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Nebulized ketamine for acute pain management in the Emergency Department: A systematic review and meta-analysis

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ABSTRACT

Introduction: Ketamine administered in sub-dissociative doses has been effective in managing a variety of painful conditions in the emergency department (ED) and pre-hospital settings. The inhalation route of ketamine administration has gained traction over the past 5 years.

Methods: We conducted a systematic review and meta-analysis to evaluate the analgesic efficacy and incidence of adverse effects of nebulized ketamine. We searched Ovid CENTRAL, EMBASE, and MEDLINE databases for randomized controlled trials (RCTs) and observational studies from inception to January 2025, assessing pain reduction, rescue analgesia, and occurrences of adverse effects.

We used the Cochrane Collaboration tool and a modified Newcastle-Ottawa Scale to evaluate the risk of bias and the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) to evaluate the confidence in the evidence. Mean differences with 95 % confidence intervals (CI) using random effects were used for the meta-analyses.

Results: Thirteen studies met the inclusion criteria. Nebulized ketamine had equivalent efficacy to active controls in 8 RCT's. Four RCTs ($n = 601$) demonstrated no difference in pain reduction between nebulized ketamine and IV morphine with mean difference (MD) 0.28 (CI -0.18 to 0.73) at 30 min, and similar rates of rescue analgesia (16.9 % vs. 17.4 %). Eleven studies reported absence of serious events and no difference in non-serious adverse events (39.1 % ketamine and 37.8 % controls). The level of confidence for the outcomes was deemed to be very low.

Conclusion: Administration of ketamine via nebulization for patients with acute painful conditions provided equivalent analgesia with similar safety profile when compared to active controls.

Clinicaltrials.gov Registration: N/A.

1. Introduction

Over the past 15 years, utilization of ketamine as an analgesic in the emergency department (ED) has significantly increased, generating an extensive body of clinical research. Ketamine, as an NMDA antagonist, alleviates pain primarily by reducing central sensitization, hyperalgesia, and the "wind-up" phenomenon within the central nervous system (CNS) and at the spinal cord [1,2]. Sub-dissociative ketamine (SDK) administered alone or in combination with opioids and non-opioid analgesics, demonstrated nearly 40 % pain reduction from the baseline, both in the ED and prehospital settings [3-6].

The most common routes of ketamine administration for analgesia are intravenous, intranasal, and less frequently, subcutaneous injections [7-9]. An alternative method, nebulized ketamine inhalation, has emerged as a promising route for analgesia in emergency care.

Initial data supporting the analgesic use of nebulized ketamine originated from the anesthesia literature on postoperative sore throat management where nebulized ketamine demonstrated up to 50 % greater pain reduction than placebo without significant adverse events [10-12]. Additionally, inhalation of ketamine at escalating doses in

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healthy volunteers resulted in a systemic bioavailability ranging from 20 % to 40 % of the intravenous route, with an inhalation duration between 20 and 40 min. Peak plasma concentrations rose by approximately 77 % from the lowest to the highest inhaled dose, with no absence of serious adverse events reported [13].

More recently, several studies have explored nebulized ketamine's effectiveness in managing acute pain within emergency settings, utilizing both conventional nebulizers and breath-actuated nebulizers, the latter delivering medication triggered by the patient's inspiratory effort [14,15]. This systematic review aimed to evaluate the analgesic efficacy and incidence of adverse events associated with nebulized ketamine in prehospital and ED environments.

2. Methods

2.1. Study design

We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16]. The review utilized the PICO (Participants, Intervention, Comparison, Outcomes) framework.

- **P**articipants: Adults and children presenting with acute painful conditions (traumatic or atraumatic) in the ED or prehospital setting.
- **I**ntervention: Ketamine administered via nebulization, aerosolization, or inhalation. Other administration routes such as intramuscular (IM), intravenous (IV), intranasal, or indications other than analgesia were excluded.
- **C**omparison: Active comparator, placebo control, or no control group were eligible. Comparison could include other opioid and non-opioid analgesics,
- **O**utcomes: Primary outcome was analgesic efficacy, defined by reduction in pain scores.

2.2. Search strategy

A medical librarian developed and executed a comprehensive search strategy across three electronic databases-Ovid CENTRAL, Ovid EMBASE, and Ovid MEDLINE from inception to January 2025. Only studies published in peer-reviewed research journals were considered. Grey literature, including conference proceedings, conference abstracts, preprints, and dissertations were excluded. There were no language or publication year restrictions.

2.3. Study selection

Eligible studies included RCTs and observational studies evaluating the analgesic efficacy or safety of nebulized or aerosolized ketamine. Single case reports were excluded. Two independent reviewers (CB, FB) screened titles and abstracts for potential eligibility. Full-text assessments were performed by three reviewers (CB, FB, LS), and disagreements were resolved by consensus.

2.4. Eligibility criteria

We included studies involving adults and children who received at least one dose of nebulized or aerosolized ketamine for analgesia for acute pain management in prehospital or ED settings. Exclusion criteria encompassed ketamine use for agitation, sedation, asthma exacerbations, or endotracheal intubation. Studies with ketamine administered intranasally, IM, IV or topically were only included if they represented control groups. No restrictions were applied regarding ketamine dosage or concurrent treatments, including opioids. Comparators included placebo, active controls (e.g., opioids, IV ketamine, nitrous oxide), or no comparison.

