletal or muscular pain The patients were randomly divided into two groups: one group received 0.3 mg/kg ketamine and the other group received 0.1 mg/kg morphine in 3 to 5 minutes. Assessments were performed at 15, 30, 60, 90, and 120 min.	There was no significant difference in the mean initial pain scores of the ketamine and morphine groups: 8.6 vs. 8.5 at baseline, and 4.1 vs. 3.9 at 30 min. There was no significant difference in the incidence of rescue fentanyl analgesia in 30 or 60 min. No serious side effects occurred in either group. Patients in the ketamine group experienced minor side effects (dizziness and nausea) within 15 min of taking the drug.
Bowers *et al*., 2015[13] a randomized, double-blinded, placebo-controlled	Ketamine as an adjunct to opioids for acute pain in the emergency department:	116 patients with a mean age of 42.46 years (65 males and 51 females) were divided into two treatment groups: The ketamine group	Patients taking ketamine experienced less pain within 120 min compared to patients receiving a placebo. The total opioid dosage was lower in the ketamine group (9.95 mg) compared with the placebo group.

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Table 1: Contd...

Author(s), year, type of study	Title	Number, age, and dosage	Results and conclusion
trial	a randomized controlled trial	received 0.1 mg/kg ketamine in 1 min, and the control group (63 patients) received an equivalent amount of normal saline. At 30-min intervals, individuals were asked about their pain level and whether they needed more pain control; also, side effects were evaluated. sedation score, which was determined by a Ramsay scale, was greater than 218. At the patient's request, repeated doses of 0.05 mg/kg morphine or equivalent doses of opioid analgesic were prescribed. The total dosage of opioid analgesic and the number of repeated doses given at the end of 120 min were recorded. At each time interval, as well as at the end of 120 min (T120), patient satisfaction on the pain control was recorded using the 4-point Likert scale, with 0 indicating "completely not satisfied" and 3 indicating" very satisfied."	Satisfaction did not differ between groups. Twelve patients in the placebo group (19%) and 27 patients in the ketamine group (51%) had side effects. Reported complications included lightheadedness and dizziness. Ketamine, as an adjunct to opioid therapy, was effective in reducing pain in more than 120 min and resulted in a reduction in the total opioid dose as well as doses of analgesics. More side effects were reported in the ketamine group (51% vs. 19%), but the side effects were tolerable.
Miller *et al*., 2015[14] A randomized controlled trial	Low-dose ketamine vs. morphine for acute pain in the ED: a randomized controlled trial	45 patients aged 18 to 59 years (23 males and 22 females) with acute abdominal, lateral, or low back pain were included in the study. Low-dose ketamine (LDK) (0.3 mg/kg) or morphine (0.1 mg/kg) were randomly injected intravenously for 5 min. The second dose was given 20 min after the initial dose and the same amount as the first dose.	ketamine was not superior to morphine in terms of the maximum change in NRS pain scores (for low-dose ketamine it was 4.9 and for morphine, it was 5). The time to achieve the maximum reduction in NRS pain score was 5 minutes for low-dose ketamine and 100 minutes for morphine. Side effects were observed in 44.44% of patients (12 in the LDK group and 8 in the morphine group). Reported complications included nausea, dizziness, dysphoria, and hallucinations. Low-dose ketamine did not cause a higher reduction in NRS pain scores compared to morphine for acute emergency pain. However, the LDK produced a significant analgesic effect within 5 minutes, reducing the average pain for 2 h.
Shimonovich *et al*., 2016[15] Single-center, randomized, prospective, parallel clinical trial	Intranasal ketamine for acute traumatic pain in the Emergency Department: a prospective, randomized clinical trial of efficacy and safety	90 patients (51 men and 24 women) 18 to 70 years old with mild to moderate pain The patients were randomly divided into three groups: one group received 0.1 mg/kg IN Ketamine, one group received 0.1 mg/kg morphine (IV MO), and the other group received 0.15 mg/kg morphine (IM MO). Pain relief and side effects were recorded for 1 h after administration.	The maximum reduction in pain was 56 mm for the ketamine IN group, 59 mm for the IV MO group, and 48 mm for the IM MO group. the ketamine IN group demonstrated clinical results that were comparable with the results of the IV MO group in terms of onset time (14.3 vs. 8.9 minutes,) and pain relief (maximum 40.4 vs. 33.54). Reported side effects included concentration difficulties (58.3% in the ketamine IN group, 20.8% in the IV MO group, and 22.2% in the IM MO group), dizziness (79.2%, 50%, and 22.2%, respectively), and dry mouth (25%, 79.2%, and 63%, respectively).
Abbasi *et al*., 2017[8] A double-blind randomized clinical trial	Can low-dose of ketamine reduce the need for morphine in renal colic? A double-blind randomized clinical trial	106 patients aged 18 to 65 years (71 males and 35 females) with renal colic were randomly divided into two groups: The MP group received a standard dose (0.1 mg/kg) of morphine plus placebo (normal saline). The MK group received the standard dose of morphine with ketamine. Ketamine was prepared in a 5 cm^3 syringe with a concentration of 10 mg/mL and 0.15 mg/kg and then administered.	There was no significant difference in the mean pain scores of the patients in the two groups, which were recorded at 0, 60, 90 and 120 minutes. At 10 and 30 minutes after starting the drug, the mean pain was lower in the MK group, and in the MP group, the morphine injection time was longer at 10 and 30 min after starting the drug. In fact, the morphine dosage was used 12 times for the MK group, while the second dose of morphine was used 28 times for the MP group, which was significantly lower in the MK group.

