American Journal of Emergency Medicine 76 (2024) 140–149

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Low-dose ketamine versus morphine in the treatment of acute pain in the emergency department: A meta-analysis of 15 randomized controlled trials

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ARTICLE INFO

Article history:
Received 10 October 2023
Received in revised form 8 November 2023
Accepted 28 November 2023

Keywords:
Ketamine
Morphine
Acute pain
Meta-analysis

ABSTRACT

Objective: To compare the effectiveness and safety of ketamine and morphine in adult patients with acute pain in emergency department (ED) by using a meta-analysis method.
Methods: This study was based on the Cochrane methodology for conducting a meta-analysis. Only randomized controlled trials (RCTs) were eligible for this study, with an experimental group that received low-dose ketamine and a control group that received morphine. The participants were adults who had acute pain in the ED. The primary outcome measures were the numeric rating scale (NRS) and visual analog scale (VAS). The secondary outcome measures were the complete resolution of pain, NRS reduction ≥3 points, NRS reduction ≥50% or 60%, change of NRS score, change of VAS score, rescue analgesia, satisfaction and adverse events. Subgroup analysis was performed for studies with intravenous and intranasal administration of ketamine. The Review Manager Database was used to analyze the included studies.
Results: 15 RCTs involving 1768 patients were included. The ketamine group had lower NRS scores than morphine group at 30 min (MD, −0.77 [95% CI, −0.93 to −0.61]; $p < 0.00001$), while the morphine had better analgesic effects at 120 min after treatment (MD, 0.33 [95% CI, 0.15 to 051]; $p = 0.0003$). The subjects of complete resolution of pain in the ketamine group performed better than those in the morphine group at 15 min (RR 3.18, 95% CI 1.75 to 5.78; $p = 0.0001$). Compared with the morphine group, the ketamine group had a lower incidence of adverse events requiring intervention (RR, 0.34 [95% CI, 0.18 to 0.66]; $p = 0.001$). Subgroup analysis of intravenous ketamine showed that ketamine had lower VAS score than the morphine group at 30 min. However, also on the 30-min VAS score, intranasal ketamine analgesia was less effective than morphine.
Conclusions: Ketamine had better analgesic effects in the early stages after treatment, while morphine maintained more durable effects. Compared with morphine, ketamine had a lower incidence of adverse events requiring intervention. The results of subgroup analysis showed that intravenous administration of ketamine was more effective than intranasal administration.

1. Introduction

Acute pain is one of the most common presentations in the emergency department (ED), occurring in more than half of patient encounters [1,2]. Therefore, 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 [3,4]. Opioids are effective analgesics and are commonly used in the ED for acute pain management. Such as traumas, fractures, renal colic, burns, and abdominal pain may warrant the use of opioids [5]. Although they exert their effects in the central and peripheral nerve system to produce positive and desirable effects (analgesia, antiinflammatory properties and euphoria) [6], opioids have been associated with dose-dependent adverse effects like respiratory and central nervous system depression, nausea, vomiting, dizziness, and constipation [7].

Recent studies have found that ketamine is an effective adjunct to opioids, providing greater pain relief than morphine alone [8,9]. Ketamine alone can provide analgesia similar to that of morphine in patients with acute visceral and musculoskeletal pain, as well as for chronic painful conditions (cancer, vaso-occlusive pain crisis associated with sickle cell disease, and in patients with high opioid tolerance and/or

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https://doi.org/10.1016/j.ajem.2023.11.056
0735-6757/

opioid dependency) [10]. Balzer et al. conducted a meta-analysis of the effectiveness and safety of low-dose ketamine and morphine in acute pain in the ED in 2021 [11], included 8 randomized controlled trials (RCTs) [12-19]. They found that ketamine and morphine had similar analgesic effectiveness within 60 min of administration with comparable safety profiles, suggesting that ketamine is an effective alternative analgesic for acute pain control. Although this meta-analysis further confirms the analgesic effect of ketamine, it is not exactly consistent with the conclusions of the new and high-quality RCTs [20-27]. The effectiveness and safety of using ketamine in the ED remains unclear.

The aim of this study was to compare the effectiveness and safety of ketamine and morphine in adult patients with acute pain in ED by using a meta-analysis method. We hypothesized that, in the treatment of acute pain, the use of ketamine could improve patients' pain earlier than morphine, without increasing the occurrence of adverse events.

2. Methods

This study was based on the Cochrane methodology for conducting a meta-analysis [28]. The present study was completed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. The study protocol was registered in PROSPERO (ID: CRD42023470001).

2.1. Search strategy

The published literature was searched using the electronic MEDLINE (1950 to September 2023), AMED (1985 to September 2023), EMBASE (1974 to September 2023), CINHAL (1982 to September 2023), Cochrane Library (2023), CNKI (1994 to September 2023), Scopus (2023) and Biomed Central (2023) databases. No language or date restrictions were applied. The Medical Subject Headings (MeSH) and keyword search adopted were 'ketamine' AND 'morphine' AND 'acute pain'. The unpublished literature was searched using the electronic OpenSIGLE (System for Information on Grey Literature in Europe) database, the WHO International Clinical Trials Registry Platform, the Current Controlled Trials database, the UKCRN Portfolio Database and the National Technical Information Service database from their inception to 1 September 2023. Finally, the reference lists of research-related papers were reviewed to prevent omissions.

2.2. Inclusion and eligibility criteria

Only RCTs were eligible for this study, with an experimental group that received low-dose ketamine and a control group that received morphine. The participants were adults who had acute pain in the ED. Subgroup analysis was performed for studies with intravenous and intranasal administration of ketamine. Exclusion criteria consisted of (1) non-randomized controlled study; (2) animal study; (3) studies without control group; (4) the intervention group was not ketamine and/or the control group was not morphine; (5) studies wasn't in the ED; (6) participants were not acute pain; or (7) participants with severe comorbidities.

2.3. Study selection

Two authors (J.G., J.B.) independently searched from these databases. The titles and abstracts of the retrieved studies were reviewed independently. When there was a doubt, the full text of the study would be reviewed. The same two authors independently assessed each full study report to see whether it met the review's inclusion criteria, and its authors were contacted for more information and clarification of the data when necessary. Any disagreement was discussed with the senior authors (F.Z., J.T.). If a consensus could not be reached, the study was excluded. A list of all pertinent papers satisfying these criteria was then constructed by each reviewer to compile an agreed list of studies for inclusion.