2.5. Outcome measures

Primary efficacy outcomes included the reduction of pain scores assessed using a numerical rating scale from (0 to 10) from baseline to post-intervention, and comparative pain score differences between nebulized ketamine and control groups at specified time points. Secondary efficacy outcomes included the need for rescue analgesia.

Safety outcomes involved the incidence of adverse events. Serious adverse events considered were seizures, dysrhythmias, apnea, respiratory depression, anaphylaxis, hypotension, intubation, and cardiac arrest. Non-serious adverse events included nausea, vomiting, dizziness, lightheadedness, drowsiness, dysphoria, dissociation, unpleasant taste, pruritus, rash, visual changes, headache, nystagmus, hallucinations, sore throat, salivation, vivid dreams, and trouble concentrating. Outcomes were ascertained through direct patient observation and monitoring.

2.6. Data collection process

Data were extracted using a predefined standardized form by one author (CB) and independently verified by a second author (LS). Collected data included authors, publication year, study design, sample size, setting, patient population, causes of pain, intervention details (doses, timing), and outcomes (pain scores, rescue analgesia, and adverse events). Data presented only graphically in the publications were extracted using WebPlotDigitizer (WebPlotDigitizer, Version 4.2, Automeris LLC) plot digitizer software.

2.7. Risk of Bias and certainty assessment

We evaluated the risk of bias using the version 2 of Cochrane Collaboration Bias Appraisal Tool for RCTs Version 2 (Appendix A) and a modified Newcastle-Ottawa Scale tool for observational studies (Appendix A). The certainty of evidence for each outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations).

2.8. Data analysis

Pain reduction outcomes were compared between nebulized ketamine and control groups, expressed as mean differences (MDs) with associated 95 % confidence intervals (CIs) at 15, 30 and 60 min. When standard deviations were unavailable, we calculated them from reported confidence intervals or imputed them according to the recommendations from the Cochrane handbook [17].

Meta-analysis was conducted using Review Manager (RevMan, Version 5.4, Cochrane). Statistical heterogeneity was assessed using the I^2 statistic. Due to anticipated clinical and statistical heterogeneity between studies, we utilized DerSimonian-Laird random-effects models. Assessment of publication bias using funnel plots was not feasible due to the small number of studies included. [18].

For the outcomes of adverse events and rescue analgesia, we performed descriptive comparisons between nebulized ketamine and active controls. We calculated absolute differences in proportions along with the corresponding 95 % CIs. Due to substantial heterogeneity and limited data, we did not conduct a formal meta-analysis for these outcomes.

3. Results

From an initial screening of 1795 titles, 36 articles underwent full-text review, and ultimately, 13 studies met the inclusion criteria. The study screening process is shown in Fig. 1. These studies included 2496 participants, of whom 722 received nebulized ketamine, while the remaining participants received active

comparators (morphine, fentanyl, IV ketamine, dexmedetomidine, or nitrous oxide). The included studies comprised 8 RCTs, 1 retrospective cohort, and 4 case series. Studies originated from the United States ($n = 7$), Iran ($n = 5$), and Thailand ($n = 1$). Eleven studies were conducted in ED settings, while two were conducted in prehospital settings. One RCT specifically focused on older adults (≥ 65 years) with musculoskeletal pain, and two case series included 6 children. Nebulized ketamine dosages ranged from 0.5 to 5 mg/kg or were administered at fixed doses of 50 mg. Observation periods Post-administration observation periods varied up to 120 min, with peak analgesic effects typically observed between 20 and 30 min. Descriptions of the included studies are summarized in Table 1, and detailed pain reduction outcomes are presented in Table 2.

3.1. Efficacy

3.1.1. Nebulized ketamine vs IV morphine

Four RCT ($n = 601$ participants) compared nebulized ketamine (NK) to IV morphine [19-22]. No significant differences in pain reduction were found between the two treatments at various time points: MD at 15 min was 0.71 (95 % CI -0.36 to 1.77), at 30 min 0.28 (95 % CI -0.18 to 0.73), and at 60 min 0.07 (CI -0.63 to 0.77) Fig. 2.

3.1.2. Nebulized ketamine vs IV ketamine

One RCT ($n = 150$) compared NK (0.75 mg/kg) administered via Breath Actuated Nebulizer (BAN) with IV ketamine (0.3 mg/kg). There was no significant difference in analgesic efficacy or serious adverse events between the two groups [23].

Table 1
Characteristics of included studies by active control group.