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Author(s), year, type of study	Title	Number, age, and dosage	Results and conclusion
		For all patients, ketamine was injected intravenously while morphine injection was continued until the pain score reached 3 or less on the VAS scale or the injection stopped at 120 min or 30 mg of morphine. The Visual Analog Scale (VAS) was used to measure pain ranging from 0 to 10. A score of zero indicated no pain, and a score of 10 indicated the worst pain	Side effects such as nausea, vomiting, dyspnea, and hypotension were significantly higher in patients of the MP group, while nystagmus was more common in patients of the MK group.
Motov *et al*., 2017[16] A prospective randomized, double-dummy trial	A prospective randomized, double-dummy trial comparing intravenous push dose of low dose ketamine to short infusion of low dose ketamine for the treatment of moderate to severe pain in the emergency department	48 patients aged 18 to 65 years (27 females and 21 males) with abdominal and back pain were admitted to IVP and SI treatment groups. IVP group: Participants received intravenous LDK (low dose ketamine) at a dose of 0.3 mg/kg with IVP for more than 5 min. SI group: Participants received intravenous LDK (low-dose ketamine) at a dose of 0.3 mg/kg mixed with 100 mL of normal saline solution through SI for more than 15 min. Scores related to pain, vital signs, and side effects were assessed at the onset, 5, 15, 30, 60, 90, and 120 min. The overall rate, as well as the severity of adverse events, was recorded based on the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA6).	The mean scores of initial NRS pain in the two groups were 8 and there was no significant difference between them. In the IVP group the overall rate of derealization was higher based on the SERSDA scale, 92% vs. 54%. At 5 min, the severity of derealization was 3 for IVP versus 0 for SI. IVP also showed more sedation on the RASS scale in 5 min: 2 vs. 0. The decrease in mean pain scores from the onset to 15 minutes was similar in the two groups: 5.2±3.53 for IVP and 5.75±3.48 for SI. The most reported side effects were derealization (91.7% in IVP and 54.2% in SI), dizziness (66.7% in IVP and 75% in SI), and vision problems (25% in IVP and 37.5% in SI). SI) were. Low-dose ketamine, given as a short injection (SI), is associated with significantly lower levels of derealization and sedative sensations and has no difference with intravenous pressure in terms of analgesic effect.
Clattenburg *et al*., 2018[17] A double-blind, double-dummy, randomized controlled trial	Slow infusion of low-dose ketamine reduces bothersome side effects compared to IV push: a double-blind, double-dummy, randomized controlled trial	59 patients with moderate to severe pain They were divided into two groups One group received 0.3 mg/kg ketamine as SI or IVP and the other group received 0.3 mg/kg placebo.	No significant difference in analgesic effect was found between the two groups. At 60 min, the mean percentage of SPID in the IVP and SI-treated patients was 39.9% and 33.5% (with a difference of 6.5%), respectively. 86.2% of the IVP-treated patients and 70% of the SI-treated patients experienced side effects. 75.9% of patients treated with IVP had moderate or severe side effects versus 43.4% in the SI patients. The IVP patients experienced more hallucinations than the SI patients.
Mahshidfar *et al*., 2017[18] randomized double-blinded clinical trial	Acute pain management in the emergency department, low dose Ketamine vs. morphine, a randomized clinical trial	300 patients (249 men and 51 women) with a mean age of 34.25 years. They were divided into two groups The first group received 0.2 mg/kg ketamine, whereas the second group received 0.1 mg/kg intravenous morphine. Pain intensity and complications were measured and compared every 15 min to 1 h.	Fifteen min after drug injection in both groups, a significant reduction in pain intensity was observed compared to the initial pain. At 15 min, there was no significant difference in pain intensity between the two groups. The mean pain intensity at 30, 45, and 60 min was lower in the morphine group than in the ketamine group. The two complications (hypoxia and hot flashes) were significantly higher in the morphine group. The results of this study show that the use of LDK, in the first minutes, leads to a significant reduction in pain compared to intravenous morphine. It also has fewer side effects than morphine
Jahanian *et al*., 2018[5] Randomized, controlled,	Efficacy and safety of morphine and low-dose ketamine for pain control of	156 patients with a mean age of 35.87 years (111 males and 4 females) Patients were randomly assigned to receive either intravenous morphine (0.1 mg/kg) or	Pain intensity decreased significantly in both groups, 240 min after the intervention. However, there was no significant difference between the two study groups in terms of pain intensity at all times.

