Review Article

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Efficacy of ketamine in the treatment of migraines and other unspecified primary headache disorders compared to placebo and other interventions: a systematic review

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Background: Migraine headaches are the second leading cause of disability worldwide and are responsible for significant morbidity, reduction in the quality of life, and loss of productivity on a global scale. The purpose of this systematic review and meta-analysis was to evaluate the efficacy of ketamine on migraines and other primary headache disorders compared to placebo and other active interventions, such as midazolam, metoclopramide/diphenhydramine, and prochlorperazine/diphenhydramine.
Methods: An electronic search of databases published up to February 2021, including Medline via PubMed, EMBASE, Web of Science, and Cochrane Library, a hand search of the bibliographies of the included studies, as well as literature and systematic reviews found through the search was conducted to identify randomized controlled trials (RCTs) investigating ketamine in the treatment of migraine/headache disorders compared to the placebo. The authors assessed the risk of bias according to the Cochrane Handbook guidelines.
Results: The initial search strategy yielded 398 unduplicated references, which were independently assessed by three review authors. After evaluation, this number was reduced to five RCTs (two unclear risk of bias and three high risk of bias). The total number of patients in all the studies was 193. Due to the high risk of bias, small sample size, heterogeneity of the outcomes reported, and heterogeneity of the comparison groups, the quality of the evidence was very low. One RCT reported that intranasal ketamine was superior to intranasal midazolam in improving the aura attack severity, but not duration, while another reported that intranasal ketamine was not superior to metoclopramide and diphenhydramine in reducing the headache severity. In one trial, subcutaneous ketamine was superior to saline in migraine severity reduction; however, intravenous (I.V.) ketamine was inferior to I.V. prochlorperazine and diphenhydramine in another study.
Conclusion: Further double-blind controlled studies are needed to assess the efficacy of ketamine in treating acute and chronic refractory migraines and other primary headaches using intranasal and subcutaneous routes. These studies should include a long-term follow-up and different ketamine dosages in diagnosed patients following international standards for diagnosing headache/migraine.

Keywords: Ketamine; Meta-Analysis; Migraine; Primary Headache Disorder; Systematic Review.

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INTRODUCTION

Primary headache (HA) is the classification descriptor of a HA or HA disorder not caused by another acute or chronic underlying disorder [1]. The primary HAs include migraine, tension-type headache, trigeminal autonomic cephalalgias, and other primary HA disorders [1]. Primary HAs comprise two-thirds of all HA diagnoses in the elderly [2], and every year, primary HAs affect nearly three billion adults [3].

Migraine is a common primary HA disorder responsible for global morbidity, diminution in the quality of life, and is the second leading cause of disability worldwide [4]. Renowned for incapacitating hemi-cranial pain, its clinical evolution from onset to resolution manifests in a phasic array of noxious and varied debilitating neurological symptoms (Table 1) [1]. Migraine and other primary HAs are responsible for a significant decrease in work production [5], affecting one in four homes, one in five women, one in sixteen men, and one billion people worldwide [4]. An estimated 23.6 million Americans suffer from migraines [6], and 15% of Americans aged 18 years or older experience chronic migraine [7]. Notably, 10% of all adults continue to endure temporary and significant functional disability and impairment daily due to migraines [8].

Acute primary HA pain is managed with several types of medications, including non-steroidal anti-inflammatory drugs (NSAIDs), dopamine receptor antagonists, corticosteroids, ergots, triptans, and opiates [5]. Triptans are considered as first-line medications for the management of moderate-to-severe migraine HA pain [9].

Ketamine is an N-methyl-D-aspartate receptor (NMDAR) antagonist that acts on the central nervous system (CNS) and acts on other CNS receptors [10]. The water and lipid solubility of ketamine allows for good bioavailability and multiple administration routes, including the intravenous (I.V.), intramuscular, oral, rectal, subcutaneous (s.c.), epidural, and intranasal routes [10]. The side effects depend on the administration route, speed, and dosage, and include laryngeal spasms, transient apnea [10,11], gastrointestinal [10,12], cardiovascular effects [12], hallucinations [10], dissociative anesthesia [10], and repeated anesthesia and analgesia leading to tolerance [10]. Previous reports link ketamine with an intraocular pressure increase and nystagmus [12], as well as hypertension and supraventricular tachycardia in patients with hyperthyroidism or taking thyroxine [10,12]. The other reported side effects include hyperreflexia, muscle hypertonicity, transient clonus, transient rash, agitation, anxiety, chest pain, palpitations, rhabdomyolysis, flashbacks, delirium, dystonia, psychosis, schizophrenic- like symptoms, dizziness, seizures, and paranoia [12]. The anesthetic effects of ketamine are primarily due to NMDAR inhibition, where cell depolarization-triggered magnesium ion loss activates NMDAR [12], allowing for the non-competitive binding of ketamine at the

Table 1. Primary migraine phase progression and associated clinical symptoms [1]

Phase of migraine	Clinical symptoms	Duration
Prodromal/Premonitory	Hyperactivity, hypoactivity, emotional changes, repetitive yawning, difficulty concentrating, urinary frequency, fluid retention, stiff neck/pain, thirst, or food cravings.	Starts up to 48 h prior to HA
Aura (not present in HA without aura)	25% of migraineurs have aura; Visual and sensory disturbance, paresthesia, dizziness, confusion, aphasia (motor or brainstem), or retinal symptoms characterized by gradual development.	Less than 1 h before HA
Headache	Recurrent increasing hemi-cranial pulsating pain (moderate-severe), sensitivity/aggravation to light, noise, odors, and physical activity. Nausea vomiting, blurred vision and cognitive impairment.	Four hours up to 3 d
Postdrome	Hyperactivity, hypoactivity, depression, fatigue, irritability, tiredness, weariness, euphoria, hangover type feeling.	May follow resolution, up to 48 h

Abbreviations: HA, headache.

magnesium binding site, thereby reducing the frequency and duration of the channel mean open time [12]. Additionally, evidence suggests that the inhibition of hyperpolarization-activated cyclic nucleotide-gated channels by ketamine and its effect on the opioid receptors may also contribute to its overall anesthetic impact [13].