2.4. Data abstraction

The authors designed and agreed to the data extraction form, and conducted a pilot test to ensure its consistency. Initially, two authors (J.G., Y.H.) independently extracted the data, and then reviewed them together to produce consistent and accurate data. Disagreements were resolved by consensus or consultation with the senior authors (F.Z., J.T.). The data extracted included date of publish, country, sample size, study design, subject age, sex, body mass index, interventions, the results and follow-up period.

2.5. Outcomes

The primary outcome measures were the numeric rating scale (NRS) and visual analog scale (VAS). The secondary outcome measures were the complete resolution of pain, NRS reduction ≥3 points, NRS reduction ≥50% or 60%, change of NRS score, change of VAS score, rescue analgesia, satisfaction and adverse events.

2.6. Quality assessment

To assess the methodological quality of the included studies, the authors used the modified scoring system [29], including the proper conduct of randomization, concealment of treatment allocation, the similarity of treatment groups at baseline, clinician blinding, and the description of withdrawals and dropouts. The methodological quality of each trial was scored and ranged from 0 (lowest quality) to 8 (highest quality). Any disagreement was resolved by the senior authors.

2.7. Statistical analysis

The Review Manager Database (RevMan version 5.4, Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen) was used to analyze the included studies. Continuous data for each arm in a particular study were expressed as the mean and standard deviation (SD), and the treatment effect was expressed as the mean differences. Dichotomous data for each arm in a particular study were expressed as proportions or risks, and the treatment effect was expressed as the relative risk (RR). Statistical heterogeneity was assessed using the value of I^2 and the result of the chi-squared test. A p-value of <0.1 and an I^2 value $>50\%$ were considered suggestive of statistical heterogeneity, prompting a random effects modeling estimate. Otherwise, a fixed effects approach was used. Conversely, a nonsignificant chi-squared test result (a p-value ≥ 0.1 and an I^2 value $\leq 50\%$) only suggested that there was no evidence of heterogeneity: it did not imply that there was necessarily homogeneity, as there may have been insufficient power to be able to detect heterogeneity. When the data allowed, we performed subgroup analysis of the trials.

3. Results

A total of 317 abstracts and titles were reviewed. Of these 15 satisfied the eligibility criteria and were included in the meta-analysis [13-27]. A flowchart is provided in Fig. 1. The number of patients included in these studies ranged from 40 to 300. A total of 1768 patients were enrolled in the study. The study characteristics of the selected studies were showed in Table 1. The RCTs were relatively well designed, and the quality assessment score was high for most of them, with a ranges of quality assessment score from 3 to 7 (Table 2). A funnel plot based on the most frequently cited outcome was broadly symmetrical, indicating minimal publication bias (Fig. 2). Ten of the 15 included studies provided data on rescue analgesia, and 9 dots are shown in the funnel

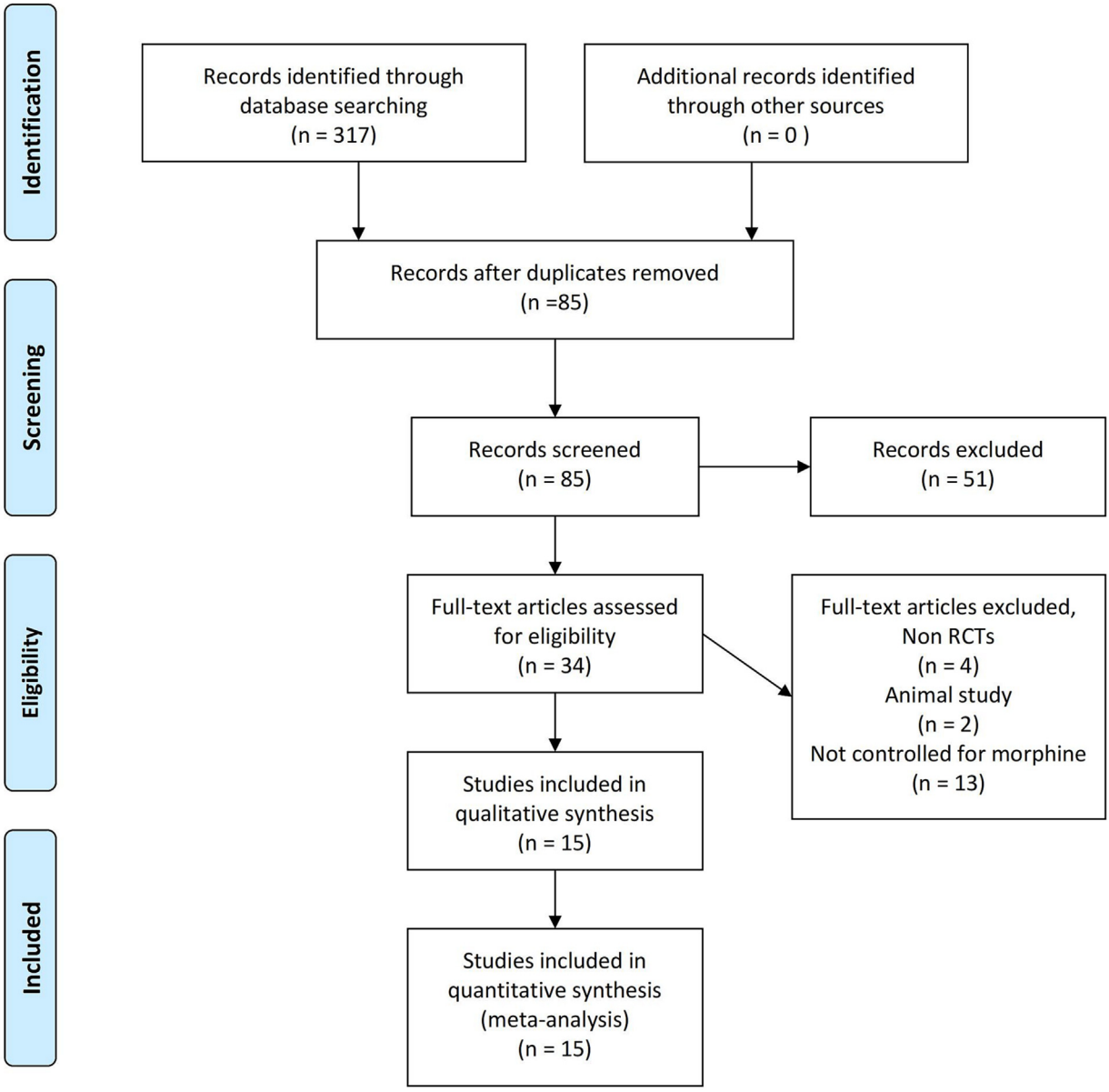

Fig. 1. Flowchart of the study selection.

plot. There are 4 on the left and 4 on the right, with a relatively even distribution.