Author Publication Year	Study type	Setting	Pain Type	Population included	Intervention (Number of Patients)	Comparison (Number of Patients)	Outcomes
Nguyen 2024	RCT	ED	Acute traumatic/ non-traumatic abdominal, flank, back, MSK, and headache pain	Adults	NB Ketamine at 0.75 mg/kg (n = 75)	Ketamine 0.3 mg/kg IV over 15 min ($n = 15$)	Pain scores at 15, 30, 70, 90 and 12 min. Rescue analgesia within 120 min. Adverse events.
Azizkhani 2020	RCT	ED	Acute trauma pain	Adults	NB Ketamine 1.6 mg/kg ($n = 195$)	Morphine IV 0.1 mg/kg twice within 10 min ($n = 196$)	Difference in pain scores between two groups at 5 and 15 min, adverse effects
Kampan 2024	RCT	ED	Acute MSK pain	Adults	NB Ketamine at 0.75 mg/kg ($n = 46$)	Morphine IV at 0.1 mg/kg (n = 46)	Pain scores at 15, 30, and 60 min. Rescue analgesia and adverse events.
Partovinezhad 2024	RCT	ED	Acute trauma pain	Adults	NB Ketamine 5 mg/kg and Lidocaine 2 mg/kg ($n = 20$)	Morphine IV 0.1 mg/kg ($n = 20$)	Pain scores at intervals of 5–60 min
Azizkhani 2018	RCT	ED	Acute traumatic long-bone fractures	Adults	NB Ketamine at 1.5 mg/kg plus NB morphine at 0.1 mg/kg ($n = 44$)	Morphine IV 0.1 mg/kg	Pain scores at 15 and 30 min.
McArthur 2025	Observational	Pre-Hospital	Traumatic pain (46.5 %), Non-traumatic pain (45.5 %), Other (8 %)	Adults	NB Ketamine 1 mg/kg ($n = 165$)	Fentanyl via any route (1 μg/kg) (IV, IM, IN, IO) ($n = 1357$)	Change in pain score.
Arumugam 2022	RCT	ED	Acute trauma pain	Adults	NB Ketamine at 50 mg fixed dose (n = 13)	Entonox (50 % nitrous oxide, 50 % oxygen) (n = 13)	Pain scores at 15 and 30 min. Adverse events.
Motamed 2021	RCT	ED	Shoulder dislocation	Adults	NB Ketamine 1 mg/kg (n = 23)	Dexmedetomidine 1 μg/kg ($n = 23$)	Pain scores at 10, 20, 30, and 60 min.
Dove 2021	RCT	ED	Acute pain or exacerbation of chronic pain	Adults	NB Ketamine at 0.75 mg/kg (n = 40), 1 mg/kg ($n = 40$), or 1.5 mg/kg (n = 40) for each group.		Pain at 15, 30, 60, 90, and 120 min. Rates of adverse effects and need for rescue analgesia.
Drapkin 2020	Case series	ED	Acute non-traumatic / traumatic MSK pain (n = 4) Acute abdominal pain (n = 1)	Adults	NB Ketamine at: 0.75 mg/kg (n = 1), 1 mg/kg (n = 1), and 1.5 mg/kg ($n = 3$).		Pain scores at 15, 30, 60, 90 and 120 min.
Fassassi 2021	Case series	ED	Acute trauma pain	Adults & Pediatrics	NB Ketamine: 0.75 mg/kg (n = 1) and 1.5 mg/kg (n = 3).		Pain scores at 60 min. Adverse events.
Rhodes 2021	Case series	ED	Acute trauma pain	Pediatrics	NB Ketamine at: 0.75 mg/kg (n = 2), 1 mg/kg (n = 1), and 1.5 mg/kg (n = 2)		Pain scores at 15, 30 and 60 min.
Patrick 2023	Case series	Pre-Hospital	MSK pain (n = 3), Neuropathic pain (n = 1), Headache (n = 1), Abdominal pain (n = 1), Vaso-occlusive Crisis (n = 1)	Adults	NB Ketamine at 1 mg/kg ($n = 7$)		Pain relief on arrival to the ED. Adverse effects.

NB: Nebulized; IV: Intravenous; RCT: Randomized Controlled Trial; ED: Emergency Department; MSK: Musculoskeletal.

Table 2
Pain Reduction by active control group.