Acute migraine HA accounts for 3% of all emergency department (ED) visits annually [7]. Despite using first-line pharmaceutical options for the acute management of these primary HAs, such as NSAIDs, acetaminophen, triptans, and combined regimens [14], the patients still present to the ED with inadequate relief from symptoms [15] or experience side effects resulting from the treatment. The reported side effects include gastrointestinal disturbances, fatigue, dizziness, chest discomfort, somnolence, and nausea [14]. Ketamine has shown positive results in other pain conditions [16]. Therefore, there is interest in evaluating the novel therapeutic options for primary HA management to improve the quality of life, reduce the strain on EDs [7], and reduce lost work production [5]. Guirimand et al. [17] noted that the wind-up phenomenon is associated with NMDAR activation, and ketamine attenuates this response. In a small case review (n = 6) Lauritsen et al. [18], showed that all patients with refractory migraine achieved adequate pain relief with ketamine.

This systematic review and meta-analysis aimed to determine the efficacy of ketamine compared to active intervention or placebo as a therapeutic agent for migraines and other primary HAs.

METHODS

1. Research question

This systematic review adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [19], and the protocol was registered with PROSPERO #CRD42021232591. The PICOS question was:

- Population: Patients with migraine or other primary HAs.
- Intervention: Ketamine (all routes of administration).
- Comparison: Placebo or other active intervention.
- Outcomes: HA frequency and pain intensity, aura severity and duration, maximal duration of relief, need for rescue medications, need for further admissions to the ED or visits to the physician for further treatment, quality of life or satisfaction rates, and functional disability.
- Setting: EDs, outpatient department, at home/community.

2. Inclusion and exclusion criteria

The studies were limited to human studies of randomized controlled trials (RCTs) on the efficacy of ketamine in patients with migraines or other primary HA compared to any active or passive intervention. The manuscripts written in languages other than English, pilot studies, open-label studies, reviews, systematic reviews, meta-analyses, commentaries/editorials, and abstracts were excluded.

3. Search methods for identification of studies

The following electronic databases were searched first on March 12, 2020 and subsequently repeated on February 1, 2021: MEDLINE via PubMed (1950 to February 1, 2021), Web of Science (1864 to February 1, 2021), Cochrane Library (up to February 1, 2021), and EMBASE (up to February 1, 2021). The search strategies for each database are presented in Table 2. All records were imported into the Mendeley software to remove duplicates. The reference lists of all the eligible trials and reviews/systematic reviews were manually searched for additional studies. The authors were not contacted for additional unpublished studies.

4. Data collection and analysis

The studies identified by the aforementioned PICOS search were reviewed by the investigators (N.C., M.J., S.M.) for inclusion/exclusion after the duplicates were

Table 2. Electronic database search strategies

Electronic database	Search strategy
MEDLINE via PubMed (searched up to 3/12/2020); re-run on 2/1/2021 search strategy:	Search term inputs: (ketamine OR esketamine OR s-ketamine) AND (migraine OR HA) Limiting filters: Species = "Humans" "Article types" = "Clinical trial" OR "Article types" = "Randomized Controlled Trial" OR "Article types" = "Review" OR "Article types" = "Systematic Reviews" Result search on 3/12/2020: 46 articles Additional records found on 2/1/2021: 4
The Web of Science (searched up to 3/12/2020); re-run on 2/1/2021 search strategy:	Search term inputs: TOPIC: ((ketamine OR esketamine OR s-ketamine)) AND TOPIC: ((migraine OR HA)) Result: 125 articles Refined by: DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR REVIEW) Result search on 3/12/2020: 104 articles Additional records found on 2/1/2021: 14
The Cochrane Library (searched up to 3/12/2020); re-run on 2/1/2021 searchstrategy	Search term inputs: #1: (ketamine OR esketamine OR s-ketamine) #2: (migraine OR HA) #3: #1 AND #2 Result search on 3/12/2020: 164 Articles; 140 Trials; 24 Cochrane reviews Additional records found on 2/1/2021: 13 Trials
EMBASE (searched up to 3/12/2020); re-run on 2/1/2021 search strategy:	Search term inputs: #1: 'ketamine'/exp OR ketamine OR 'esketamine'/exp OR esketamine OR 's ketamine'/exp OR 's ketamine' #2: ' HA ' OR 'migraine' #3: #1 AND #2 #4: #3 AND ('meta-analysis'/de OR 'practice guideline'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) Result search on 3/12/2020: 240 articles Additional records found on 2/1/2021: 27

Abbreviations: HA, headache.

removed. If the three investigators did not agree on inclusion/exclusion, the full article was reviewed. If the consensus was not met after reviewing the full article, a fourth author (R.E.) was queried to categorize the study. The reference sections of all the included studies, reviews, and systematic reviews from the original search were reviewed by the investigators (N.C., M.J., S.M.) for any additional relevant references that met the inclusion criteria. Any new reference was reviewed by three investigators and was categorized by the same inclusion/exclusion criteria. If the investigators disagreed on categorization, the fourth investigator (R.E.) was consulted.

5. Data extraction and management

Each investigator (N.C., M.J., S.M.) individually extracted the relevant data from the full texts of all the eligible RCTs. The relevant data included the study design, recruitment period, patient demographics, inclusion and exclusion criteria, intervention and control group characteristics, methods of intervention, sample size, outcomes measured, and the results from both the groups. Any disagreement with the data and information extracted between the three authors (N.C., M.J., S.M.) was resolved by consensus with a fourth author (R.E.).

6. Assessment of the risk of bias in included studies

The three reviewers individually (N.C., M.J., S.M.) completed a risk of bias assessment, followed by a consensus and reviewed by a fourth author (R.E.), as part of the data extraction process, and in accordance with the approach described in the Cochrane Handbook [19].

7. Statistical analyses

The outcomes reported as medians and interquartile range (IQR) as (q1, q3) with q1 the 25% quartile and q3 the 75% quartile were converted to mean and standard deviation (SD) using the following formula: mean = (q1