3.1. NRS score

NRS scores were reported by two, six, five, two, five, four and five studies at 10 (Fig. 3a), 15 (Fig. 3b), 30 (Fig. 3c), 45 (Fig. 3d), 60 (Fig. 3e), 90 (Fig. 3f) and 120 (Fig. 3g) minutes after analgesia, respectively. The analysis found that at 30 min after treatment, the ketamine group had lower NRS scores than morphine group (MD, −0.77 [95% CI, −0.93 to −0.61]; $p < 0.00001$, Heterogeneity $I^2 = 25\%$; $p = 0.25$). Although there was no statistical difference between the two groups at 15 min, the ketamine group had a trend towards lower NRS scores (MD, −0.51 [95% CI, −1.02 to −0.00]; $p = 0.05$, Heterogeneity $I^2 = 65\%$; $p = 0.01$). At 120 min, morphine had a better analgesic effect (MD, 0.33 [95% CI, 0.15 to 051]; $p = 0.0003$, Heterogeneity $I^2 = 0\%$; $p = 0.54$). There was no significant difference in NRS scores between the two groups at other time points.

3.2. VAS score

There was no significant difference in VAS scores between the two groups at 5 (MD, 0.68 [95% CI, −1.39 to 2.74]; $p = 0.52$, Heterogeneity $I^2 = 90\%$; $p = 0.001$), 15 (MD, 0.74 [95% CI, −0.39 to 1.86]; $p = 0.20$, Heterogeneity $I^2 = 65\%$; $p = 0.09$), 30 (MD, 0.14 [95% CI, −0.41 to 0.69]; $p = 0.61$, Heterogeneity $I^2 = 78\%$; $p = 0.003$) and 60 min (MD, −0.05 [95% CI, −0.22 to 0.12]; $p = 0.57$, Heterogeneity $I^2 = 36\%$; $p = 0.21$) after treatment (Table 3).

3.3. Complete resolution of pain

This outcome measure was available in 2 studies (150 patients) at 15, 30, 60, 90 and 120 min after analgesia (Table 3). The subjects in the ketamine group performed better than those in the morphine group at 15 min (RR 3.18, 95% CI 1.75 to 5.78; $p = 0.0001$, Heterogeneity $I^2 = 0\%$; $p = 0.86$). However, there was no significant difference in complete resolution of pain between the two groups at other time points.

Table 1
Characteristics of the included studies.

Author	Country	Groups	Number	Age	Sex (M/F)	Interventions	Rescue analgesia protocol	Outcome	Year
Majidinejad [13]	Iran	Ketamine Morphine	63 63	35.1 ± 13.5 53.6 ± 14.3	45/18 51/12	Ketamine: IV 0.5 mg/kg Morphine: IV 0.1 mg/kg	In cases in which pain did not subside after 10 min (a decrease in pain severity ≤3), the patient received half the initial dose again	NRS, NRS reduction >3, Rescue analgesia and Adverse events	2014
Miller [14]	USA	Ketamine Morphine	24 21	31 ± 12 29 ± 10	9/15 14/7	Ketamine: IV 0.3 mg/kg Morphine: IV 0.1 mg/kg	A second dose could be given as early as 20 min after completion of the initial dose and was the same dose as the first dose	NRS, Satisfaction, Rescue analgesia and Adverse events	2015
Motov [15]	USA	Ketamine Morphine	45 45	35 ± 9.5 36 ± 10.5	15/30 17/28	Ketamine: IV 0.3 mg/kg Morphine: IV 0.1 mg/kg	If patients reported a pain NRS score of 5 or greater and requested additional pain relief, fentanyl 1 μg/kg was administered as a rescue analgesic	NRS, Complete resolution, NRS reduction ≥3, Rescue analgesia and Adverse events	2015
Shimonovich [20]	Israel	Ketamine Morphine	24 24	37.9 42.9	17/7 18/6	Ketamine: IN 1.0 mg/kg Morphine: IV 0.1 mg/kg	NA	VAS, Satisfaction and Adverse events	2016
Farnia [21]	Iran	Ketamine Morphine	20 20	39.25 ± 10.75 34.75 ± 10.71	12/8 17/3	Ketamine: IN 1.0 mg/kg Morphine: IV 0.1 mg/kg	In case of failure and no decrease in VAS scores in either group after 30 min, fentanyl was administered. The rate of fentanyl infusion was 1–2 μg/kg administered every 5 min and titrated to the effect	VAS, Rescue analgesia and Adverse events	2017
Mahshidfar [16]	Iran	Ketamine Morphine	150 150	34.4 ± 7.6 34.1 ± 7.3	126/24 123/27	Ketamine: IV 0.2 mg/kg Morphine: IV 0.1 mg/kg	Sufficient pain reduction was defined as a decrease in pain score ≥ 3. In case of insufficient pain reduction, 3 mg of intravenous morphine was injected every 5 min as a rescue analgesic	NRS, Satisfaction, Rescue analgesia and Adverse events	2017
Jahanian [17]	Iran	Ketamine Morphine	78 78	35.87 ± 7.3 36.38 ± 9.3	56/22 55/23	Ketamine: IV 0.5 mg/kg Morphine: IV 0.1 mg/kg	Achieving pain score of 3 or 50% below the initial score was the goal. In the absence of pain relief at any time of the study, half of the previous doses of the same group was administered. If the pain score remains 9 or 10, or >2 times to the administered drug, rescue analgesic (fentanyl intravenously at a dose of 1 μg/kg) was given	VAS, Rescue analgesia and Adverse events	2018
Forouzan [18]	Iran	Ketamine Morphine	68 68	33.36 ± 10.21 33.45 ± 11.3	56/12 54/14	Ketamine: IV 0.3 mg/kg Morphine: IV 0.1 mg/kg	NA	VAS, Rescue analgesia dose and Adverse events	2019
Motov [19]	USA	Ketamine Morphine	30 30	77.3 ± 8.4 77.1 ± 8.5	7/23 7/23	Ketamine: IV 0.3 mg/kg Morphine: IV 0.1 mg/kg	If patients reported a pain NRS score of 5 or greater and requested additional pain relief, fentanyl at 0.5 μg/kg was administered as a rescue analgesic	NRS, Complete resolution, NRS reduction ≥3, Rescue analgesia and Adverse events	2019
Eddie [22]	Malaysia	Ketamine Morphine	31 27	27 ± 17 25 ± 12	28/3 24/3	Ketamine: IV 0.3 mg/kg Morphine: IV 0.1 mg/kg	For participants reported of NRS score ≥ 6 and still desiring pain medication 30 min after study drug administration, investigator offered intravenous fentanyl 1–2μg/kg, maximum 100 μg, as rescue analgesia	NRS, Change of NRS, Rescue analgesia and Adverse events	2021
Esfahani [23]	Iran	Ketamine Morphine	36 37	32.5 ± 10.0 33.4 ± 10.8	30/6 29/8	Ketamine: IV 0.1 mg/kg Morphine: IV 0.05 mg/kg	NA	NRS, NRS reduction ≥50% or 60%, Rescue analgesia and Adverse events	2021
Pouraghaei [24]	Iran	Ketamine Morphine	95 89	39.39 41.27	NA	Ketamine: IN 1.0 mg/kg Morphine: IV 0.1 mg/kg	NA	NRS and Adverse events	2021
Alshahrani [25]	Saudi Arabia	Ketamine Morphine	138 140	29.1 ± 8.4 29.4 ± 7.9	80/58 82/58	Ketamine: IV 0.3 mg/kg Morphine: IV 0.1 mg/kg	NA	NRS and Adverse events	2022
Tongbua [26]	Thailand	Ketamine Morphine	37 37	74.1 ± 6.8 72.7 ± 6.0	8/29 8/29	Ketamine: IN 0.3 mg/kg Morphine: IV 0.1 mg/kg	If the research assistants reported unimproved pain score or a need for rescue therapy, 0.5 μg/kg fentanyl was administered intravenously by a nurse after consulting with the attending emergency physicians	NRS, Change of NRS, NRS reduction ≥3, Rescue analgesia and Adverse events	2022
Ziaei [27]	Iran	Ketamine Morphine	50 50	35.44 ± 12.69 32.88 ± 10.82	34/16 34/16	Ketamine: IN 1.5 mg/kg Morphine: IV 0.1 mg/kg	If the patient does not report relief of pain for at least 30 mm lower than initial pain after 30 min, 2 μg/kg of fentanyl was given in each group	VAS, Change of VAS, Rescue analgesia and Adverse events	2022

