

# Ketamine in the Management of Acute Pain: A Comprehensive Meta-Analysis

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## ABSTRACT

This review was conducted to find the effectiveness and safety of ketamine in managing acute or sudden pain in the emergency scenarios. The research was carried out using databases such as PubMed, MEDLINE, Cochrane trial registries, and EMBASE from inception up to July 2022. The meta-analysis employed using the random-effects model and presented results as pooled standardised mean difference (SMD) and risk ratio (RR) alongside their 95% confidence intervals (CIs). The pooled SMD for pain assessment within 15 minutes stood at -0.72 (95% CI: -1.55 to 0.12). At 30 minutes, SMD was -0.27 (95% CI: -0.48 to -0.05), and by 45 minutes, it was -0.04 (95% CI: -0.26 to 0.18). Between the 45-minute and 60-minute mark, the SMD was -0.03 (95% CI: -0.22 to 0.17), and after the 60-minute interval, it was registered at 0.11 (95% CI: -0.10 to 0.22). Pooled RR reflecting the requirement for supplementary analgesics was 0.96 (95% CI: 0.65-1.41). The study found that ketamine's efficacy and safety were comparable or even superior to opioids in addressing sudden pain in the emergency contexts.

**Key Words:** Ketamine, Meta-analysis, Opioids, Acute pain, Emergency.

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## INTRODUCTION

Over half of the visits to emergency facilities, such as emergency departments (ED), are attributed to acute pain.<sup>1,2</sup> Addressing acute pain is pivotal for both patient contentment and overall care. At present, opioids stand as the primary analgesics prescribed for alleviating acute pain.<sup>3</sup> Yet, due to the potential complications linked with opioid consumption, there is a distinct segment of patients who could greatly benefit from an alternative pain relief option. Specifically, groups with opioid naive individuals (children and adults), elderly individuals, chronic opioid users, those with opioid addiction, and those on medications for opioid misuse disorders or alcohol dependency, often seek a viable alternative to opioids.<sup>4,5</sup>

Ketamine, characterised as an N-methyl-D-aspartate receptor antagonist, possesses both anaesthetic and analgesic capacities.<sup>6</sup> Historically, it was predominantly employed as an anaesthetic agent. However, its popularity diminished, making way for a new generation of anaesthetics that offer enhanced effectiveness and fewer adverse effects.

In recent times, ketamine's application in the emergency contexts has shifted towards inducing prior intubation and facilitating procedural sedation, attributing to its dissociative characteristics which preserve airway reflexes and ensure hemodynamic stability.<sup>7</sup> In certain dosage regimens, ketamine has exhibited superior pain relief properties for both acute and chronic pain scenarios.<sup>8</sup>

While the adoption of ketamine to address acute pain is still an emerging approach, it offers several unique attributes conducive to enhancing patient outcomes. Numerous investigations have explored the impact of ketamine *vis-a-vis* opioids for controlling acute pain.<sup>9-11</sup> Although several reviews had been conducted on this subject, many encompass a limited set of studies, yielding indecisive evidence regarding ketamine's efficiency and safety in treating acute pain.<sup>12,13</sup> Thus, this meta-analysis embarked on a comprehensive review to assess ketamine's role in acute pain management within the emergency environments.

## METHODOLOGY

Randomised controlled trials (RCTs) published from inception of a database until July 2022 were included. Full-texts or abstracts were included, while grey literature was not. Studies done on patients reporting to urgent/emergency care with acute/sudden pain were eligible (irrespective of the definition, cause, specification, or nature of the pain). Studies conducted on post-operative patients were excluded. Studies using intravenous ketamine as an intervention for acute onset pain were included.

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Comparison groups could be opioids or standard care. Studies reporting any one of the following outcomes: pain intensity, requirement of rescue analgaesics, adverse reactions in terms of gastrointestinal (nausea and vomiting), neurological (emergence phenomenon, drowsiness, dysphoria/dissociation, dizziness), psychological (delirium, hallucinations, and mood changes), or cardiopulmonary (respiratory failure, hypotension, and hypoxia) were included in the study.

Extensive, systematic, and thorough evaluation of the literature was conducted by doing searches in numerous databases, including EMBASE database, PubMed, Cochrane Library, and MEDLINE. The medical subject heading (MeSH) were combined with free-text headings to execute the search. Search criteria were refined to include articles up to July 2022 and only those written in English. All the aspects of review were done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020.<sup>14</sup>

In the initial phase of study selection, two separate researchers screened titles, keywords, and abstracts. Subsequently, these researchers acquired the full-text studies, further refining the selection based on the defined eligibility standards. In the following step, both experts scrutinised the full-texts, selecting those that met the eligibility criteria for in-depth analysis.