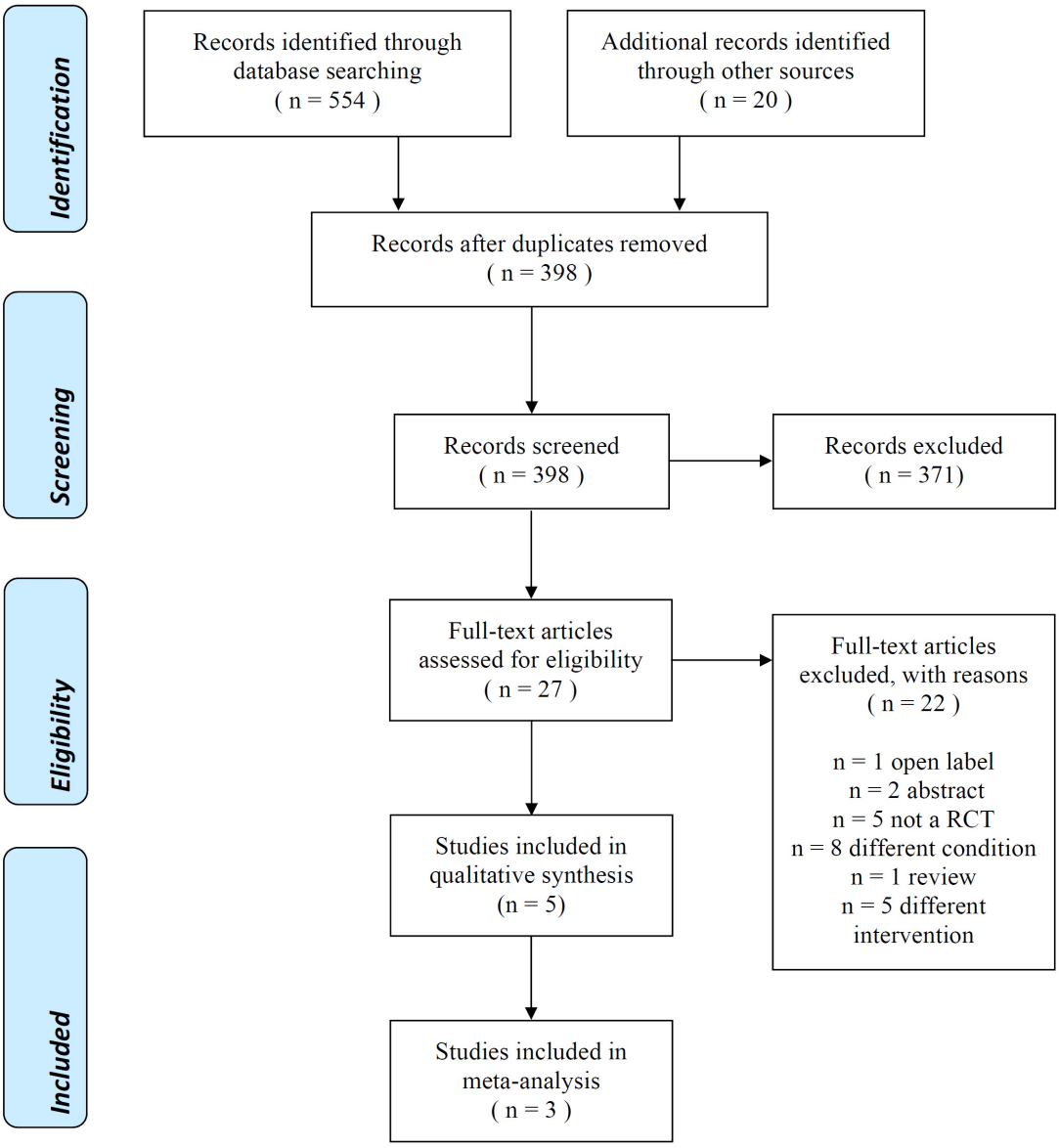

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

+ median + q3)/3; SD = (q3 − q1)/1.35.

Due to the heterogeneity of the comparison groups, the subgroup analyses for each outcome (pain intensity, satisfaction scores, and the need for rescue medications) and for each comparison group were undertaken. For differences in the pain intensity reduction from baseline (0−100 scale) and the differences in the post-treatment satisfaction score, the treatment effects were expressed as the difference in means (DM) with 95% confidence intervals (CI). For the number of patients in need of rescue medications, the treatment effects were expressed as risk ratios (RR) with 95% CI. The statistical heterogeneity was tested using the Cochran's Q test [20] and the I2 statistic [21]. The estimates of effect were combined with a random-effects model if there was heterogeneity (Q test $P < 0.10$) or with the fixed-effect model otherwise. All statistical analyses were performed using the Comprehensive Meta-Analysis version 3 software (Biostat, Englewood, NJ, USA). Due to the small number of studies, sensitivity analyses for low risk of bias studies could not be conducted, nor a funnel plot to assess for publication bias.

8. Quality of the evidence

Quality of evidence assessment was conducted according to the Cochrane Collaboration and GRADE Working Group [19].

RESULTS

1. Results of the search

The initial search strategy through database searching yielded 554 references and 20 additional records identified through other sources up to 3/12/2020. After the duplicates were removed, 398 references were scanned and reduced to 27 relevant manuscripts, which were searched for full-text and analyzed for inclusion. A total of five manuscripts were included in this study. The main reasons for exclusion were that the study was open-label (n = 1), abstract only (n = 2), not an RCT (n = 5), different conditions (n = 8), a review (n = 1), and a different intervention than ketamine (n = 5). All four databases were searched again on 2/1/2021, and no relevant results were found. The PRISMA flowchart provides a summary of the results (Fig. 1).

2. Included studies

A total of five publications were eligible for the qualitative analysis, as shown in Table 3, including three double-blind RCTs [22-24], one single-blind RCT [25], and one double-blind, randomized crossover trial [26].

1) Diagnosis of HA

Three studies [22,23,26] included patients diagnosed with migraine (refer to Table 3 for specific diagnoses and criteria). Two studies enrolled patients at the ED with unspecified primary HAs [24,25] (Table 3).

2) Population

The studies included men and women patients, and the age of the participants ranged from a minimum of 18 [22] to 65 years old [26]. The number of participants ranged from 17 [26] to 54 [24]. RCTs were conducted in the United States of America [23-25], the UK, and Italy [22,26]. The exclusions from the studies were often due to medical conditions, pregnancy, trauma, prior adverse drug reactions, history of psychiatric illness, and abnormal vital signs.

3) Interventions

- Intranasal ketamine was compared to:
  - o intranasal midazolam [22] or,
  - o intranasal saline plus I.V. metoclopramide and diphenhydramine [25].
- I.V. ketamine was compared to I.V. saline [23].
- I.V. ketamine and ondansetron with saline were compared to I.V. prochlorperazine plus diphenhydramine and saline [24].
- S.c. ketamine was compared to saline s.c. in a crossover fashion [26].

To achieve blinding and/or facilitate drug delivery, saline was administered to the ketamine groups [23-26] and control groups [23-26]. To mitigate the common side effects of the primary medication, the ketamine group also received ondansetron intravenously [24], and the control group received diphenhydramine [24,25].

4) Length of treatment and follow-up times

In one study [25], the treatment was administered intranasally with the option of a repeat dose 30 min later, and a follow-up was carried out 48-72 h post-ED treatment. In another study [24], the treatment was administered by the I.V. route over 2 min, and the follow-up was completed at 24-48 h post-treatment.