IN = Intranasal; IV = Intravenous; M/F = Male/Female; NA = Not available; NRS = Numeric rating scale; USA = United States of America; VAS = Visual analogue scale.

Table 2
Description of quality assessment of RCTs.

Author	Multicenter	Randomization	Method to generate randomization clear and appropriate	Double blind	Methods for blinding appropriate	Methods of allocation concealment	Description of withdrawal or dropout	Completeness of follow-up (%)	Total score
Majidinejad [13]	No	Yes	No	Yes	Yes	Yes	Yes	100%	6
Miller [14]	No	Yes	Yes	Yes	Yes	Yes	Yes	100%	7
Motov [15]	No	Yes	Yes	Yes	Yes	Yes	Yes	92.2%	6
Shimonovich [20]	No	Yes	Yes	No	No	No	Yes	80%	3
Farnia [21]	No	Yes	Yes	Yes	Yes	Yes	Yes	100%	7
Mahshidfar [16]	No	Yes	No	Yes	No	No	Yes	98.4%	4
Jahanian [17]	No	Yes	Yes	Yes	Yes	Yes	Yes	98.1%	7
Forouzan [18]	No	Yes	Yes	Yes	Yes	Yes	Yes	100%	7
Motov [19]	No	Yes	Yes	Yes	Yes	Yes	Yes	98.3%	7
Eddie [22]	No	Yes	Yes	No	No	No	Yes	100%	4
Esfahani [23]	No	Yes	Yes	Yes	Yes	Yes	Yes	96.1%	7
Pouraghaei [24]	No	Yes	Yes	Yes	Yes	Yes	Yes	92%	6
Alshahrani [25]	No	Yes	Yes	Yes	Yes	Yes	Yes	100%	7
Tongbua [26]	No	Yes	Yes	Yes	Yes	Yes	Yes	100%	7
Ziaei [27]	No	Yes	No	No	No	No	Yes	100%	3

Yes 1 point; No 0 point; follow-up ≥95% 1 point, follow-up <95% or unreported 0 point.
NRS = Numeric rating scale; RCT = Randomized controlled trial; VAS = Visual analogue scale.

3.4. NRS reduction ≥ 3 points

There was no significant difference in NRS reduction ≥3 points between the two groups at 15 (RR, 1.17 [95% CI, 0.94 to 1.46]; $p = 0.17$, Heterogeneity $I^2 = 0\%$; $p = 0.62$), 30 (RR, 1.08 [95% CI, 0.88 to 1.33]; $p = 0.47$, Heterogeneity $I^2 = 0\%$; $p = 0.78$), 60 (RR, 0.99 [95% CI, 0.75 to 1.30]; $p = 0.94$, Heterogeneity $I^2 = 52\%$; $p = 0.12$), 90 (RR, 0.99 [95% CI, 0.71 to 1.38]; $p = 0.96$, Heterogeneity $I^2 = 75\%$; $p = 0.02$) and 120 min (RR, 1.02 [95% CI, 0.88 to 1.20]; $p = 0.76$, Heterogeneity $I^2 = 8\%$; $p = 0.34$) after treatment (Table 3).