Once the pertinent full-text articles were determined, both researchers took part in manual data extraction using a pre-established form for the data collection. The primary researcher documented the data, and the second researcher rechecked these entries to confirm the data accuracy.

Both researchers took on the task of gauging the quality of the incorporated studies, utilising RoB-2 instrument, namely, Cochrane risk of bias tool for RCTs.<sup>15</sup> Bias risk was evaluated across facets like randomisation, deviation from intended interventions, absent data, outcome measurements, and selective outcome reporting. Based on these assessments, rating was given as low, high, or uncertain bias risk.

Utilising STATA version 14.2, the analysis was conducted. As the pain score and total analgaesic requirement were continuous variables, mean, standard deviation (SD), and overall sample size were determined. The collective effect size was represented as a standardised mean difference (SMD) with 95% confidence interval (CI). For binary results such as postoperative pain alleviation, cosmetic satisfaction, symptom reduction, haematoma occurrence, hoarseness, and hypothyroidism, frequencies of events, and participation in both the groups were tabulated, yielding a pooled estimate expressed as the risk ratio (RR) and its accompanying 95% CI. A random-effects model, incorporating the inverse variance technique, was employed to cater for heterogeneity.<sup>16</sup> The extent of heterogeneity was gauged via the Chi-square test and the  $I^2$  statistic, which quantifies variability.

Subgroup evaluations were conducted accounting for potential covariates, including the administration route, dosage,

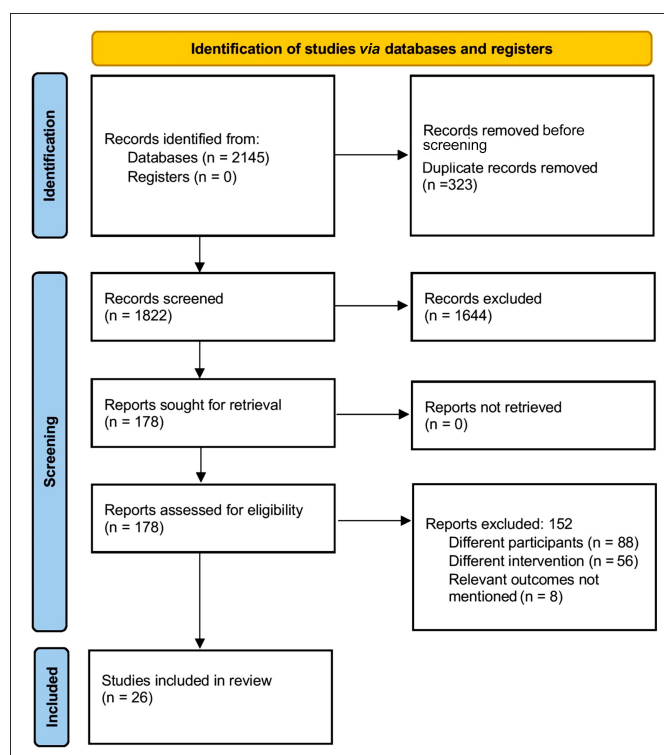
comparison group, research setting, average age, and measurement scales in both ketamine and the comparison group. To determine publication bias, a visual funnel plot and statistical testing using Egger's test were employed, with  $p < 0.05$  indicating presence of publication bias.<sup>17</sup>

## RESULTS

Figure 1 depicts the PRISMA flowchart. In the first stage of screening, 234 studies were retrieved, which became 178 studies after duplications were removed. These studies underwent secondary screening, and finally 26 studies were included.<sup>9-11,18-40</sup>

Most studies (11) were conducted in the Middle Eastern countries. The sample sizes varied from 22 to 1102. Majority studies had checked the efficacy of intravenous ketamine, while the rest of the studies assessed the efficacy of intranasal ketamine. The intravenous dose of ketamine varied from 0.1 to 0.6 mg/kg, while the commonly used dose for the intranasal route was 1 mg/kg. The commonly used drug in the control group was morphine (14 studies). Half of the studies had a high bias risk, while the rest of them had some concerns (Table I).

The combined SMD for pain scores at the 15-minute mark was -0.72 (95% CI: -1.55 to 0.12;  $I^2 = 95.4\%$ ;  $n = 7$ ), showcasing no remarkable distinction in pain management between the ketamine-administered and the control groups within this period (Figure 2A). When broken down into subgroups, no significant disparities emerged (intravenous combined SMD = -0.70; 95% CI: -1.73 to 0.34; intranasal combined SMD = -0.77; 95% CI: -2.57 to 1.03).