In one migraine study [22], the length of observation was 1 h following the intranasal administration of treatment for the inpatient arm. The outpatient treatment arm was rendered at the onset of aura with three attacks treated with the spray and three without the spray, with data being recorded every half hour until the aura symptoms subsided; no follow-up data were disclosed. In another RCT [26], the treatment was given by the s.c. route in one single administration in the acute trial with

Table 3. Summary of eligible studies

Reference	Year, Country, N, Gender	Age (mean ± SD, range in years)	Interventions, sample size per group (randomized)	HA Diagnosis	Study Type/ Risk of bias
MIGRAINE WITH OR WITHOUT AURA					
Afridi, et al. [22]	2013, UK, N = 18 4M/14F	ketamine: 35 ± 10.1 y (18-48) midazolam: 39 ± 7.19 y (32-57)	• 25 mg intranasal ketamine (n = 15) • 2 mg intranasal midazolam (n = 14)	• Hemiplegic migraine or migraine with probable aura ICHD 2004 [43] • None of the patients were related and all had been fully investigated with blood tests and imaging for secondary mimics of aura. • Aura duration of at least 3 hours	DBRCT/ HIGH
Etchison, et al. [23]	2018, USA, N = 34 8M/26F	34 ± 11.8 y (18-65)	• 0.2 mg/kg I.V. ketamine (n = 16) • 0.9% I.V. saline (n = 18)	• Meet ICHD 3rd edition criteria (2013) [44] for one of the following: (a) Migraine without aura (ICHD 1.1) (b) Migraine with aura (ICHD 1.2) (c) Probable migraine with (ICHD 1.5.2) or without aura (ICHD 1.5.1)	DBRCT/ UNCLEAR
Nicolodi, and Sicuteri [26]	1995, Italy, N = 34 18M/16F	Trial #1: 32 ± 8.4 y (21-53) Trial #2: 36 ± 10.7 y (22-56)	Trial #1 (n = 17) Crossover • ketamine hydrochloride (80 μg/kg) s.c. • saline (0.9% NaCl) s.c. Trial #2 (n = 17) Crossover • Daily ketamine (80 /kg s.c. injection/3x day) • 0.9% NaCl s.c. for 3 weeks • wash-out period = 2 weeks	• Patients suffering from migraine without aura [45]	DBR crossover /UNCLEAR
UNSPECIFIED PRIMARY HA					
Benish, et al. [25]	2019, USA, N = 53 16M/37F	ketamine: mean: 35 y (27-43) Controls: mean: 31 y (25-42)	• Intranasal ketamine + I.V. saline (n = 27) • Intranasal saline + I.V. metoclopramide and diphenhydramine (n = 26)	• Adults (18-65 y) with HA at ED. • HA believed to be primary HA syndrome severe enough to require parenteral meds • Exclusion criteria: 2nd HA symptoms • Self-reported severity 5 or greater (0-10)	Single blinded RCT/ HIGH
Zitek, et al. [24]	2018, USA, N = 54 12M/42F	ketamine: 32 ± 10.3 y (18-58) Controls: 37 ± 10.4 y (18-58)	• 0.3 mg/kg I.V. ketamine + I.V. 4 mg ondansetron + I.V. saline (n = 25) • I.V. 10 mg prochlorperazine + 25 mg diphenhydramine + I.V. saline (n = 29)	• Adults 18-65 presenting to ED with primary HA • Normal neurologic examination	DBRCT/ HIGH

Abbreviations: DBRCT, double-blinded randomized controlled trial; ED, emergency department; F, female; HA, headache; ICHD, International Classification of Headache Disorders; I.V., intravenous; M, male; N, total sample size; n, sample size per group; RCT, randomized controlled trial; s.c., subcutaneously; SD, standard deviation.

follow-up at 4 h, and in the chronic HA patients, s.c. administration three times a day for three weeks with follow-up three weeks later was reported. Finally, in one trial [23], the treatment was administered over one minute by slow I.V. push, and the data were recorded over a 60 min period during which participation in the study was completed.

5) Setting

The inclusion criteria for three studies [23-25] were adults presenting to the ED with a chief complaint of migraine or HAs. Two studies [22,26] enrolled patients at university research HA centers with the treatment completed at home in one study [22].

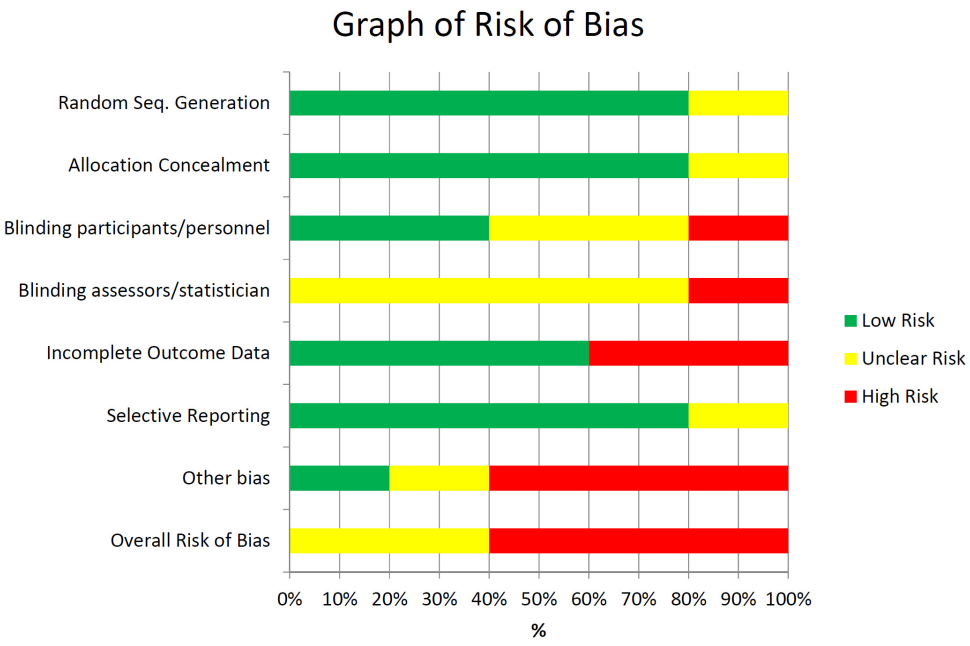

Fig. 2. Summary of risk of bias of eligible studies

6) Rescue medications

The rescue medications were used to control HA in three studies [23-25] in the ketamine and control groups. In a study by Afridi et al. [22], the use of ergotamine and triptans was prohibited; however, migraine preventive medication use of valproate, propranolol, flunarizine, and pizotifen was permitted in four unspecified patients. Additionally, 12 other patients maintained the regular use of ibuprofen, paracetamol/acetaminophen (seven patients in the control group, five in the ketamine group) [22]. Nicolodi and Sicuteri did not permit the use of any medications for seven days prior to the acute trial arm of their study. Additionally, the patients in the chronic trial arm of the study only permitted moderate use of aspirin for up to three days prior to the study period, after which no additional medications were permitted [26].