Author Publication Year	Comparison	Pain Scores Mean (SD)			Pain Reduction Mean		
			NB Ketamine (n = 75)	IV Ketamine		NB Ketamine	Fentanyl
		Baseline	8.2 (1.5) (n = 75)	8.2 (1.6) (n = 75)	10–15 min	−4.4 (n = 75)	−5.6 (n = 71)
Nguyen		10–15 min	3.8 (3.4) (n = 75)	2.6 (3.1) (n = 71)			
		30 min	3.8 (3.4) (n = 75)	3.6 (3.3) (n = 72)	30 min	−4.4 (n = 75)	−4.6 (n = 72)
2024	Ketamine IV	60 min	4.1 (3.4) (n = 75)	3.3 (2.8) (n = 68)	60 min	−4.1 (n = 75)	−4.9 (n = 68)
			NB Ketamine	IV Morphine		NB Ketamine	IV Morphine
		Baseline	7.33 (0.64) (n = 195)	7.25 (0.51) (n = 196)	10–15 min	−2.49 (n = 186)	−2.57 (n = 195)
		10–15 min	4.84 (1.25) (n = 186)	4.68 (1.13) (n-195)			
Azizkhani		30 min			30 min		
2020	Morphine IV	60 min			60 min		
			NB Ketamine	Morphine IV		NB Ketamine	IV Morphine
		Baseline	7.2 (1.8) (n = 46)	7.8 (1.5) (n = 46)	10–15 min	−1.11 (n = 46)	−1.2 (n = 46)
Kampan		10–15 min	6 (1.9) (n = 46)	6.6 (2.2) (n = 46)			
		30 min	5.2 (1.9) (n = 46)	5.7 (2.3) (n = 46)	30 min	−1.96 (n = 46)	−2.15 (n = 46)
2024	Morphine IV	60 min	3.7 (2.1) (n = 46)	4.6 (2.3) (n = 46)	60 min	−3.41 (n = 46)	−3.2 (n = 46)
						NB Ketamine	IV Morphine
		Baseline			10–15 min	−4.65 (n = 20)	−4.94 (n = 20)
		10–15 min					
Partovinezhad		30 min			30 min	−4.2 (n = 20)	−4.52 (n = 20)
2024	Morphine IV	60 min			60 min	−3.2 (n = 20)	−3.73 (n = 20)
			NB Ketamine & NB Morphine (n = 44)	Morphine IV (n = 44)		NB Ketamine & NB Morphine (n = 44)	IV Morphine
		Baseline	9.43 (0.57)	9.63 (0.62)	10–15 min	−2.68	−5.05
Azizkhani		10–15 min	6.75 (0.92)	4.58 (1.82)			
		30 min	2.43 (1.04)	2.28 (1.1)	30 min	−7	−7.35
2018	Morphine IV	60 min			60 min		
			NB Ketamine (n = 163)	Fentanyl (n = 1317)		NB Ketamine (n = 163)	Fentanyl (n = 1317)
		Baseline 10–15 min	9.5 (1.2)	8.1 (1.7)	10–15 min		
McArthur	Fentanyl via any route (IV, IM, IN,	30 min			30 min	−3.5 (3.4)*	−2.9 (3)*
2025	IO)	60 min			60 min		
				Entonox & Nitrous			Entonox & Nitrous
			NB Ketamine	Oxide		NB Ketamine	Oxide
		Baseline	5.77 (0.44) (n = 13)	5.62 (0.15) (n = 13)	10–15 min	−1.7 (n = 13)	−2.55 (n = 13)
		10–15 min	4.07 (1.038) (n = 13)	3.07 (0.76) (n = 13)			
Arumugam		30 min	2.92 (1.25 (n = 13)	2.62 (0.63) (n = 13)	30 min	−2.85 (n = 13)	−3 (n = 13)
	Entonox (50 % nitrous oxide and						
2022	50 % oxygen) Inhaled	60 min			60 min		
			NB Ketamine	Dexmedetomidine		NB Ketamine	Dexmedetomidine
		Baseline	9.3 (n = 46)	9.3 (n = 46)	10–15 min	−0.4 (n = 46)	−0.4 (n = 46)
Motamed		10–15 min	8.9 (n = 46)	8.9 (n = 46)			
		30 min	7.03 (n = 46)	6.3 (n = 46)	30 min	−2.27 (n = 46)	−3 (n = 46)
2021**	Dexmedetomidine Neb	60 min	5.66 (n = 46)	4.9 (n-46)	60 min	−3.64 (n = 46)	−4.4 (n = 46)
			0.75 mg/kg 1.0 mg/kg	1.5 mg/kg			
		Baseline:	8.7 (1.4) 8.6 (1.4)	8.7 (1.4)			
			(n = 40) (n = 40)	(n = 40)		0.75 mg/kg 1.0 mg/kg	1.5 mg/kg
		10–15 min:	5.8 (3) 5.2 (3.4)	6 (2.7)	10–15 min:	−2.9 −3.4	−2.7 (n = 40)
			(n = 40) (n = 40)	(n = 40)		(n = 40) (n = 40)	
		30 min:	4.7 (2.7) 4.4 (3.2)	4.6 (2.8)	30 min:	−4 −4.2	−4.1 (n = 40)
Dove			(n = 40) (n = 40)	(n = 40)		(n = 40) (n = 40)	
		60 min:	4.7 (2.9) 4.4 (3.1)	4.2 (2.8)	60 min:	−4 −4.2	−4.5 (n-40)
2021	No comparator		n = 39 (n = 37)	(n = 40)		(n = 39) (n = 37)	
				Baseline (n = 5): 8.4 (0.49)			
				10–15 min (n = 5): 4.8 (1.5)			10–15 min (n = 5): −3.6
				30 min (n = 5): 3.6 (1.01)			30 min (n = 5): −4.8
Drapkin 2020		No comparator		60 min (n = 5): 2 (1.7)			60 min (n = 5): −6.4
				Baseline (n = 4): 8 (1.6)			
				10–15 min: Not reported			10–15 min: Not reported
				30 min: Not reported			30 min: Not reported
Fassassi 2021		No comparator		60 min (n = 4: 0.25 (0.5)			60 min (n = 4):-7.75
				Baseline (n = 5): 78 (1.4)			
				10–15 min (n = 5): 5.4 (2.5)			10–15 min (n = 5): −2.4
				30 min (n = 5): 4.8 (2.8)			30 min (n = 5): −3
Rhodes 2021		No comparator		60 min (n = 5): 3.6 (2.3)			60 min (n = 5): −4.2
Patrick 2023		No comparator		Baseline (n = 7): 9.4 (0.96)			
				10–15 min (n = 1): 2			10–15 min (n = 1): =7.4
				30 min (n = 6): 4.3 (3.6)			30 min (n = 6): −5.1
				60 min: Not reported			60 min: Not reported

* No reported follow-up time. First to final pain score.
** WebPlotDigitizer version 4.2. https://automeris.io/WebPlotDigitizer.

3.1.3. Nebulized ketamine vs other active controls

One prehospital retrospective observational study ($n = 165$ receiving NK 1 mg/kg and $n = 1357$ receiving fentanyl 1 μg/kg via IV, intramuscular, intranasal, or intraosseous routes reported no significant differences in pain reduction overall (MD -0.36, 95 % CI -0.93 to 0.21). However, a subgroup analysis favored nebulized ketamine for traumatic injuries (MD -0.92, 95 % CI -1.17 to −0.12) [24].