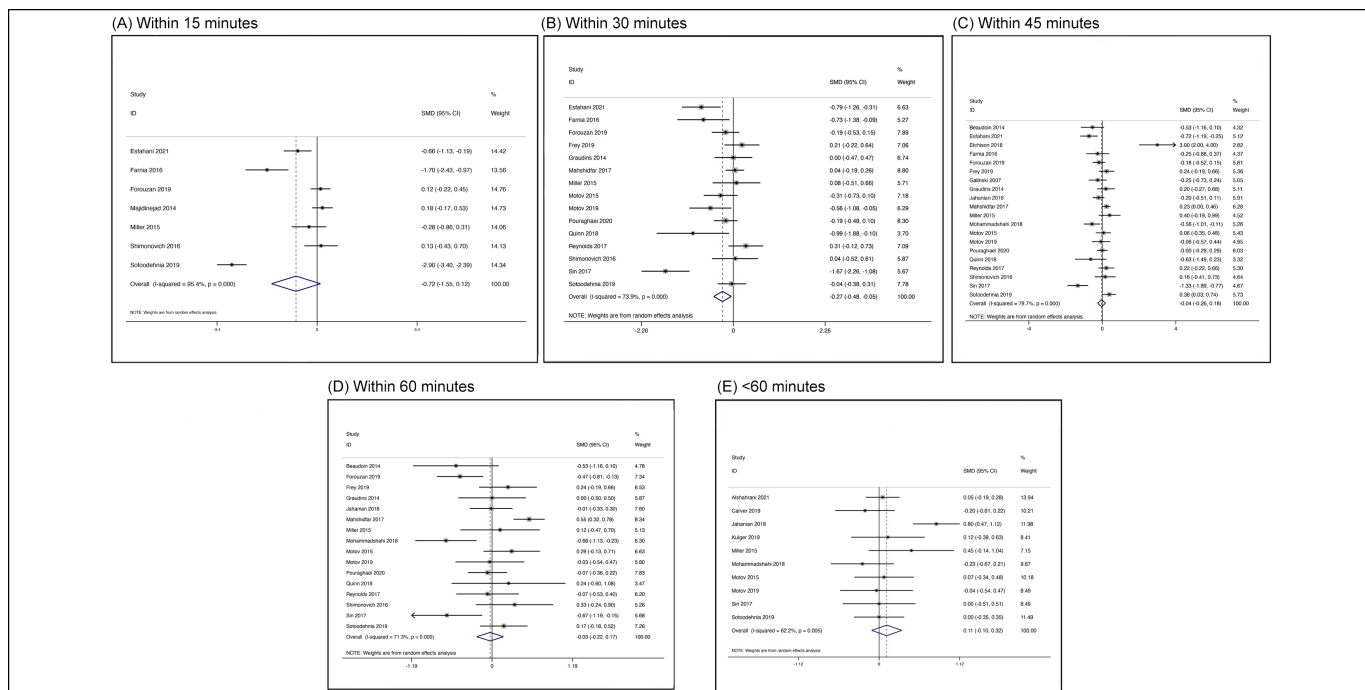


**Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included the search of data.**

**Table I: Characteristics of the included studies (n=26).**

Author and year	Country	Sample size	Study participants	Pain scale	Route of administration of Ketamine	Dose of Ketamine	Comparator group	Mean age	Risk of bias
Alshahrani <i>et al.</i> 2022	Saudi Arabia	I=138 C=140	Adults diagnosed with sickle cell disease experiencing an acute vaso-occlusive episode.	NRS	Intravenous	0.3 mg/kg	Morphine	I=29.1 C=29.6	High
Beaudoin <i>et al.</i> 2014	USA	I=20 C=20	Individuals between the ages of 18 and 65 presenting with acute moderate to intense pain lasting less than 7 days, for whom their attending doctor deemed IV opioid administration necessary.	NRS	Intravenous	0.3 mg/kg	Morphine	I=37.5 C=32.5	Some concerns
Boudia <i>et al.</i> 2020	Tunisia	I=552 C=550	Individuals who arrived at the emergency room due to acute limb injury pain, registering a Visual Analogue Scale (VAS) score of 50 or higher.	VAS	Intranasal	250 mg/5 ml	Placebo	I=37.7 C=36.6	High
Carver <i>et al.</i> 2019	USA	I=45 C=46	Adult individuals with a minimum of three rib breaks who were taken to a Level I trauma facility.	NRS	Intravenous	2.5 µg/kg	Placebo	I=46 C=50	High
Esfahani <i>et al.</i> 2021	Iran	I=36 C=37	Individuals directed to emergency units due to singular limb trauma incidents.	NRS	Intravenous	0.1 mg/kg	Morphine	I=32.5 C=33.4	High
Etchison <i>et al.</i> 2018	USA	I=16 C=18	Adults between 18 and 65 years suffering from an acute migraine episode at a singular educational emergency facility.	NRS	Intravenous	0.2 mg/kg	Placebo	I=38.5 C=30.5	Some concerns
Farnia <i>et al.</i> 2017	Iran	I=20 C=20	Individuals experiencing kidney stone pain and sourced from the emergency room.	VAS	Intranasal	1 mg/kg	Morphine	I=39.7 C=34.2	High
Forouzan <i>et al.</i> 2019	Iran	I=68 C=68	Patients with kidney pain from renal stones directed to Ahvaz Imam Khomeini Hospital.	NRS	Intravenous	0.3 mg/kg	Morphine	NR	High
Frey <i>et al.</i> 2019	USA	I=43 C=42	Young patients arriving at emergency units due to pain from limb trauma.	VAS	Intranasal	1.5 mg/kg	Fentanyl	I=11.8 C=12.2	Some concerns
Galinski <i>et al.</i> 2007	France	I=33 C=32	Trauma-affected individuals exhibiting severe pain marked by a VAS score equal to or above 60/100.	VAS	Intravenous	0.2 mg/kg	Placebo	I=35 C=40	Some concerns
Graudins <i>et al.</i> 2014	Australia	I=34 C=34	Youngsters aged 3-13, weighing under 50 kg, with singular limb damage and a pain score exceeding 6 out of 10 at initial assessment.	VAS	Intranasal	1 mg/kg	Fentanyl	I=7 C=9	Some concerns
Jahanian <i>et al.</i> 2018	Iran	I=78 C=78	Adult patients between 18 and 65 years with fractures in long bones of the limbs from blunt injuries, visiting our emergency unit.	VAS	Intravenous	0.5 mg/kg	Morphine	I=35.8 C=36.3	High
