Acta Neurologica Indonesia
Department of Neurology, Faculty of Medicine Universitas Indonesia
ISSN 3032-6303

Original Research

DUAL ROLE OF MAGNESIUM IN MIGRAINE: EFFICACY & SAFETY IN TREATMENT AND PREVENTION—A META-ANALYSIS

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ABSTRACT

Introduction: Magnesium deficiency has been associated with migraines, suggesting its potential as a therapeutic intervention.
Objective: To assess the efficacy and safety of intravenous (IV) and oral magnesium for the treatment and prevention of migraines in adults.
Material and methods: A systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted across multiple databases for randomized controlled trials (RCT) involving adult migraine patients treated with IV magnesium (1-2g) for acute attacks or oral magnesium (≥8 weeks) for prevention. Study quality was assessed using the Cochrane Risk of Bias 2 tool, and meta-analysis was conducted with Review Manager 5.4.
Result: Twelve trials were included. IV magnesium showed significant benefits for acute migraines, including better headache response ($p = 0.02$), reduced pain intensity ($p = 0.03$), and less rescue medication use ($p = 0.02$). Oral magnesium was as effective as sodium valproate for prevention but showed limited benefits over placebo for attack frequency ($p = 0.09$). Gastrointestinal side effects were more common with oral magnesium ($p = 0.01$).
Discussion: Magnesium modulates methyl-D-aspartate (NMDA) receptors, preventing excessive calcium influx and cortical spreading depression, which are key in migraine pathophysiology. IV magnesium is effective for acute treatment with a favorable safety profile. Oral magnesium shows potential for migraine prevention, with efficacy similar to sodium valproate, though gastrointestinal side effects limit its use.
Conclusion: IV magnesium should be considered for acute attacks, while oral magnesium may be an alternative for prophylaxis in patients intolerant to first-line treatments.

Keywords: migraine; magnesium; pain reduction; treatment outcome

INTRODUCTION

Migraine is a prevalent neurological disorder characterized by episodic moderate-to-severe headaches, typically unilateral and accompanied by nausea, photophobia, and phonophobia.[1] Affecting about 14–15% of the global population, it ranked second among neurological disorders contributing to disability-adjusted life years (DALYs) in 2021, after stroke. The substantial personal and societal burden highlights the need for effective and tolerable

management strategies.[2,3]

Current treatments for migraine include NSAIDs and triptans for acute attacks and anticonvulsants, antidepressants, and beta-blockers for prophylaxis. However, their modest efficacy and adverse effects often result in suboptimal control and risks like medication overuse headache.[4] Targeting N-methyl-D-aspartate (NMDA) receptors has emerged as a promising approach, as excessive calcium influx may trigger cortical spreading depression, a key mechanism in migraine pathogenesis.[5] Magnesium, a natural NMDA antagonist and calcium channel blocker, has been proposed as a potential therapeutic agent due to its role in regulating neuronal excitability and vasomotor tone.[3,5]

Several clinical trials have evaluated intravenous (IV) and oral magnesium for acute migraine and prophylaxis. However, inconsistencies in study designs, protocols, and patient populations have led to inconclusive recommendations. Safety concerns, particularly gastrointestinal side effects from oral magnesium, further complicate its use. This meta-analysis aims to critically evaluate the efficacy and safety of IV and oral magnesium for migraine treatment. The findings will provide updated, evidence-based recommendations for clinical practice and guide future research to optimize migraine management.

MATERIAL AND METHODS

This systematic review and meta-analysis followed PRISMA guidelines and was registered with PROSPERO (CRD42025649917). A comprehensive search of PubMed, Scopus, Cochrane Library, and EBSCOhost was conducted for RCTs published up to January 2025, using relevant MeSH terms and keywords for “migraine” and “magnesium.” Duplicate records were removed, and the study selection process is illustrated in Figure 1.

Eligibility Criteria

We included RCTs involving adults (≥18 years) with migraine diagnosed by International Headache Society criteria, treated with IV magnesium sulfate (1–2 g) for acute attacks or oral magnesium for at least eight weeks for prophylaxis. Exclusion

criteria were secondary headaches, contraindications to magnesium, pregnancy or lactation (unless separately analyzed), menstrual migraine, incomplete data, or unavailable full text.