One RCT ($n = 26$) compared NK (50 mg) with Enotox (50 % Nitrous Oxide 50 %/50 % Oxygen) and found no differences in pain scores or patient satisfaction [25]. Another RCT ($n = 46$) comparing NK 1 mg/kg with nebulized dexmedetomidine 1 μg/kg, showed similar analgesic effects; however, dexmedetomidine had a faster onset of analgesia (10 min versus 20 min for ketamine) [26].

3.1.4. Nebulized ketamine without control

One clinical trial ($n = 120$) and four case series ($n = 21$) groups reported improved pain scores following nebulized ketamine administration at various assessment intervals [27-31].

3.2. Rescue analgesia

Rates of rescue analgesia were similar between groups, with 16.9 % (42/248) of participants receiving nebulized ketamine, and 17.4 % (21/121) in control groups (difference 0.5 %, 95 % CI -7.2 to 9.3 %, $p = 0.91$) (Table 3).

3.3. Safety

Among 11 studies (RCTs, case series, and non-comparative study) reporting serious adverse events, none occurred in either the nebulized ketamine ($n = 0/393$), control groups (n = 0/394) the case series, or non-comparative studies (n = 0/141).

For non-serious adverse events reported across 11 studies, the added number of events was 39.1 % ($n = 206/527$) in the ketamine group and 37.8 % ($n = 149/394$) in active controls, (difference 1.3 %, 95 % CI -5.1 to 7.6 %, $p = 0.69$). Sub-analysis of the 6 RCTs had an incidence of non-serious adverse events in the ketamine group compared to controls of 21.9 % ($n = 86/393$) vs. 37.8 % (n = 149/394); difference 15.9 %, 95 % CI 9.5 % to 22.1 %, $p < 0.0001$. Case series and non-comparative studies reported an incidence of non-serious adverse events of 89.6 per 100 patients (120 events among 134 patients). The most common adverse events were nausea/vomiting (3.6 % in ketamine and 21.9 % in controls; difference − 18.3 % 95 % CI -23.5 to −13.2 %, $P < 0.0001$), and dizziness (55.2 events per 100 patients in ketamine and 37.7 events in 100 patients in controls; difference 17.5 %, 95 % CI 7.7 to 26.7 %, $p < 0.001$). Adverse event data are reported in Table 4. Of note, patients could report multiple non-serious events (i.e., nausea and dizziness), and repeated observations at different time points in observational studies contributed to the overall higher event counts.

3.4. Quality assessment

Risk of bias was assessed using the second version of the Cochrane risk of bias tool for RCTs, with four studies rated as low risk, one with some concerns, and three considered high risk. (Supplemental Table 1) For observational studies and case series assessed via the Newcastle Ottawa scale, all were deemed high risk of bias. (Supplemental Table 2).

3.5. GRADE assessment

The overall confidence in the evidence for the outcomes was very low due to high risk of bias of included studies, inconsistency across results, heterogeneity in the meta-analyses, and imprecision as measured by the boundaries of the confidence intervals and small sample sizes.

4. Discussion

In this systematic review of 2496 participants, NK ($n = 722$) demonstrated similar pain reduction across multiple time points to IV

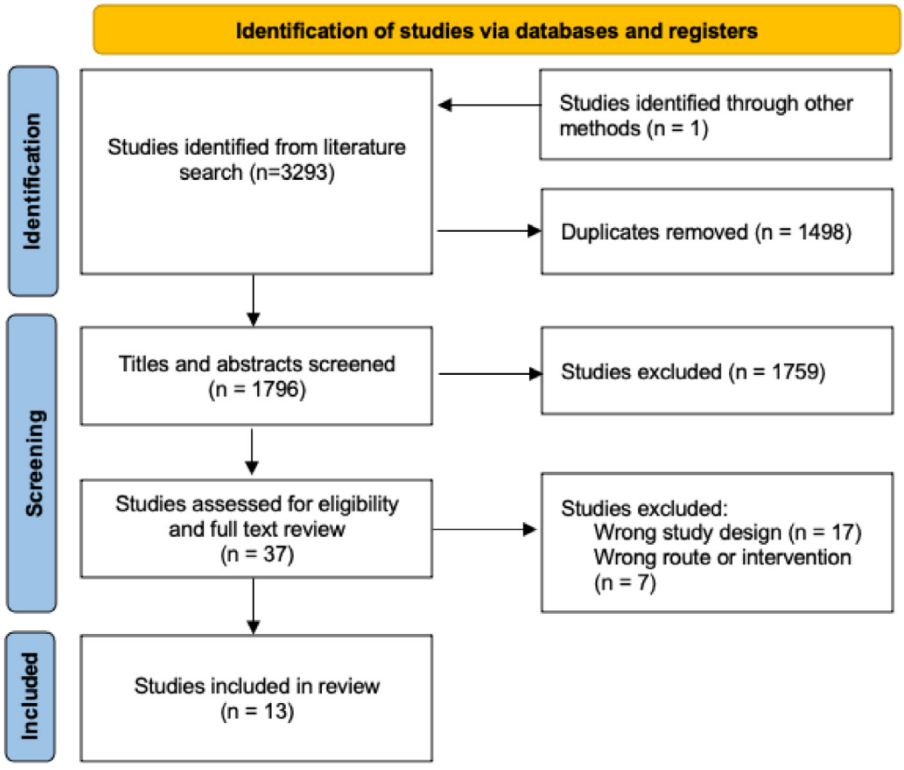

Fig. 1. PRISMA 2020 Study Flow Diagram.