Kugler <i>et al.</i> 2019	USA	I=30 C=29	Senior patients, aged 65 or older, with at least three rib fractures, admitted to a primary trauma facility.	NRS	Intravenous	2 µg/kg/min	Placebo	I=75 C=73	High
Mahshidfar <i>et al.</i> 2017	Iran	I=150 C=150	Trauma-affected individuals aged between 18 and 70 years, with musculoskeletal pain scoring 5 or above on an 11-point NRS, directed to emergency units.	NRS	Intravenous	0.2 mg/kg	Morphine	I=34.4 C=34.1	Some concerns
Majidinejad 2014	Iran	I=63 C=63	Patients with fractures in extended bones, directed to the emergency section.	NRS	Intravenous	0.5 mg/kg	Morphine	I=35.1 C=53.6	Some concerns
Miller <i>et al.</i> 2015	USA	I=24 C=21	Adults between 18 and 59 years experiencing acute pain in the abdomen, side, lower back, or limbs were included.	NRS	Intravenous	0.3 mg/kg	Morphine	I=31 C=29	Some concerns
Mohammadshahi <i>et al.</i> 2018	Iran	I=40 C=40	Individuals with acute single limb injuries attending the emergency ward.	NRS	Intranasal	0.02 mg/kg	Morphine	I=31.4 C=31.7	High
Motov <i>et al.</i> 2015	USA	I=45 C=45	Emergency ward attendees between 18 and 55 years undergoing moderate to intense pain in the abdomen, flank, or muscles and bones.	NRS	Intravenous	0.3 mg/kg	Morphine	I=35 C=36	Some concerns
Motov <i>et al.</i> 2019	USA	I=30 C=30	[Repeated sentence from 14] Emergency ward attendees between 18 and 55 years undergoing moderate to intense pain in the abdomen, flank, or muscles and bones.	NRS	Intravenous	0.3 mg/kg	Morphine	I=77.3 C=77.1	Some concerns
Mozafari <i>et al.</i> 2020	Iran	I=65 C=65	Individuals between 15 and 65 years showing symptoms typical of kidney stones on hospital arrival.	VAS	Intranasal	1 mg/kg	Fentanyl	NR	Some concerns
Pouraghaei <i>et al.</i> 2021	Iran	I=95 C=89	Adults with kidney stone pain received in a high-level hospital's emergency section.	NRS	Intranasal	1 mg/kg	Morphine	I=39.4 C=41.3	High
Quinn <i>et al.</i> 2021	USA	I=11 C=11	Children between 3 and 17 years in a pediatric emergency ward experiencing acute pain of moderate to high intensity.	FPS	Intranasal	1 mg/kg	Fentanyl	I=9.7 C=9.5	High
Reynolds <i>et al.</i> 2017	USA	I=42 C=44	Children aged 4 to 17 years, with suspected singular limb fractures, arriving at an urban secondary pediatric trauma facility.	FPS	Intranasal	1 mg/kg	Fentanyl	NR	High
Shimonovich <i>et al.</i> 2016	Israel	I=24 C=24	Adults between 18 and 70 years undergoing moderate to intense traumatic pain.	VAS	Intranasal	1 mg/kg	Morphine	I=37.9 C=42.9	Some concerns
Sin <i>et al.</i> 2017	USA	I=30 C=30	Adults older than 18 years arriving at the emergency unit primarily complaining of moderate to intense acute pain.	NRS	Intravenous	0.3 mg/kg	Placebo	I=41 C=48	High
Sotoodehnia <i>et al.</i> 2019	Iran	I=62 C=64	Individuals over 18 years reaching the ED with acute kidney stone pain, especially those with prior kidney stone history and symptoms mirroring past episodes.	NRS	Intravenous	0.6 mg/kg	Ketorolac	I=34.2 C=37.9	Some concerns