3. Risk of bias in the included studies

Two studies were assigned an overall unclear risk of bias [23,26], and three studies were assigned an overall high risk of bias [22,24,25] (Fig. 2).

4. Adverse events

The side effects and their incidences were reported in all the studies included in this review [22-26]. The details of the reported adverse events and side effects are presented in Table 4. The feeling of unreality, fatigue, and nausea were among the side effects reported most commonly in the ketamine group. Fatigue, vomiting, and nausea were also reported in the control group among hallucinations and restlessness.

5. Primary outcomes reported in the migraine studies

Aura severity/duration: The aura duration and severity score was a composite score measuring the severity as mild, moderate, and severe, and the aura duration was measured in hours [22]. The test results showed that intranasal ketamine at 25 mg/ml performance was superior to intranasal midazolam in the composite reduction of aura severity ($P = 0.032$); however, the aura duration improvement was similar to that of midazolam ($P = 0.20$) [22] (Table 5).

Pain intensity: One study [23] used a 0–10 Numerical Rating Scale (NRS) pain score at 30 min from baseline and another [26] reported a 0–100 mm Visual Analog

Table 4. Adverse events

Reference	Interventions, sample size per group	Outcomes Reported	Outcome in Ketamine Group	Outcome in Control Group
Afridi, et al. [22]	Intranasal ketamine (n = 9) midazolam (n = 9)	Adverse effects (scale 0-3)	5/9 Type: "feelings of unreality, euphoria, or mild giddiness temporarily"	4/9 Type: "transient sedation or giddiness"
Benish, et al. [25]	Intranasal ketamine + I.V. saline (n = 27) I.V. metoclopramide and diphenhydramine + saline (n = 26)	Side-effects	Dizziness, fatigue, changes in mood, nausea, feeling of unreality, discomfort (generalized), diffuse body paresthesia	Fatigue, nausea, dizziness, discomfort (generalized), changes in hearing, auditory hallucinations
Etchison, et al. [23]	I.V. ketamine (n = 16) I.V. saline (n = 18)	Side-effects	Fatigue, nausea, generalized discomfort	Fatigue, nausea, generalized discomfort, hallucinations
Nicolodi and Sicuteri [26]	Trial #1 (n = 17): Acute ketamine or saline was given s.c. if migraine attack of level 3 Trial #2 (n = 17): Severe Migraine sufferers ketamine s.c. (n = 17) saline (n = 17)	Blood pressure/heart rate (Trial #1: acute and Trial #2: chronic) and Side-effects	Trial #1- a weak feeling of insobriety, fatigue, no significant changes in blood pressure, no heart rate change Trial #2- a very mild insobriety sensation, short-lasting asthenia sensation, stomach-ache	Trial #1 No changes in heart rate or blood pressure Trial #2- Dizziness, nausea, asthenia, stomach-ache, dysphoria
Zitek, et al. [24]	I.V. ketamine + I.V. ondansetron (n = 25) I.V. prochlorperazine + diphenhydramine (n = 29)	Side-effects	Dysphoria (2/23) Vomiting (3/23) Nystagmus Confusion, Subjective Restlessness	Akathisia (1/29) Vomiting (2/28) Subjective Restlessness

Abbreviations: I.V., intravenous; n, sample size per group; s.c., subcutaneous.

Table 5. Migraine severity or HA pain intensity outcomes reported in included studies

Study	Intervention Group	Comparison Group	Outcome	Differences between Groups	Ketamine versus Comparison Group
MIGRAINE WITH OR WIHTOUT AURA					
Afridi, et al. [22]	25 mg intranasal ketamine	2 mg intranasal midazolam	Severity of aura composite score	ketamine vs midazolam (P = 0.032)	Intranasal ketamine better than midazolam
			Duration of aura (in h)	ketamine vs midazolam (P = 0.2)	Intranasal ketamine not superior to midazolam
Etchison, et al. [23]	ketamine 0.2 mg/kg slow I.V. push	Equivalent volume of saline by I.V. push	Reduction in NRS 0-10 (at 30 min)	ketamine vs saline (P = 0.5035)	I.V. push ketamine not superior to saline
Nicolodi and Sicuteri [26]	80 μg/kg ketamine hydrochloride diluted in 0.9% saline solution s.c.	Saline 0.9% subcutaneous	Pain intensity and pain relief in VAS scale 0-100 (Trial 1: 30 and 60 min; Trial 2: 3 weeks)	Trial 1: ketamine-induced relief was significantly larger than the control group (P = 0.0001)	Subcutaneous ketamine better than saline
				Trial 2: ketamine vs. saline (P ≤ 0.0001)	Subcutaneous ketamine better than saline
PRIMARY HEADACHES					
Benish, et al. [25]	50 mg/ml intranasal ketamine + 1000 ml normal saline I.V	0.015 ml/kg intranasal saline + 5 mg/ml metoclopramide and 50 mg/ml diphenhydramine in 1000 ml I.V.	Reduction in VAS 0 -100 (at 30 min)	ketamine group improved with the intranasal treatment comparable to the control group (p-value not reported)	Intranasal ketamine not superior to combination I.V. therapy
Zitek, et al. [24]	I.V. ketamine 0.3 mg/kg + ondansetron 4 mg + 500 ml saline	I.V. prochlorperazine 10 mg + diphenhydramine 25 mg + 500 ml saline solution	Reduction in VAS 0 -100 (at 60 min)	ketamine did not produce a greater reduction in VAS at 60 min (P = 0.03)	ketamine + ondansetron inferior to prochlorperazine + diphenhydramine

P > 0.05 not significant; P ≤ 0.05 statistically significant.
Abbreviations: I.V., intravenous; NRS, numerical rating scale; VAS, visual analogue scale.