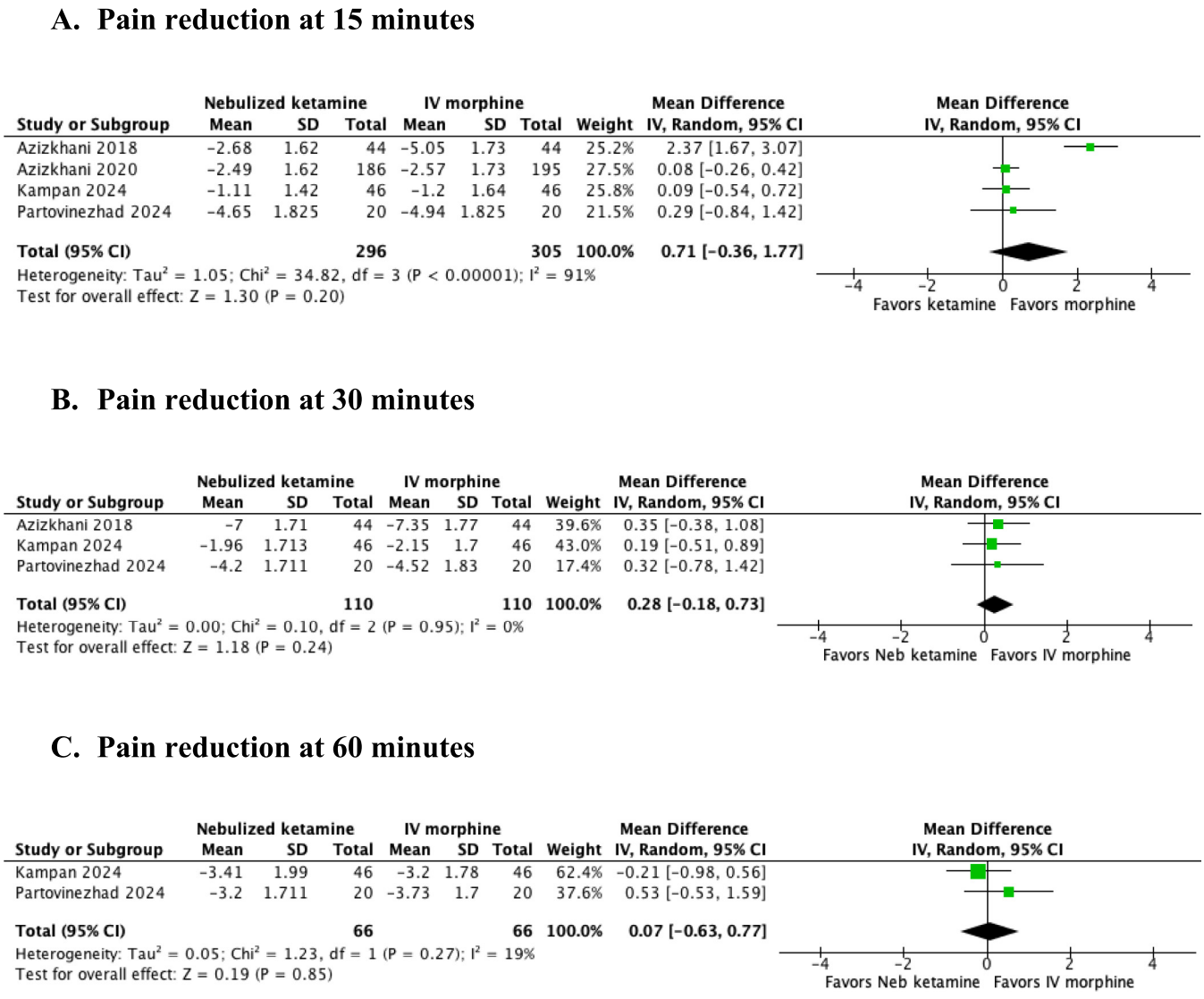

Fig. 2. Mean differences in pain reduction between nebulized ketamine and intravenous morphine across randomized trials.

Table 3
Rescue Analgesia by active control group

Author/Year	Outcome Definition	Neb K	Control
Nguyen 2024	Rescue within 120 min	28.0 % (n = 21/75)	13.3 % (n = 10/75)
Azizkhani 2020	Not reported		
Kampan 2024	At 30 min if unimproved pain scores	10.9 % (n = 5/46)	23.9 % (n = 11/46)
Partovinezhad 2024	Not reported		
Azizkhani 2018	Not reported		
McArthur 2025	Not reported		
Arumugam 2022	Not reported		
Motamed 2021	Not reported		
Dove 2021	Received second dose of ketamine or rescue morphine	12.5 % (n = 15/120)	
Drapkin 2020	Not reported		
Fassassi 2021	Not reported		
Rhodes 2021	Not reported		
Patrick 2023	EMS rescue opioids	14.3 % (n = 1/7)	
	Total	16.9 % (n = 42/248)	17.4 % (n = 21/121)

EMS: Emergency Medical Services; NR: Not reported; Neb K: Nebulized ketamine.