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Table 1: Contd...

Author(s), year, type of study	Title	Number, age, and dosage	Results and conclusion
double-blinded, clinical trial	patients with long bone fractures: a randomized, double-blind, clinical trial	low-dose ketamine (0.5 mg/kg). Pain intensity was assessed by the nurse using the visual analog scale (VAS) at 30, 60, 90, 12, 180, and 240 min after the intervention.	Side effects included nausea and vomiting (15.4% in the morphine group and 11.5% in the ketamine group) and drowsiness (6.4% in the morphine group and 3.8% in the ketamine group). However, low-dose ketamine was associated with a greater need for rescue analgesics.
Etchison *et al.*, 2018[19] A randomized placebo-controlled trial	Low-dose ketamine does not improve migraine in the emergency department: a randomized placebo-controlled trial	34 patients (26 men and 8 women) aged between 18 and 65 years with acute migraine Patients were divided into two groups One group (16 patients) received 0.2 mg/kg ketamine and the other group (18 patients) received 0.2 mg/kg placebo (normal saline).	There was no statistically significant difference in terms of the reduction of NRS score between the ketamine group and the placebo group after 30 min. The mean NRS score at 30 minutes was 1 for the ketamine group and 2 for the placebo group. There were no significant differences between treatment groups in terms of pain scores, functional disability scores, need for rescue drugs, and treatment satisfaction. Reported side effects, including blurred vision (36.4%), confusion (24.7%), and hallucinations (20.8%), were not serious in this study.