Scale (VAS) measuring the pain intensity and relief. Low-dose I.V. ketamine (0.2 mg/kg) performed inferior to normal saline in NRS reduction (P = 0.5035) [23]. The percent relief of pain intensity with subcutaneous

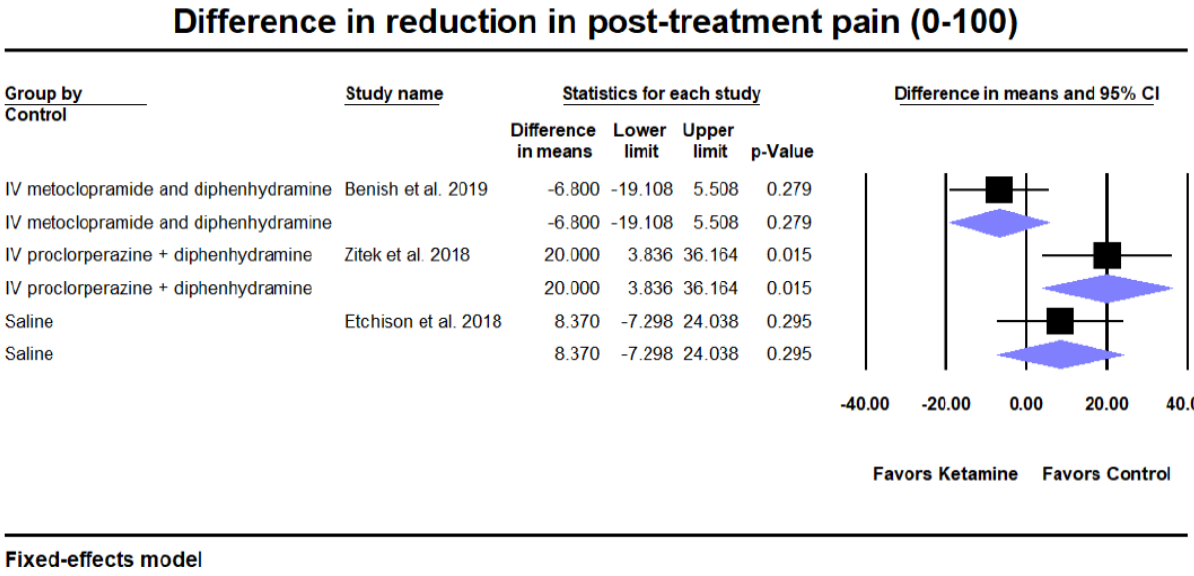

Fig. 3. Differences in reduction in post-treatment pain‡ (scale 0-100); Results of the subgroup analysis comparing ketamine to other interventions for patients with migraines (Etchison et al. [23]) or unspecified primary HAs (Benish et al. [25] and Zitek et al. [24]).
‡ Note: Differences in the reduction in post-treatment pain were calculated as the change from baseline in the ketamine group less the change from baseline in the control group. A negative overall difference in the mean represents a favorable outcome for the ketamine group [25]. CI, confidence interval.

administration of ketamine at 80 µg/kg was superior to saline with 45–100% relief of pain, compared to an average of 18% relief with normal saline in acute migraine (P = 0.0001) [26]. In chronic migraineurs, s.c. ketamine significantly reduced the VAS pain score compared to the control [26], (Table 5).

6. Primary outcomes reported in primary HA studies

In one primary HA study, a 0–100 mm VAS was used to quantify the HA pain reported at 15, 30, and 60 min post-infusion of all medications, with the primary outcome being change from the baseline in pain at 30 min [25]. When compared to the control group, intranasal ketamine at 50 mg/ml combined with I.V. saline therapy was not superior to standard HA therapy of combination intranasal I.V. therapy (saline, metoclopramide, and diphenhydramine) in the measured analgesic effect from baseline (-29 mm vs. -22 mm, p-value not reported) [25]. The second primary HA study measured the pain score change at 60 min as the primary outcome, using a 0–100 mm VAS, where a defined decrease in the average pain score of 25 mm from baseline measurement after intervention indicated significant pain relief [24]. I.V. ketamine at 0.3 mg/kg and ondansetron were inferior to I.V. prochlorperazine and diphenhydramine in HA pain score reduction (43.5 mm vs. 63.5 mm, respectively, P = 0.03) [24] (Table 5).

7. Summary of subgroup analyses for migraine studies

The data from Afridi et al. [22] were not included in any meta-analyses because the authors reported an aura composite score (duration in hours of aura and severity of the aura on a mild/moderate/severe scale), not a VAS scale. Nicolodi and Sicuteri [26] did not report the baseline and post-treatment severity of migraines; they only reported the P-values.

In one study [23] comparing I.V. ketamine to I.V. saline, there was no significant difference in the pain NRS score reduction from baseline (P > 0.05; Fig. 3) or in the need for rescue medications in patients with acute migraine in the ED (P > 0.05; Fig. 4).

8. Summary of subgroup analyses for primary HA studies

HA Pain intensity: In one study [25] comparing intranasal ketamine and I.V. saline to intranasal saline and

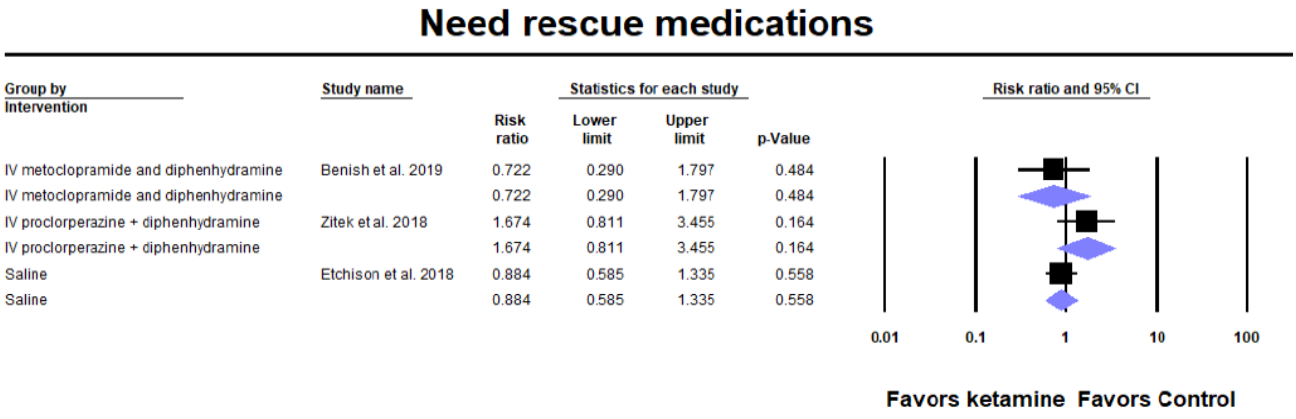

Fig. 4. Patients in need for rescue medications‡. Results of the subgroup analysis comparing ketamine to other interventions for patients with migraines (Etchison et al. [23]) or unspecified primary HAs (Benish et al. [25] and Zitek et al. [24]).
‡Note: A risk ratio (RR) of 1 indicates no difference in the need for rescue medications between groups; RR < 1 is favorable to the ketamine group; [23,25] RR > 1 is favorable to the control group [24]. CI, confidence interval.