Table 4
Adverse events

First Author	Any serious adverse event		Any adverse event		Nausea/vomiting (non-serious)		Dizziness (non-serious)	
	Neb-K	Control	Neb-K	Control	Neb-K	Control	Neb-K	Control
Nguyen	0 %	0 %	78.7 %	90.7 %			48 %	58.6 %
2024	(*n* = 0/75)	(*n* = 0/75)	(*n* = 59/75)	(n = 68/75)	NR	NR	(*n* = 36/75)	(*n* = 44/75)
Azizkhani	0 %	0 %	5.1 %	27 %	5.1 %	27 %		
2020	(n = 0/195)	(n = 0/196)	(n = 10/195)	(*n* = 53/196)	(n = 10/195)	(n = 53/196)	NR	NR
Kampan	0 %	0 %	2.2 %	37 %	0 %	17.4 %		19.6 %
2024	(n = 0/46)	(n = 0/46)	(n = 1/46)	(*n* = 17/46)	(n = 0/46)	(*n* = 8/46)	2.2 % (n = 1/46)	(*n* = 9/46)
Partovinezhad	0 %	0 %	40 %	35 %	0 %	15 %	10 %	50 %
2024	(n = 0/20)	(n = 0/20	(n = 8/20)	(*n* = 7/20)	(n = 0/20)	(n = 3/20)	(*n* = 2/20)	(n = 4/20)
Azizkhani	0 %	0 %	2.3 %	6.8 %	2.3 %	6.8 %		
2018	(n = 0/44)	(n = 0/44)	(n = 1/44)	(n = 3/44)	(n = 1/44)	(n = 3/44)	NR	NR
McArthur								
2025	NR	NR	NR	NR	NR	NR	NR	NR
Arumugam	0 %	0 %	53.8 %	7.7 %				7.9 %
2022	(n = 0/13)	(n = 0/13)	(n = 7/13)	(n = 1/13)	NR	NR	53.8 % (n = 7/13)	(n = 1/13)
Motamed								
2021	NR	NR	NR	NR	NR	NR	NR	NR
Dove	0 %				2.5 %			
2021*	n = (0/120)		* (*n* = 106/120)		(n = 3/120)		*(n = 106/120)	
Drapkin	0 %		20 %					
2020	(n = 0/5)		(n = 1 /5)		NR		20 % (n = 1/5)	
Fassassi	0 %				25 %			
2021	(n = 0/4)		100 % (n = 4/4)		(n = 1/4)		50 % (n = 2/40)	
Rhodes	0 %				20 %		80 %	
2021	(n0/5)		120 % (n = 6/5)		(n = 1/5)		(n = 4/5)	
Patrick	0 %							
2023	(n = 0/7)		NR		NR		NR	
	0 %	0 %			3.6 %			37.7 %
Total	(n = 0/534)	(n = 0/394)	39.1 % (n = 206/527)	37.8 % (n = 149/394)	(*n* = 16/434)	21.9 % (*n* = 67/306)	55.2 % (*n* = 159/288)	(*n* = 58/154)

Patients could have experienced more than one adverse effect.
Neb K: Nebulized Ketamine; NR: Not reported.
* Adverse events were measured at 15, 30, 60, 90, and 120 min - patients could have experienced adverse events multiple times.

morphine, IV ketamine, and other active controls. Observational studies without control groups revealed analgesic efficacy of NK in the ED and prehospital settings. There were no severe adverse events, with approximately 40 % experienced mild adverse (nausea or dizziness), comparable to the active comparators.

The comparable analgesic efficacy between nebulized ketamine and established IV analgesics supports its utility, particularly when IV access is unavailable. Pharmacokinetic studies support the use of inhalation route align, well with clinical observations of analgesic duration in included studies [19-27].

Our results align closely with prior literature confirming the efficacy and safety profile of low-dose ketamine in management of acute pain syndromes. Previous systemic reviews demonstrated meaningful and comparable to opioids pain reduction of SDK [32,33]. This systematic review explores the role of inhalation route, reinforcing practical value of nebulized ketamine while highlighting critical knowledge gaps, such as the optimal dosing strategy, device variability, and efficacy in specific populations such as pediatrics and older adults [20,31].

In terms of practical application, nebulized ketamine offers several operational advantages in the ED and prehospital settings, though with some noteworthy drawbacks. First, a noninvasive nature allows for timely provision of analgesia in patients with not readily available IV access potentially mitigating the under treatment of pain in busy settings. Second, ED clinicians are quite comfortable with nebulized route of drug delivery that, furthermore, might obviate the need for the intensive monitoring. Third, patient acceptance of inhaled analgesia appears to be good as demonstrated in the NK vs. Entonox comparative trial, in which patient-reported satisfaction with pain control was high and did not differ between the NK group and the nitrous oxide group [25]. Lastly, NK has minimal effect on respiratory drive and hemodynamics: none of the studies reported respiratory depression, hypoxia, or hemodynamic abnormalities. However, there are some drawbacks to consider when administer nebulized ketamine. The short duration of analgesia after a single dose (often on the order of 30–60 min), might require additional and/or rescue pain relief in the form of opioid or non-opioid analgesics [34]. Of note, re-dosing with nebulized ketamine is feasible, but optimal timing and frequency has not been well studied. Another limitation is that effective nebulized analgesia requires the patient's cooperation to inhale the medication, thus, patients in severe distress, with altered mental status, or with contraindications to inhalation (e.g. facial trauma or risk of laryngospasm) may not receive the full benefit of this modality. In addition, there is variability in drug delivery based on the device and technique. For example, breath-actuated nebulizers used in several trials improve drug deposition in pulmonary system but may not be readily available in the ED's across the country. Furthermore, the occupational exposure to aerosolized ketamine raised concerns among ED clinicians, even though the use of a mask/nebulizer interface and standard room ventilation likely keeps any environmental ketamine levels very low. Lastly, while adverse effects of nebulized ketamine are mild and short-lived, 25 to 40 % of patients in this systematic review reported dizziness, dysphoria, or feeling of unreality that might require a brief observation and reassurance.