C-Control group, FPS – Faces pain scale, I-Intervention group, NR-Not reported, NRS-Numerical Rating Scale, USA – United States of America, VAS-Visual Analogue Scale.

**Figure 2: Forest plot showing the difference in pain score between ketamine and control group (A) within 15 minutes (B) within 30 minutes (C) within 45 minutes (D) within 60 minutes (E) >60 minutes.**

Attempting to analyse on the basis of ketamine dosage proved challenging since each research study employed varied dosages, complicating the efforts to arrive at a collective estimate for each dosage tier. In a similar vein, analyses grounded on the control group were untenable, with the exception of the study by Sotoodehnia *et al.* (2019) that used morphine as the consistent comparison across studies.

Within 30 minutes, pooled SMD for pain scores stood at -0.27 (95% CI: -0.48 to -0.05;  $I^2=73.9\%$ ;  $n = 15$ ), reflecting a notable reduction in pain levels for patients administered with ketamine in comparison to the control group (Figure 2B). The sensitivity analysis did not point to any specific study with a pronounced impact on the combined estimate. The funnel plot appeared to be skewed, a finding that was corroborated by the significant result from Egger's test ( $p = 0.049$ ). Diving into subgroup evaluations, it was observed that the individuals who were given ketamine intravenously experienced a marked reduction in pain (pooled SMD=-0.39; 95% CI: -0.72 to -0.07). Those who received the drug intranasally did not display any noteworthy changes (pooled SMD = -0.10; 95% CI: -0.38 to 0.18). Among the studies, the prevalent dosage of ketamine was 0.3 mg/kg (across 5 studies) and this dosage demonstrated a discernible disparity in pain scores (pooled SMD = -0.51; 95% CI: -1.01 to -0.02). When delving into comparisons based on the control groups, it was discerned that ketamine offered improved outcomes *vis-à-vis* morphine (pooled SMD = -0.25; 95% CI: -0.45 to -0.06). Yet, when juxtaposed with fentanyl, the results were inconclusive (pooled SMD = 0.02; 95% CI: -0.38 to 0.41).

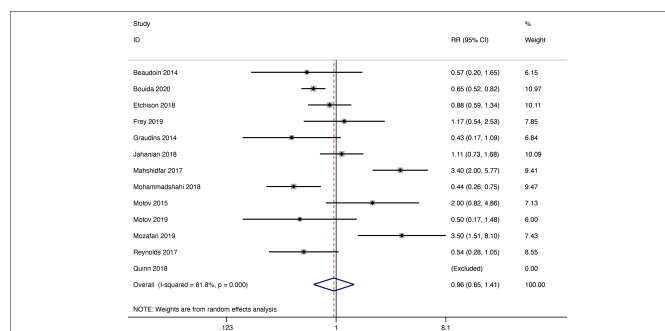
At the 45-minute mark, the combined SMD for pain scores was -0.04 (95% CI: -0.26 to 0.18;  $I^2 = 79.7\%$ ;  $n = 20$ ), suggesting that there was not a marked difference in level of pain between the ketamine-treated group and control (Figure 2C). The sensitivity analysis ruled out pronounced influences from any individual study on the combined result. The funnel plot depicted a balanced layout, confirmed by the non-significant outcome of the Egger's test ( $p=0.81$ ). On further probing with subgroup evaluations, no significant disparities were observed, be it for the intravenous method (combined SMD = -0.01; 95% CI: -0.35 to 0.32) or the intranasal method (combined SMD = -0.03; 95% CI: -0.25 to 0.19). When the analysis was anchored on the ketamine dosage, there was not any discernible advantage linked to any dosage, spanning from 0.1 to 1 mg/kg. Moreover, when the data was parsed based on the control substances, ketamine did not exhibit notable benefits against morphine (combined SMD = -0.12; 95% CI: -0.30 to 0.06), fentanyl (combined SMD = 0.14; 95% CI: -0.13 to 0.41), or even a placebo (combined SMD = 0.38; 95% CI: -0.83 to 1.59).