Table 2: Comparison of the incidence of severe complications and the duration of analgesia after drug administration

Reviewed articles	Incidence of severe complication	Duration of analgesia after drug administration
Cevik *et al*, 2013 [10]	Hypoxia was observed in 14 patients in the KM group and 23 patients in the MF group An increase in systolic blood pressure was observed in the KM group at 5, 10, and 30 min, and a decrease was observed in the MF group	Not reported
Ahern *et al*, 2013 [9]	Absence of significant cardiopulmonary side effects such as tachycardia, dysrhythmia, hypertension, or hypoxia	Persistence of analgesia up to 5 min
Beaudoin *et al*, 2014[11]	Observation of hypotension in one patient in standard care group after rescue analgesic dose, as well as transient respiratory depression (oxygen saturation<92%) after rescue analgesic dose in another patient Incidence of sinus tachycardia (heart rate >100 beats per min) in three patients in group 2 after administration of the studied drug (elimination of this problem within 30 min) Absence of behavioral disorders or dysrhythmias during the study period	Less than 2 h in the standard care group compared to group 1 and group 2
Motov *et al*, 2015 [12]	Absence of complications such as respiratory distress, seizures, and cardiac arrest	Up to 120 min in both groups
Bowers *et al*, 2015 [13]	Severe complications were not reported	Persistence of analgesia up to 30 min
Miller *et al*, 2015 [14]	No difference in diastolic blood pressure, heart rate, respiration rate, or oxygen saturation in all groups transient oxygen desaturation in one patient in the morphine group (elimination of this problem within 5 min using the nasal cannula at a rate of 4 liters per minute)	Only 5 to 10 min in the low-dose ketamine group, and up to 100 min after injection in the morphine group
Shimonovich *et al*, 2016[15]	Presence of higher increase and lower decrease in systolic and diastolic blood pressure in ketamine-treated patients compared with both morphine groups.	Persistence of analgesia up to 40.4 min for ketamine group, 33.4 min for morphine IV, and 46.7 min for morphine IM group
Abbasi *et al*, 2017 [8]	Hypotension was observed in 3 patients in the MP group	Up to 120 min in both groups
Motov *et al*, 2017 [16]	Severe complications were not reported	Up to 15 min
Clattenburg *et al*, 2018[17]	Severe complications were not reported	Up to 60 min in both groups
Mahshidfar *et al*, 2017[18]	Severe complications were not reported	Up to 15 min in the ketamine group and 60 min in the morphine group
Jahanian *et al*, 2018[5]	Severe complications were not reported	Up to 240 min in both groups
Etchison *et al*, 2018[19]	Severe complications were not reported	Up to 30 min in both groups

Discussion

For decades, emergency physicians have welcomed sedatives and analgesics as a common component of care. However, the safety and effectiveness of these sedatives are still questionable.[20] In contrast, ketamine is being considered in the ED as a complementary and alternative to opioid analgesics for the management of a variety of acute and chronic painful conditions.[12] IV doses of 1 to 4 mg/kg cause dissociative anesthesia, whereas doses less than 0.3 mg/kg cause analgesia

with dissociative effects.[9] Today, it has been proven that the high incidence of unpleasant side effects associated with ketamine administration is a significant obstacle to the widespread and tolerable use of this analgesic method.[12]

The aim of this study was to evaluate the use of LDK as an analgesic agent in the ED and the results showed that in 46.66% of articles, a significant reduction or more than 50% reduction in pain in the group of patients treated with ketamine (alone or combined with other analgesics) was reported. However, in 26.66% of the articles (4 out of 15), there was no significant difference in terms of pain reduction in the groups treated with ketamine alone or ketamine with other drugs. Also, in a systematic study by Balzer *et al*.,[21] the results showed that there was no significant difference between LDK and morphine-treated groups in terms of the mean pain scores reported in the first 60 min after administration; however, a slight difference in pain scores in 60 to 120 min was observed, and the use of morphine was more efficient.

In the study by Abbasi *et al*.,[8] it was found that the combination of morphine with low doses of ketamine significantly reduced morphine intake compared with the administration of morphine singly to control and reduce pain in patients with renal colic. In this study, this combination was studied in patients with renal colic pain, which is one of the main causes of referral to ED, and it was found that during the first 30 min after treatment, the pain was significantly reduced in the Morphine-Ketamine (MK) group, and the use of morphine also considerably reduced the pain in this period. The study also showed that 30 min after the end of the study, there was no significant difference between the two groups in terms of pain control. Although morphine is used to control severe pain in patients with renal colic, it still has disadvantages, the most important of which are hypertension and respiratory depression. In the present study, it was also found that in two of the reviewed articles, more side effects were observed in the group treated with morphine. However, Beaudoin *et al*.[11] reported that LDK is a viable alternative to morphine only for the control of moderate to severe acute pain in ED and that at least half of patients in each ketamine group experienced a clinically significant reduction in pain intensity. They also reported that the use of 0.15 to 0.3 mg/kg ketamine in adult patients reduced postoperative nausea and vomiting and that other side effects were mild in comparison with the use of morphine.