Lastly, this review highlights several gaps in the literature and directions for future research on nebulized ketamine. Most of the existing studies were modest in size and scope, thus larger multicenter trials are needed to increase confidence in these findings and to detect any infrequent adverse outcomes. In particular, pediatric patients remain an understudied population – current evidence for nebulized ketamine in children is limited, so pediatric-specific randomized trials are warranted to establish appropriate dosing, efficacy, and safety in the prehospital settings. Optimal dosing strategies for nebulized ketamine also require clarification and refinement. While one dose-ranging trial found that doses of 0.75, 1.0, and 1.5 mg/kg via breath-actuated nebulizer had statistically indistinguishable analgesic effects at 30 min, [27] it remains unclear whether higher doses might confer longer duration of pain relief, or whether repeated administration could improve pain control without adding adverse effects. Future studies should explore the possibility of longer lasting analgesia with a higher (> 0.75 mg/kg) dose of

NK (since exceeding ~0.75 mg/kg appears to confer no short-term benefit). Additionally, further comparative trials would define nebulized ketamine's role relative to other analgesic modalities. Thus far, studies have benchmarked it against IV morphine, IV ketamine, and inhaled nitrous oxide; head-to-head comparisons with other common ED analgesics – for example, intranasal fentanyl (commonly used in pediatrics) or IV nonsteroidal anti-inflammatory drugs – would help clinicians choose the best modality for a given scenario. It may also be fruitful to investigate nebulized ketamine as an adjunct to opioids and assess its analgesic efficacy, safety, and opioid-sparing. Future clinical trials should (in addition to pain relief) focus on patient and provider satisfaction, time to meaningful pain relief, ED length of stay, and long-term outcomes (sustain pain relief and functional improvement). Such information would evaluate the real-world impact of nebulized ketamine on emergency care processes. As the evidence base grows, systematic collection of safety data will remain crucial, particularly in detecting any rare adverse events that might not have appeared in the relatively small cohorts studied to date.

In summary, pursuing larger RCTs in special populations), dose-optimization studies, and comparative trials against a range of analgesic classes will help fill current knowledge gaps. These future investigations will better determine where nebulized ketamine fits in acute pain management and guide the evidence-based protocols to maximize its benefits while addressing its limitations.

4.1. Limitations

This review has several limitations. First, many of the included studies had small sample sizes and various sources of potential bias. Some RCTs were single-center pilot studies with suboptimal blinding – for example, trials comparing nebulized ketamine to an IV analgesic could not fully mask the route of administration unless a double-dummy design was used, raising the risk of performance or detection bias. The overall quality of evidence was judged to be very low, owing to issues of risk of bias, inconsistency between study results, and imprecision in effect estimates. We noted considerable clinical and methodological heterogeneity across studies such as: age groups and clinical presentations of patients (young adults with traumatic injuries to elderly patients with atraumatic pain), lack of dosing uniformity (from 0.5 mg/kg to 1.5 mg/kg) and various nebulization techniques, and differences among comparator arm (placebo, morphine, nitrous oxide, or no control), all of which make it challenging to generalize the findings.

Additionally, most studies assessed pain relief only in the short term (15 to 60 min post-administration); outcomes beyond one hour were seldom reported, leading to uncertainty regarding the total the duration of analgesia and potential of delayed effects of nebulized ketamine. Another limitation is the possibility of publication bias as the number of included trails is small. This raises the concern that negative or inconclusive studies (if any exist) might not have been published, potentially skewing the available evidence toward positive results.

Finally, while we performed a comprehensive literature search up to January 2025, it is always possible that we missed relevant studies or that new data (emerging after our search window) could alter the conclusions. These limitations warrant caution in results interpretation; however, they also highlight the need for more high-quality research to confirm and expand upon our findings.

5. Conclusion

Nebulized ketamine provides analgesic efficacy comparable to IV morphine, IV ketamine, and other active analgesic controls in patients presenting with various acute painful conditions to the ED or prehospital settings. No severe adverse events were reported in these studies. These findings support the consideration of nebulized ketamine as a viable analgesic option in acute pain management.

CRediT authorship contribution statement

Murat Cetin: Writing – review & editing, Methodology, Investigation. **Caitlin S. Brown:** Writing – review & editing, Resources. **Fernanda Bellolio:** Writing – review & editing, Resources. **Jefferson Drapkin:** Writing – review & editing, Resources. **Robert Glatter:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Sergey Motov:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Conceptualization. **Lucas Oliveira J. e Silva:** Writing – review & editing, Resources.

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Conflicts of Interest

The authors have no independent disclosures or conflicts of interest.

Declaration of competing interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential

Appendix A. Supplementary data

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