Between the 45-minute and 60-minute intervals, pooled estimate (SMD) for pain scores stood at -0.03 (95% CI: -0.22 to 0.17;  $I^2 = 71.3\%$ ;  $n = 16$ ) as seen in Figure 2D. The meticu-

lous sensitivity check did not point towards biases from any particular smaller study. The funnel plot was balanced in representation, a sentiment further reinforced by the non-significant outcome from Egger's test ( $p = 0.14$ ). Dissecting the results *via* subgroup analyses, no meaningful deviations were detected, be it for the intravenous method (pooled estimate = -0.04; 95% CI: -0.33 to 0.25) or the intranasal approach (pooled estimate = -0.03; 95% CI: -0.28 to 0.21). Scrutiny based on varying ketamine dosages, spanning from 0.1 to 1 mg/kg, did not exhibit a notable advantage for any specific dosage. Additionally, when the comparative lens was pivoted to the control substances, ketamine did not seem to provide discernible benefits over morphine (pooled estimate = -0.04; 95% CI: -0.31 to 0.23), fentanyl (pooled estimate = 0.08; 95% CI: -0.17 to 0.34), or even a placebo (pooled estimate = -0.22; 95% CI: -1.05 to 0.60).

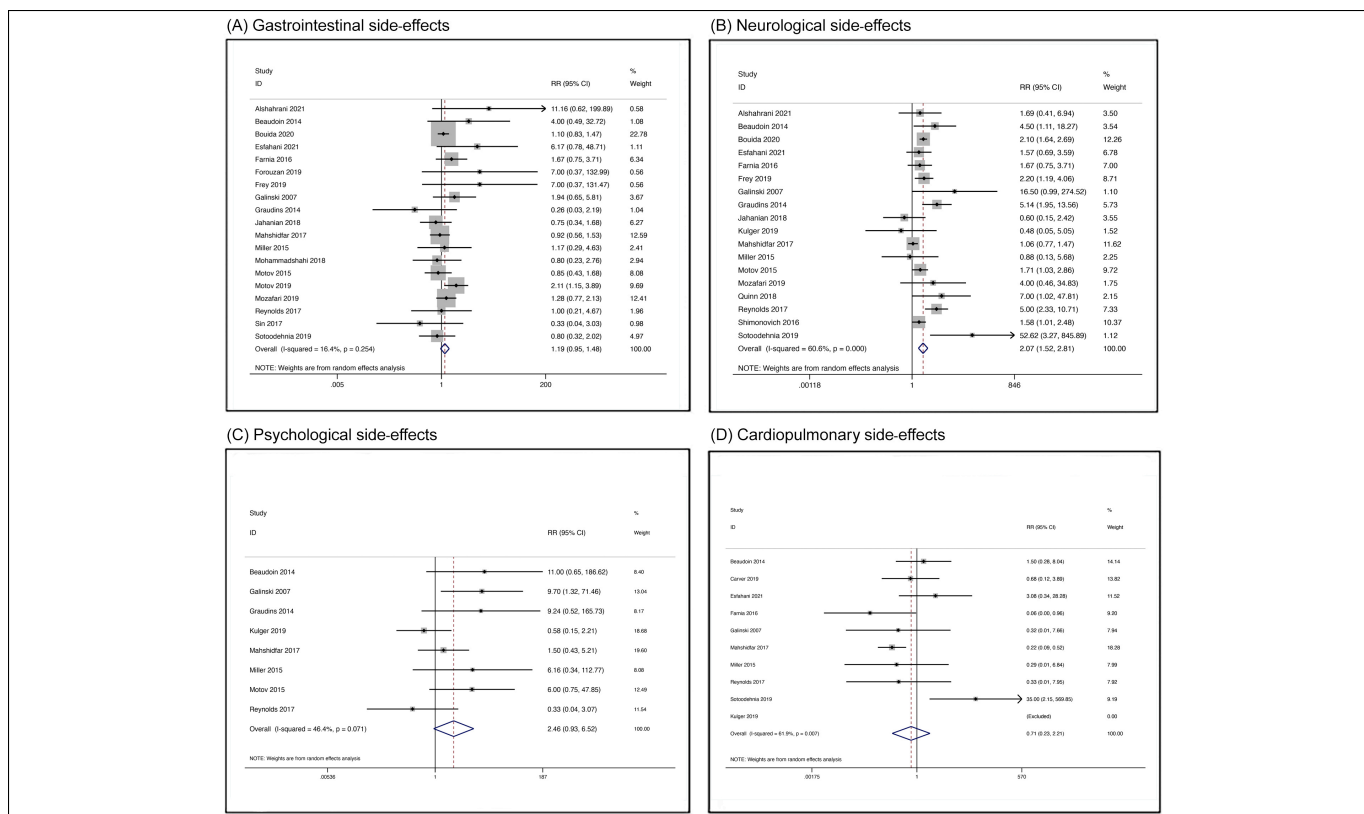
After the 60-minute mark, pooled SMD for pain scores was 0.11 (95% CI: -0.10 to 0.22;  $I^2 = 62.2\%$ ;  $n = 10$ ), as depicted in Figure 2E. Scrutiny through sensitivity analysis did not identify biases from specific smaller studies. The funnel plot demonstrated even distribution, a finding corroborated by the non-significant result ( $p = 0.76$ ). When attempting a subgroup evaluation based on the administration method, a comprehensive analysis could not be carried out. This was because only one study, specifically Mohammadshahi *et al.* (2018), utilised the intravenous approach. Hence, a combined assessment for the intranasal method was unattainable given its singular representation. Moreover, breaking down results based on varying ketamine dosages was not feasible due to the diverse dosage metrics used across the studies. When juxtaposed against control substances, ketamine did not exhibit pronounced benefits over either morphine (pooled SMD = 0.16; 95% CI: -0.09 to 0.42) or a placebo (pooled SMD = -0.08; 95% CI: -0.27 to 0.12).