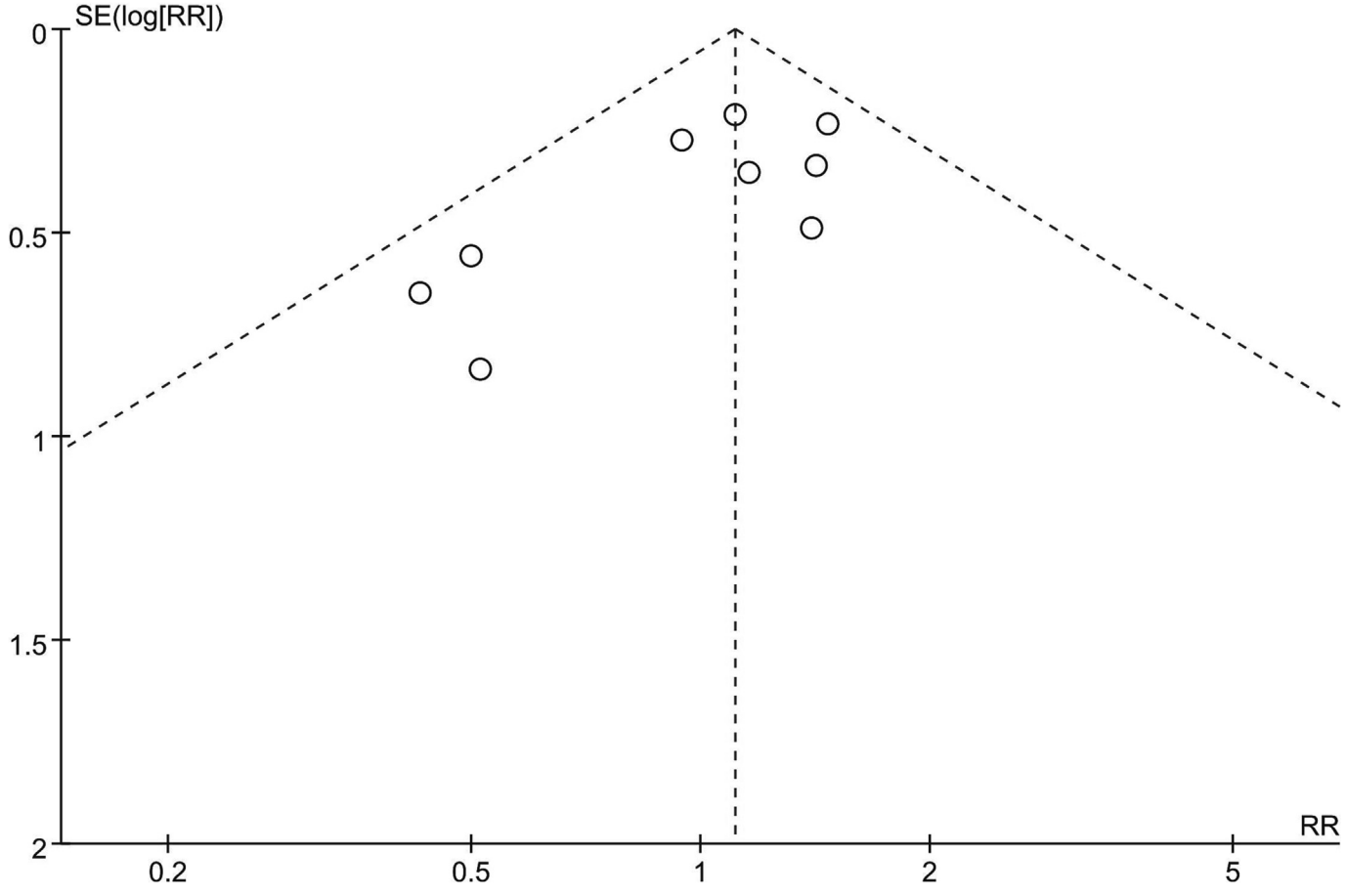

Fig. 2. Trials of ketamine vs morphine: funnel-plot of rescue analgesia.

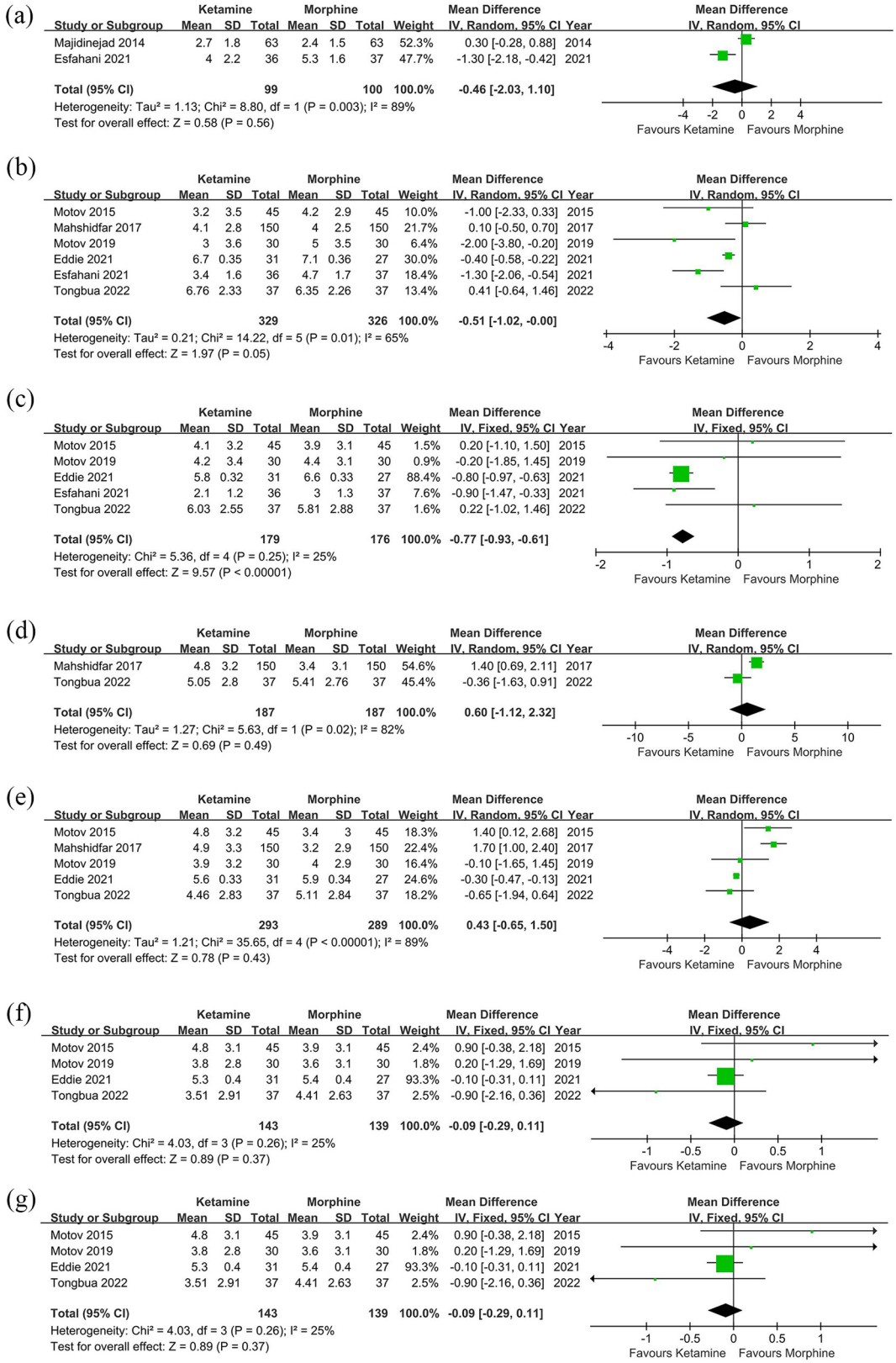

Fig. 3. a Trials of ketamine vs morphine: Forest-plot of NRS score at 10 min.
b Trials of ketamine vs morphine: Forest-plot of NRS score at 15 min.
c Trials of ketamine vs morphine: Forest-plot of NRS score at 30 min.
d Trials of ketamine vs morphine: Forest-plot of NRS score at 45 min.
e Trials of ketamine vs morphine: Forest-plot of NRS score at 60 min.
f Trials of ketamine vs morphine: Forest-plot of NRS score at 90 min.
g Trials of ketamine vs morphine: Forest-plot of NRS score at 120 min.