Ahern *et al*.[9] prospectively administered 15 mg of intravenous ketamine to patients, which was immediately followed by a continuous injection of 20 mg per h for 1 h in 38 patients with acute pain. At 10 min, 7 patients had no pain, and 25 and 26 patients had significant pain relief at 60 and 120 min, respectively. However, 87% of patients experienced side effects of nausea, fatigue, headache, and derealization. These researchers reported that low doses of ketamine combined with hydromorphone could relieve pain quickly and deeply and are well tolerated in patients. Thus, LDK can play a promising role in pain management in ED. Based on the results of the present study, four of the reviewed articles (26.66%) showed fewer side effects in the groups treated with ketamine, and in four articles the side effects in this treatment group were higher than in other analgesics. However, none of them reported permanent and severe side effects.

Bowers *et al*.[13] reported that although there was a statistically significant difference between pain scores of the ketamine and control groups, there was less difference than the amount reported in studies with higher doses of ketamine. Also, there was no statistically significant difference between the two studied groups in terms of the level of patient satisfaction with their pain control, and satisfaction with pain control was equal between the two groups. Also, in a study conducted by Etchison *et al*.,[19] the difference in NRS pain scores after 30 min was not statistically and clinically significant between the two groups of ketamine and placebo. They reported that 0.2 mg/kg of IV ketamine was not effective in treating acute migraine. According to another study comparing two low doses of ketamine (0.15 and 0.3 mg/kg) as adjunctive therapy with morphine for acute pain in ED, the results showed that both doses reduced pain; however, the 0.3 mg/kg dosage caused more side effects such as nausea and tachycardia.[11] In a double-blind, double-dummy randomized clinical trial, the effects of intravenous pressure of sub-dissociative ketamine dose were compared with the efficacy of short injections. Experimental results showed that the administration of LDK by short infusion (SI), instead of intravenous push (IVP) significantly reduced the two major side effects of derealization and drowsiness. As a result, the sub-dissociative dose of intravenous ketamine administered as a short injection significantly reduces derealization and drowsiness in the first 15 min of administration without eliminating the analgesic effect. These results support the widespread and tolerable use of ketamine as an adjunct or alternative to opioid analgesics for the treatment of emergency pain.[16]

Conclusion

The present study aimed to evaluate the efficacy and safety of the use of LDK as an analgesic agent in the ED. The results demonstrated that in 53.84% (7 of 13) of articles, a significant reduction of more than 50% reduction in pain in the group of patients treated with ketamine (alone or combined with other analgesics) was reported. However, in 46.15% (6 out of 13) of the reviewed articles, no significant difference was observed between the pain reduction in the groups treated with ketamine alone and ketamine with other analgesics. The results showed that in six of the reviewed articles, severe complications either did not exist or were not reported. In other articles, increased systolic blood pressure (15.38%, in 2 of 13), decreased blood pressure (30.76%, in 4 of 13), hypoxia (7.69%, 1 of 13), transient respiratory depression (15.38%, in 2 of 13), and sinus tachycardia (7.69%, 1 of 13) were reported. Although side effects were observed in 100% of the articles, none of them reported persistent or severe side effects. The most commonly reported side effects were dizziness, blurred vision, nausea, and vomiting, all of which were tolerable. Therefore, the use of LDK can be

suggested as an analgesic with low side effects. However, further research is needed to determine the appropriate concentration with fewer side effects.

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Conflicts of interest

There are no conflicts of interest.

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