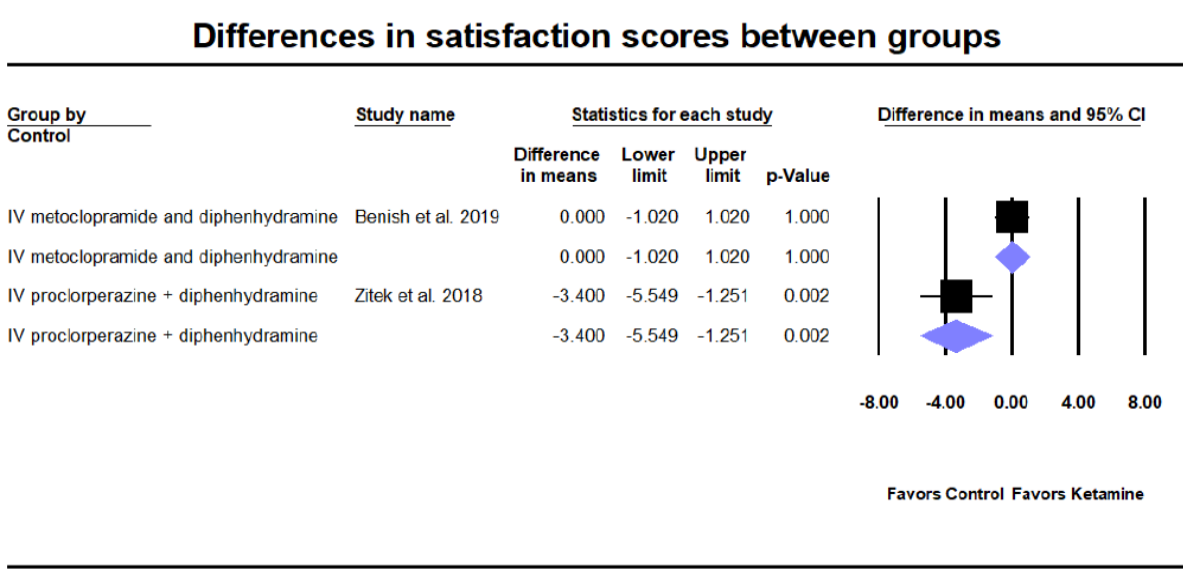

Fig. 5. Differences in the satisfaction scores between groups‡; Results of the subgroup analysis comparing ketamine to other interventions for patients with unspecified primary HAs (Benish et al. [25] and Zitek et al. [24]).
‡Note: A difference in means = 0 represents no difference in the satisfaction scores. A negative overall difference in the means represents a favorable outcome in the control group [24]. CI, confidence interval.

I.V. diphenhydramine and metoclopramide, there was no significant difference in the reduction in the post-treatment pain on a 0–100 VAS scale (P > 0.05; Fig. 3). However, in another study [24], the combination of diphenhydramine and prochlorperazine significantly improved the post-treatment pain by 20 units on a 0–100 scale (95% CI = 3.836 to 36.164; P = 0.015; Fig. 3) compared to I.V. ketamine and ondansetron.

Need of rescue medications: The number of patients in need of rescue medication was not significantly different in the ketamine group compared to the control group (P > 0.05; Fig. 4) [24,25].

Satisfaction score: Satisfaction with the drug received on a scale of 0–10 was high in both ketamine and control

groups at 9/10 [25], with no statistical differences between the groups (Fig. 5). However, in another trial [24], the assessment of satisfaction at the follow-up was statistically significantly favorable to prochlorperazine 10 mg I.V. and diphenhydramine (score 8.3/10) compared to ketamine 0.3 mg/kg I.V. (score 4.9/10).

9. Quality of the evidence (GRADE)

The overall quality of the evidence (according to the GRADE system) was remarkably low due to the risk of bias (which was unclear or high in all of the studies), a small number of studies for each comparison (n = 1 study for each subgroup analysis), and a small sample size (< 400 patients for each outcome).

DISCUSSION

1. Summary of main findings

The main findings of this systematic review are that ketamine failed to show consistently superior benefits to the placebo or active intervention in the treatment of migraine and acute primary HAs. The three studies [22,23,26] that focused solely on migraines with or without aura showed some equivocal findings. Subcutaneously administered ketamine showed statistically significant relief over saline placebo [26], and intranasal ketamine significantly improved the severity of migraine aura compared to intranasal midazolam, but not the duration in hours [22]. However, one study using I.V. ketamine showed inferior results in reducing the pain score compared to saline [23]. In one of the studies that focused on primary HAs, including migraines, only a non-significant improvement in the VAS compared to the control group (metoclopramide and diphenhydramine) was noted [25]. Another primary HA study found that the control group (prochlorperazine and diphenhydramine) was superior to the ketamine group (ketamine combined with ondansetron) [24] in VAS reported pain reduction.

2. Discussion

The sub-dissociative dosing of ketamine has shown promise in the management of refractory HA pain [18, 27] and chronic pain conditions [28] because of its analgesic properties and safety profile [29]. In this systematic review, the included five RCTs evaluated ketamine via either the intranasal, subcutaneous, or intravenous routes of administration. Each study chose different sub-dissociative doses depending on the route of administration. The ketamine dosage that was evaluated in the intravenous groups [23,24] was in the low-dose range of 0.3 mg/kg or less, as defined by a previous study [30]. Previous studies have shown that the higher end of this range appears to be more effective, but has more adverse effects, such as sinus tachycardia and emesis [31]. The intranasal route of administration was evaluated in two studies [22,25]. Afridi et al. [22] chose a 25 mg intranasal dose based on a previous study that determined that a 10–50 mg intranasal dose of ketamine was safe and effective for patients with chronic pain [32]. Benish et al. [25] administered two doses of ketamine, based on the patient's weight. The authors determined that the analgesia, safety profile, and ability to utilize the intranasal route of administration, thus avoiding the need for intravenous access were all the distinct advantages of using ketamine. The subcutaneous dosing of 80 μg/kg in the study by Nicolodi and Sicuteri was chosen from a previous pilot study [26]. The benefits of ketamine in the management of primary HAs are unclear.