Table 3
Summary of other analysis results of the ketamine vs morphine group.

Other analysis	Studies	Patients (ketamine/morphine)	Retive risk or mean difference [95% CI]	Heterogeneity
VAS at 5 min	2	70/70	0.68 [−1.39, 2.74]; $p = 0.52$	$I^2 = 90\%$; $p = 0.001$
VAS at 15 min	2	70/70	0.74 [−0.39, 1.86]; $p = 0.20$	$I^2 = 65\%$; $p = 0.09$
VAS at 30 min	4	216/216	0.14 [−0.41, 0.69]; $p = 0.61$	$I^2 = 78\%$; $p = 0.003$
VAS at 60 min	3	196/196	−0.05 [−0.22, 0.12]; $p = 0.57$	$I^2 = 36\%$; $p = 0.21$
Complete resolution at 15 min	2	75/75	3.18 [1.75, 5.78]; $p = 0.0001$	$I^2 = 0\%$; p = 0.86
Complete resolution at 30 min	2	75/75	1.27 [0.70, 2.30]; $p = 0.44$	$I^2 = 0\%$; $p = 0.48$
Complete resolution at 60 min	2	75/75	0.94 [0.51, 1.72]; $p = 0.84$	$I^2 = 0\%$; $p = 0.34$
Complete resolution at 90 min	2	75/75	0.80[0.40, 1.59]; $p = 0.53$	$I^2 = 0\%$; $p = 0.92$
Complete resolution at 120 min	2	75/75	0.94 [0.50, 1.76]; p = 0.84	$I^2 = 0\%$; $p = 0.81$
NRS reduction ≥3 at 15 min	3	112/112	1.17 [0.94, 1.46]; $p = 0.17$	$I^2 = 0\%$; $p = 0.62$
NRS reduction ≥3 at 30 min	3	112/112	1.08 [0.88, 1.33]; $p = 0.47$	$I^2 = 0\%$; $p = 0.78$
NRS reduction ≥3 at 60 min	3	112/112	0.99 [0.75, 1.30]; $p = 0.94$	$I^2 = 52\%$; $p = 0.12$
NRS reduction ≥3 at 90 min	3	112/112	0.99 [0.71, 1.38]; $p = 0.96$	$I^2 = 75\%$; $p = 0.02$
NRS reduction ≥3 at 120 min	3	112/112	1.02 [0.88, 1.20]; $p = 0.76$	$I^2 = 8\%$; p = 0.34
Rescue analgesia	10	414/408	1.11 [0.89, 1.37]; p = 0.35	$I^2 = 7\%$; p = 0.38

NRS = Numeric rating scale; VAS = Visual analogue scale.

3.5. Rescue analgesia

10 studies (822 patients) reported rescue analgesia (Table 3). The number of rescue analgesia in the ketamine and morphine groups was 117 of 414 participants and 103 of 408 participants, respectively. There was no significant difference in the rescue analgesia between the two groups (RR, 1.11 [95% CI, 0.89 to 1.37]; $p = 0.35$, Heterogeneity $I^2 = 7\%$; $p = 0.38$).

3.6. Adverse events

In all, 14 trials including 1720 patients provided useful data on adverse events (Fig. 4a). The number of adverse events in the ketamine and morphine groups was 297 of 865 participants and 323 of 855 participants, respectively. There was no significant difference in adverse events between the two groups (RR, 1.13 [95% CI, 0.84 to 1.53]; $p = 0.42$, Heterogeneity $I^2 = 87\%$; $p < 0.00001$). Adverse events included