The pooled RR indicating the requirement for rescue analgaesic treatment was observed to be 0.96 (95% CI: 0.65-1.41;  $I^2 = 81.8\%$ ;  $n = 13$ ), as highlighted in Figure 3. Further probing *via* sensitivity analysis did not indicate biases from any specific smaller studies. The data distribution on the funnel plot was found to be even, a conclusion further supported by the non-significant result ( $p = 0.43$ ).



**Figure 3: Need for rescue analgaesic between intervention and comparison groups.**





**Figure 4: Forest plot showing difference in adverse reaction between ketamine and control group (A) Gastrointestinal side-effects (B) Neurological side-effects (C) Psychological side-effects (D) Cardiopulmonary side-effects.**

In efforts to draw distinctions based on the administration method, the outcome remained consistent, showing no notable variance (for intravenous, RR = 1.19 with 95% CI: 0.69-2.07 and for intranasal, RR = 0.77 with 95% CI: 0.47-1.25). Dividing and analysing based on the specific doses of ketamine proved challenging due to the varying dose metrics across studies. When compared against other control agents, ketamine demonstrated favourable outcomes against a placebo (pooled RR = 0.72 with 95% CI: 0.53-0.98). However, statistically significant differences were not found when set against morphine (RR = 1.03; 95% CI: 0.51-2.09) or fentanyl (RR = 0.98; 95% CI: 0.40-2.40).

The combined RR for side effects related to the gastrointestinal system stood at 1.19 (95% CI: 0.95-1.48;  $I^2 = 16.4\%$ ;  $n = 19$ ) as depicted in Figure 4A. When broken down by the method of drug administration, the results remained statistically unchanged (with intravenous administration, RR = 1.25 and a 95% CI: 0.86-1.83; and for intranasal administration, RR = 1.15 and a 95% CI: 0.92-1.45). Evaluating based on varying ketamine doses, varying from 0.1 to 1 mg/kg, did not indicate any discernible disparities in gastrointestinal side effects. Similarly, when juxtaposed with other controls, ketamine did not exhibit a significant deviation in its side-effect profile.