3. Agreements and disagreements with other studies or reviews

The conclusions obtained by our systematic review are in agreement with another review by Bilhimer et al. [33], in which ketamine was shown to be beneficial in the treatment of migraine and other primary HAs. However, given the small sample size in most of the studies included in our systematic review, the varied modes of administration, dosage, and heterogeneity of the outcomes

reported, definite conclusions are not possible at this time to recommend this treatment as a first-line treatment in the management of migraines and other primary HA, which is also in agreement with Bilhimer et al. [33]. A position paper by the American Academy of Emergency Medicine deemed sub-dissociative dose ketamine as a safe and effective treatment (either in isolation or in combination with opioids) for the treatment of acute pain [34,35]. In contrast, Orr et al. [36] in 2016, which comprised an expert panel by the American Headache Society to investigate the level of evidence for different parenteral pharmacotherapies in the management of adults with acute migraine in the ED; no recommendation could be made regarding the efficacy of ketamine. This was further substantiated by the consensus guidelines on the use of I.V. ketamine in the management of chronic pain, where I.V. ketamine was given a grade D, low certainty due to the weak or no evidence for an immediate improvement in chronic HA pain [37].

A further review by Naeem et al. [38] in 2018 reported that although there is evidence for the use of ketamine in the management of migraine, it does not translate to primary HA patients. In 2019, Rashed et al. [39] stated that ketamine is best reserved for use in patients who are refractory to other first-line and second-line treatments. It should be noted that in three retrospective studies on chronic refractory migraines and new daily persistent headaches, positive results were shown in those cohorts of patients using ketamine infusions [18,27,40]. In another retrospective study using intranasal ketamine in a pediatric population, the intervention showed promising outcomes in both pain relief and side effect minimization [41].

4. Overall completeness and applicability of evidence

The electronic databases searched were the Cochrane Library, PubMed, Web of Science, and EMBASE up to February 1, 2021, limited to the English language. To find additional RCTs, the review authors manually searched the reference sections of the included studies and reviews. The results of this systematic review are applicable to 18 to 65-year old patients with acute migraine or other primary HAs. One study had an equivalent ratio of men to women [26], while the other four studies had 2-4 times more women than men [22-25]. The results might be biased toward women, which is not unusual with the higher prevalence of HA and migraine in women. These results are applicable to the United Kingdom, Italy, and the USA; these results may not be applicable to other regions of the world.

5. Heterogeneity of the review

The five RCTs included in this review had clinical and methodological heterogeneity in the diagnosis of migraine and primary HAs, route of administration and dosage, and the outcomes. It is unclear how these parameters may have affected the results. Due to the heterogeneity in the migraine phenotype and comparison groups (saline or active intervention), the review authors performed a subgroup analysis for each outcome reported in the included trials for the different comparison groups (active intervention or placebo) (Fig. 3–5).

6. Implications for research and clinical practice

The ability of ketamine to antagonize NMDAR [28] and change the patient's response to pain has raised interest in investigating ketamine as a drug for the treatment of acute migraines and primary HAs. Guirimand et al. [17] found significant increases (i.e. wind-up) in the sensations of pain observed during electrical stimulations at 1.2 times the reflex threshold of the volunteers were significantly reduced after the administration of ketamine, but not the placebo. The studies in this systematic review focused on a sub-dissociative dosing regimen that showed promise for analgesia during sedation and acute pain management in an emergency setting [29,30].

Additional studies are needed to evaluate the efficacy and side effects of higher doses of ketamine. The role of combination therapy with other medications and how it might improve the reported side effects is also important. Niesters et al. [28] found that chronic pain

patients showed benefits from ketamine infusions for up to three months; however, an additional long-term follow-up is needed to determine if any additional effects occur after the initial therapy is completed.

Furthermore, one study has shown that long-term ketamine infusions of 4–14 days imparted long-term analgesic effects for up to three months after infusions [28]. In addition, Lauritsen et al. [18] stated that at least 4–5 days of continuous infusion was required to achieve a reduction in allodynia, a marker for chronic pain. Hence, further prospective studies on migraine and other primary HAs with long-term continuous infusions of ketamine are warranted to investigate its efficacy.

One of the limiting factors for the use of ketamine in clinical situations is its side effects, particularly the feeling of unreality and insobriety [42]. Motov et al. [42] showed that the administration of ketamine in a short infusion fashion rather than an I.V. push reduced the side effects without compromising its analgesic efficacy. Future studies should perhaps use this method of administration to evaluate the efficacy of ketamine in primary HAs when the I.V. route is chosen.

Once the efficacy and the side effect profile of ketamine are established with additional research and follow-up, it may become a valuable tool in the management of migraine and other primary HAs. Its ability to be absorbed in the intranasal form [25] avoids the need for I.V. access and potentially allows the patient to self-administer. If the number of work/school days lost and emergency room visits due to migraine and other primary HAs could be reduced, the use of ketamine could significantly improve the patient's quality of life.

Finally, two retrospective studies by Lauritsen et al. [18] and Pomeroy et al. [27] showed promising results with the use of I.V. ketamine in patients with refractory migraine and other intractable HA disorders. Future prospective studies should also focus on using this agent in this cohort of patients, where other treatments were ineffective in controlling their symptoms.

CONCLUSIONS

The aim of this systematic review and meta-analysis was to evaluate the efficacy of managing migraine and other primary HAs with ketamine using any route of administration. The included studies used sub-dissociative dosing regimens to avoid the side effects observed with higher doses. The benefits of ketamine in the management of primary HAs are unclear. The studies included in this systematic review did not show ketamine to be uniformly superior to traditional treatments; however, varying amounts of benefits have been reported. Additional research is needed to evaluate higher sub-dissociative dosages, side effect profiles for these doses, and long-term effects. Furthermore, future studies should evaluate the use of ketamine in chronic, refractory migraines, and other primary HAs using various administration routes, especially the intranasal and subcutaneous routes.

The limitations of this study include the small number of included studies. The method of delivery varied throughout the studies, which made the dose comparison difficult. Finally, in many of the control groups, the route of the delivery (such as with I.V. saline) and the additional medications could potentially have a confounding effect in the comparison of ketamine with control therapies.

Table of Abbreviations:

CI	confidence intervals
CNS	central nervous system
DM	difference in means
ED	emergency department
HA	headache
IQR	interquartile range
I.V.	intravenous
n	sample size per group
N	total sample size
NMDAR	N-methyl-D-aspartate receptor
NRS	numerical rating scale
NSAIDs	non-steroidal anti-inflammatory drugs
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCT	randomized controlled trials
RR	risk ratio
s.c.	subcutaneous
SD	standard deviation
VAS	visual analog scale

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