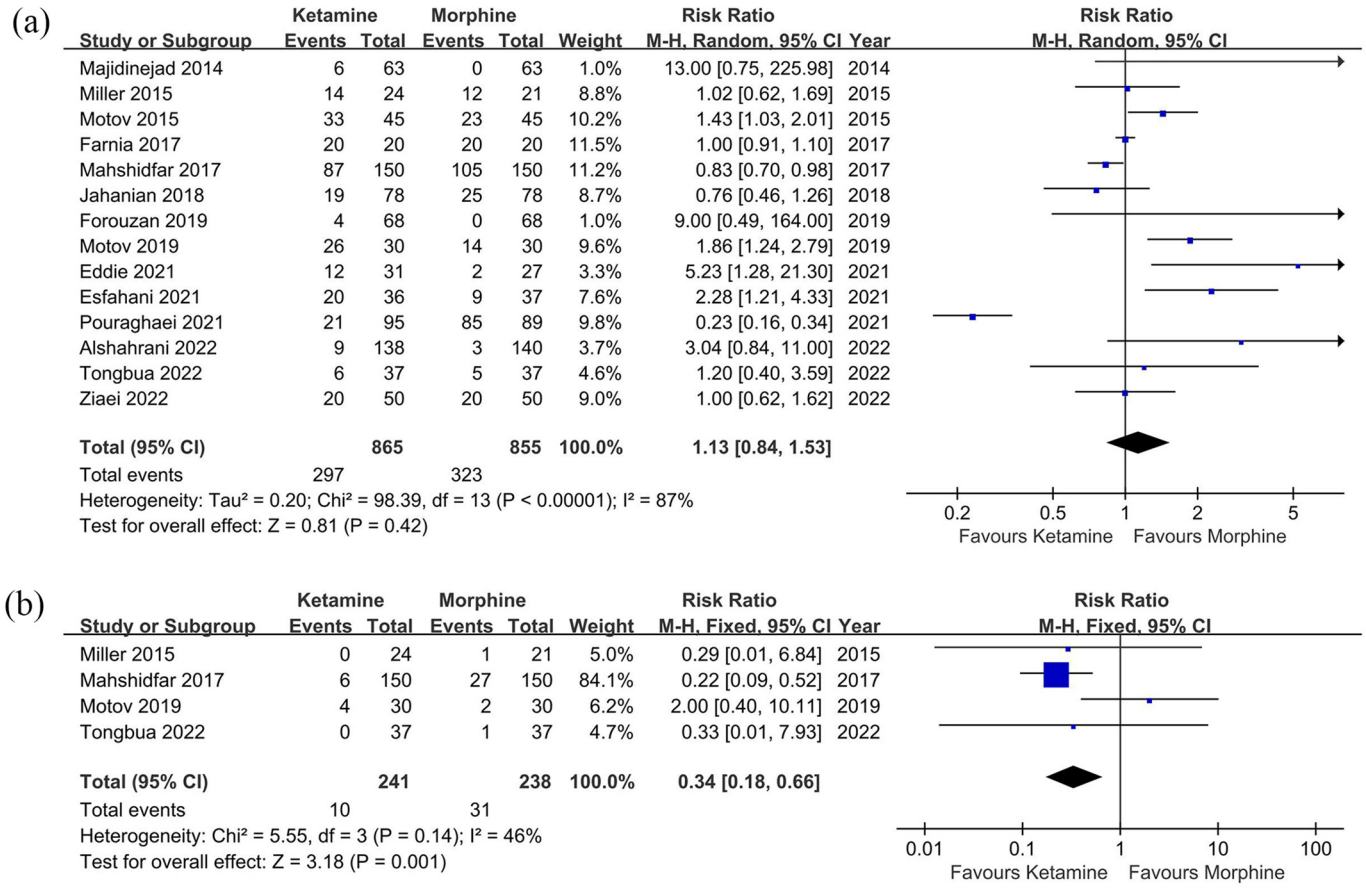

Fig. 4. a Trials of ketamine vs morphine: Forest-plot of adverse events (total). b Trials of ketamine vs morphine: Forest-plot of adverse events (require intervention).

nausea, vomiting, dizziness, fatigue, headache, mood changes, difficulty concentrating, drowsiness, confusion, dyspepsia, hallucinations, O_2 saturation < 90% or 88%, bradycardia, tachycardia, hypotension and disorientation. Most adverse effects were transient and did not require treatment. No serious or life-threatening adverse events occurred in either group; these included, but were not limited to respiratory distress, seizures, and cardiac arrest.

Only a small number of patients were given oxygen therapy and antiemetic treatment. The number of cases requiring intervention in the ketamine and morphine groups was 10 (oxygen therapy 8 and antiemetic 2) of 241 participants and 31 (oxygen therapy 28 and antiemetic 3) of 238 participants, respectively (Fig. 4b). Compared with the morphine group, the ketamine group had a lower incidence of requiring intervention (RR, 0.34 [95% CI, 0.18 to 0.66]; $p = 0.001$, Heterogeneity $I^2 = 46\%$; $p = 0.14$).

3.7. Subgroup analysis

Ketamine was administered intravenously in 10 of the 15 studies and intranasally in 5. This study conducted a subgroup analysis of the different administration of ketamine. The detailed subgroup analysis results were shown in Table 4. Subgroup analysis of intravenous ketamine showed the ketamine group had lower NRS scores than morphine group at 15 (MD, −0.65 [95% CI, −1.19 to −0.11]; $p = 0.02$, Heterogeneity $I^2 = 66\%$; p = 0.02) and 30 (MD, −0.79 [95% CI, −0.95 to −0.63]; $p < 0.00001$, Heterogeneity $I^2 = 0\%$; $p = 0.41$) minutes after treatment. At 120 min, the analgesic effect was better in the morphine group (MD, 0.34 [95% CI, 0.16 to 0.52]; $p = 0.0002$, Heterogeneity $I^2 = 0\%$; $p = 0.62$).

Subgroup analysis of intravenous ketamine found that ketamine had lower VAS score than the morphine group at 30 min (MD, −0.32 [95% CI, −0.53 to −0.10]; $p = 0.004$, Heterogeneity $I^2 = 0\%$; $p = 0.39$). However, also on the 30-min VAS score, intranasal ketamine analgesia was less effective than morphine (MD, 1.07 [95% CI, 0.34 to 1.79]; p = 0.004, Heterogeneity $I^2 = 0\%$; $p = 0.94$).

Although most adverse effects were transient and did not require treatment. However, subgroup analysis found that the incidence of adverse events was higher with intravenous ketamine than with morphine (RR, 1.50 [95% CI, 1.02 to 2.18]; $p = 0.04$, Heterogeneity $I^2 = 78\%$; $p < 0.00001$).

4. Discussion

This meta-analysis showed that ketamine had better analgesic effects in the early stages after treatment, while morphine maintained more durable effects. The ketamine group had lower NRS scores than morphine group at 30 min and the number of patients who had complete resolution of pain were higher at 15 min. Although there was no statistical difference between the two groups at 15 min, the ketamine group had a trend towards lower NRS scores ($p = 0.05$). However, by the final stage after treatment (120 min), the morphine group had lower NRS scores. There was no significant difference in adverse events between the two groups, but the ketamine group had a lower incidence of requiring intervention. The reason for this was that morphine caused more patients to be hypoxic. In subgroup analysis of NRS scores, the effectiveness of intravenous administration of ketamine remained consistent. No positive results were found due to limited data from intranasal administration studies. Subgroup analysis of the VAS scores also showed that intravenous administration of ketamine was more effective than morphine in early analgesia, but interestingly, intranasal administration was less effective than morphine in early analgesia.

Previously, one meta-analysis compared the use of ketamine and morphine in the treatment of acute pain in the ED [11], included 8 RCTs. The meta-analysis study showed that no significant difference in NRS scores between the two groups within 60 min, with morphine providing better analgesia at 60 to 120 min. There was no difference between the two groups in rescue analgesia, nausea and hypoxia and there were no results of subgroup analysis. These findings were not entirely consistent with our results. The reasons might be that they had included fewer studies, collected the NRS scores over a period of time (within 15, 15 to 30, 30 to 45, 45 to 60, 60 to 90 and 90 to 120 min), and that one included study [12] varied from its final published data [25]. Our meta-analysis included a total of 15 RCTs. Our meta-analysis included 15 RCTs, collected data only at one point in time, and excluded data published by Alshahrani et al. in 2019.

Ketamine is a highly lipophilic molecule with rapid distribution and immediate passage through the central nervous system. It has low plasma protein binding, ranging from 10% to 50%, an alpha half-life of 2 to 4 min and a beta half-life of 2 to 4 h [30,31]. This might be the reason why in our study it had better analgesic effects in the early stages.

Table 4
Subgroup analysis of intravenous and intranasal administration of ketamine.