The consolidated RR for neurological adverse reactions stood at 2.07 (95% CI: 1.52-2.81;  $I^2 = 60.6\%$ ;  $n = 18$ ), pointing to a notably elevated risk of these side effects in patients administered with ketamine *versus* those in the control group (Figure

4B). In a subgroup assessment, it emerged that using the intranasal administration method posed a substantially elevated risk for neurological side effects (with a pooled RR of 2.42 and a 95% CI of 1.76-3.32). In contrast, the intravenous method did not showcase a statistically noteworthy risk (having a pooled RR of 1.64 and a 95% CI of 0.96-2.79). Exploring the correlation based on the dosage of ketamine, there was a discerned heightened risk of neurological adverse reactions across all dosage levels, varying from 0.1 to 1 mg/kg. When contextualised against various control groups, it was observed that ketamine had a notably elevated risk in comparison to morphine (with a pooled RR of 1.37 and a 95% CI of 1.10-1.70) and fentanyl (with a pooled RR of 3.57 and a 95% CI of 2.30 - 5.54). However, this heightened risk was not statistically significant when juxtaposed against the placebo group, showcasing a pooled RR of 4.21 and a 95% CI ranging from 0.73 to 24.43.

The pooled RR for psychological side-effects was 2.46 (95% CI: 0.93-6.52;  $I^2 = 46.4\%$ ;  $n = 8$ ), and the RR for cardiopulmonary side effects was 0.71 (95% CI: 0.22-2.20;  $I^2 = 61.9\%$ ;  $n = 10$ ), indicating no significant difference between the two groups (Figure 4, C and D). Additional analysis using administration route, dosage, or comparison group could not be done due to lack of studies under these subgroups.

## DISCUSSION

Ketamine can be helpful, particularly in instances like patients already on high doses of opioids with a history of addiction or opioid-naïve children and adults. In addition,

ketamine acts as a unique alternate medication for managing acute onset pain with the ever-growing burden of patients in emergency departments. However, it is necessary to understand the profile of ketamine compared to opioids to identify the best approach for managing a patient with acute or sudden pain.

In total, data from 26 trials were analysed. Half of the studies had a high bias risk. This analysis demonstrated that, relative to other control groups, ketamine significantly reduced pain scores within the initial 30-minute post-infusion. An optimal efficacy was noted with a 0.3 mg/kg dose administered intravenously. When compared to morphine, ketamine presented enhanced benefits, while showing comparable advantages when compared to fentanyl. However, for durations beyond 30 minutes, ketamine's beneficial effects were similar to other therapeutic agents. Prior studies, too, had highlighted ketamine's comparable or superior pain management at both short and extended durations when set against opioids such as morphine or fentanyl.<sup>12,13,41-43</sup> Another study emphasised that the 0.3 mg/kg dose is the sweet spot for ketamine's optimal benefits.

Ketamine's effectiveness can be attributed to its ability to bind spinal receptors, enhancing the signalling induced by opioids.<sup>44</sup> It also operates as an NMDA antagonist, acting post-synaptically to diminish hyperexcitability.<sup>45</sup> This blockage of NMDA could potentially boost opioid efficacy, resulting in opioid conservation effects. Furthermore, ketamine can not only counter the adverse effects of opioids but also prevent the emergence of chronic pain due to opioid tolerance.<sup>46,47</sup> At doses that achieve full anaesthesia, ketamine can activate a spectrum of opioid receptors with diverse affinities, exhibiting a higher preference for NMDA receptors.<sup>48,49</sup>

In terms of adverse outcomes, a pronounced risk of neurological side-effects exist with ketamine when compared to opioid drugs. Prior studies also cautioned about the potential neurological implications of ketamine, especially at elevated doses. Interestingly, the heightened neurological side effects were predominantly associated with the intranasal administration. This suggested that intravenous administration might be more favourable, given its comparable side-effect profile to opioids. Other side-effects, encompassing gastrointestinal and cardiac, pulmonary, and psychological manifestations, were almost on par between ketamine and opioid categories.

This study was not without limitations. A significant proportion (half) of the incorporated studies carried a high bias risk. Notable inconsistencies were observed across the incorporated studies, which could potentially lead to biased conclusions with restricted applicability. Despite the attempt to counter this challenge through meta-regression

analyses, no discernible factors contributing to significant heterogeneity were identified.

## CONCLUSION

This review showed that ketamine can be used for acute onset pain management among patients presenting to the emergency rooms. The review also showed the optimal route and dose of ketamine for the control of acute pain (intravenous route at an optimal dose of 0.3 mg/kg) with maximal efficacy and minimal side-effects. Further studies comparing ketamine combination with various specific opioids will help clinicians to find the best combination intervention and manage the patients with the lowest complication rate and the best success rate.

## COMPETING INTEREST:

The authors declared no conflict of interest.

## AUTHORS' CONTRIBUTION:

XS, JZ: Contributed to the study conception and design, wrote the first draft.

HJ, KX, XS, JZ: Collected and analysed the data, commented on the previous versions of the manuscript.

All authors read and approved the final manuscript.

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