Outcome or subgroup	Studies	Patients (ketamine/ morphine)	Retive risk or mean difference [95% CI]	Heterogeneity	Outcome or subgroup	Studies	Patients (ketamine/ morphine)	Retive risk or mean difference [95% CI]	Heterogeneity
NRS at 15 min					VAS at 30 min				
IV	5	292/289	−0.65 [−1.19, −0.11]; $p = 0.02$	$I^2 = 66\%$; p = 0.02	IV	2	146/146	−0.32 [−0.53, −0.10]; p = 0.004	$I^2 = 0\%$; p = 0.39
IN	1	37/37	0.41 [−0.64, 1.46]; p = 0.44	Not applicable	IN	2	70/70	1.07 [0.34, 1.79]; p = 0.004	$I^2 = 0\%$; $p = 0.94$
NRS at 30 min					VAS at 60 min				
IV	4	142/139	−0.79 [−0.95, −0.63]; $p < 0.00001$	$I^2 = 0\%$; $p = 0.41$	IV	2	146/146	−0.07 [−0.25, 0.10]; p = 0.41	$I^2 = 0\%$; $p = 0.50$
IN	1	37/37	0.22 [−1.02, 1.46]; $p = 0.73$	Not applicable	IN	1	50/50	0.80 [−0.24, 1.84]; $p = 0.13$	Not applicable
NRS at 60 min					Rescue analgesia				
IV	4	256/252	0.67 [−0.62, 1.96]; $p = 0.31$	$I^2 = 91\%$; p < 0.00001	IV	7	307/301	1.19 [0.93, 1.52]; $p = 0.16$	$I^2 = 8\%$; $p = 0.37$
IN	1	37/37	−0.65 [−1.94, 0.64]; $p = 0.32$	Not applicable	IN	3	107/107	0.90 [0.58, 1.39]; $p = 0.64$	$I^2 = 7\%$; p = 0.34
NRS at 90 min					Adverse events (Total)				
IV	3	106/102	−0.07 [−0.27, 0.13]; p = 0.50	$I^2 = 17\%$; $p = 0.30$	IV	10	663/659	1.50 [1.02, 2.18]; $p = 0.04$	$I^2 = 78\%$; p < 0.00001
IN	1	37/37	−0.90 [−2.16, 0.36]; p = 0.16	Not applicable	IN	4	202/196	0.72 [0.14, 3.64]; $p = 0.69$	$I^2 = 99\%$; p < 0.00001
NRS at 120 min					Adverse events (Require intervention)				
IV	4	244/242	0.34 [0.16, 0.52]; p = 0.0002	$I^2 = 0\%$; p = 0.62	IV	3	204/201	0.50 [0.10, 2.51]; $p = 0.40$	$I^2 = 64\%$; $p = 0.06$
IN	1	37/37	−0.49 [−1.87, 0.89]; $p = 0.49$	Not applicable	IN	1	37/37	0.33 [0.01, 7.93]; p = 0.50	Not applicable

IN = Intranasal; IV = Intravenous; NRS = Numeric rating scale; VAS = Visual analogue scale.

Bioavailability and duration of action vary depending on the route of administration. With intravenous administration, bioavailability is 100% and maximum effect is achieved within 1 to 2 min [32-34] and maximum effect is achieved within 20 to 120 min [33]. Intranasal administration shows a bioavailability of 35 to 50% [35-37], an analgesic effect with onset of action within 10 min, a time-to-peak effect of 10 to 14 min [38] and a duration of up to 60 min [39]. These reasons might contribute to the less duration of effective analgesia with ketamine than morphine, especially when intranasal administration. In general, current evidence suggests that ketamine in analgesic doses has a better safety profile than opioids [40]. This conclusion is also reflected in our meta-analysis. In addition, effective and safe dosages of ketamine remain the focus of current discussions. The optimal analgesic dosage of ketamine varies widely in the literature, ranging from 0.15 to 0.5 mg/kg [33]. Doses above 0.3 mg/kg can lead to psychomimetic symptoms, and 0.5 mg/kg is considered a subdissociative dose and is associated with a higher rate of adverse events [41-44]. Many authors define effective and safe dosages as 0.15 to 0.3 mg/kg bolus, 0.15 to 0.3 mg/kg/h continuous infusion and 1 mg/kg intranasal administration [33]. Even so, given the high social risk of the drug, a high threshold of attention needs to be maintained and its use controlled [45-47].

In this meta-analysis, only RCTs were eligible, and only data from one experimental group that used of ketamine and a control group that received morphine were extracted from a multigroup comparison study. Significant heterogeneity among the included studies was demonstrated when the the NRS scores (10, 15, 45 and 60 min), NRS scores (5, 15 and 30 min), NRS reduction ≥3 points (60 and 90 min) and adverse events were evaluated. This phenomenon could not be well explained by the differences in the treatment protocols, enrolled patients or interventions in each study, and could not be simply considered to be caused by one or two studies. Rather, the authors of this study believed that the sample size differences, patient characteristics variations, inclusion and exclusion criteria diversity, differences between treating centers in terms of management protocols and logistics, and different strategies for measuring outcomes may be responsible for such heterogeneity. For these results with significant heterogeneity, we chose the random effects approach in this meta-analysis. Even so, the reliability would still be affected.

Limitations of this meta-analysis include the small sample size, nonmulticenter study and different causes of acute pain in the ED and the significant heterogeneity in the NRS scores (10, 15, 45 and 60 min), NRS scores (5, 15 and 30 min), NRS reduction ≥3 points (60 and 90 min) and adverse events. In addition, no sufficient data were available to analyze the change of NRS score, change of VAS score or satisfaction.

5. Conclusion

Ketamine had better analgesic effects in the early stages after treatment, while morphine maintained more durable effects. Compared with the morphine group, the ketamine group had a lower incidence of adverse events requiring intervention. The results of subgroup analysis showed that intravenous administration of ketamine was more effective than intranasal administration.

Ethical approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Funding

Dr. Jixiang Tan received grant support from the Basic Science and Cuttingedge Technology Research Projects of Chongqing Science and Technology Commission (Grant No. cstc2020jcyj-msxmX0336).

Author contributions

Conceived and designed the study: JG, JT; selected the references: JG, JB; extracted the data: JG, YH; analyzed and interpreted the data: YH, JT, FZ, JB; wrote the paper: JG; provided critical revisions: FZ, JT; approved the final version of the manuscript: FZ, JT.

CRediT authorship contribution statement

Juan Guo: Writing – original draft, Resources, Investigation, Data curation, Conceptualization. **Fei Zhao:** Writing – review & editing, Validation, Methodology, Investigation. **Jinglan Bian:** Visualization, Software, Project administration. **Yunlong Hu:** Formal analysis, Data curation. **Jixiang Tan:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors report no conflicts of interest and alone are responsible for the content and the writing of the article.

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