Study Selection and Data Extraction

Four reviewers independently screened studies and extracted data on study characteristics, participant demographics, interventions, comparators, and outcomes. For IV magnesium, outcomes included pain intensity, headache response, rescue medication use, and adverse events at multiple time points. For oral magnesium, outcomes included monthly migraine frequency, pain intensity, duration, validated questionnaire scores (HIT-6, MIDAS), and adverse events.

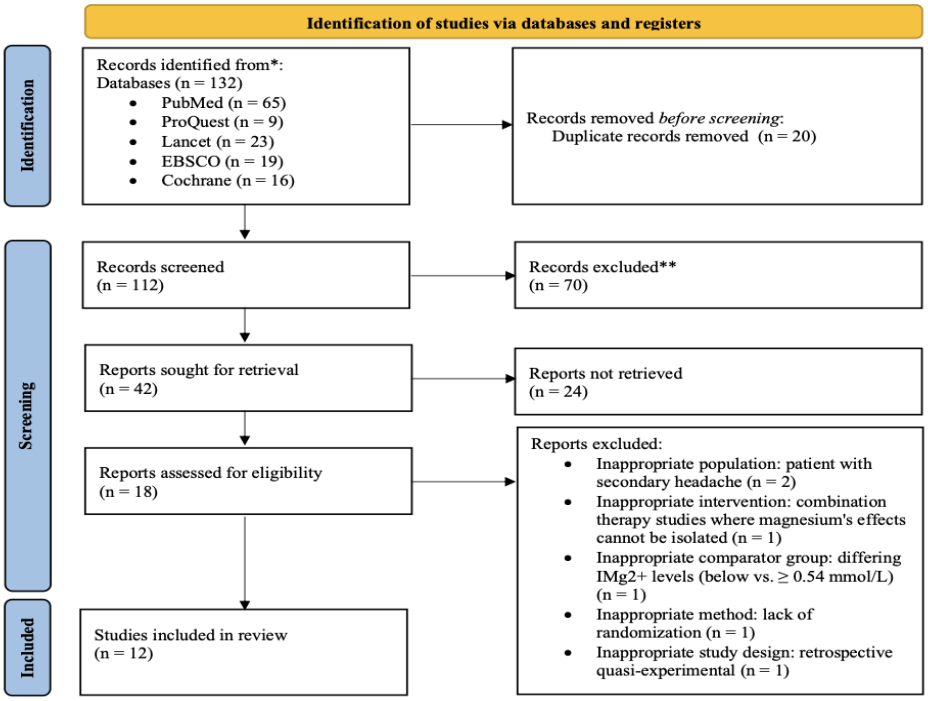

Figure 1. Literature Search Strategy Flow Diagram.
Flowchart showing database search using predefined keywords, with exclusion of records based on irrelevant titles and abstracts.

Data Synthesis

Meta-analysis was performed using Review Manager 5.4 with a random-effects model. Risk ratios (RRs) and mean differences (MDs), each with 95% confidence intervals, were calculated for dichotomous and continuous outcomes, respectively. Safety outcomes were analyzed for both magnesium formulations.

Risk of Bias and Quality Assessment

The quality of included studies was assessed using the Cochrane Risk of Bias tool by four independent reviewers, with disagreements resolved by a fifth reviewer. The full risk of bias assessment is presented in Figure 2.

RESULT

Study Selection and Characteristics

Our systematic literature search identified potentially relevant studies. After removing duplicates and screening titles and abstracts, full-text articles were assessed for eligibility. Following application of inclusion and exclusion criteria, 12 randomized controlled trials were included in the final analysis. The complete selection process is illustrated in Figure 1.

The included studies comprised 5 trials investigating IV magnesium for acute migraine treatment and 7 trials evaluating oral magnesium for migraine prophylaxis. The characteristics of these studies are summarized in Tables 1 and 2.

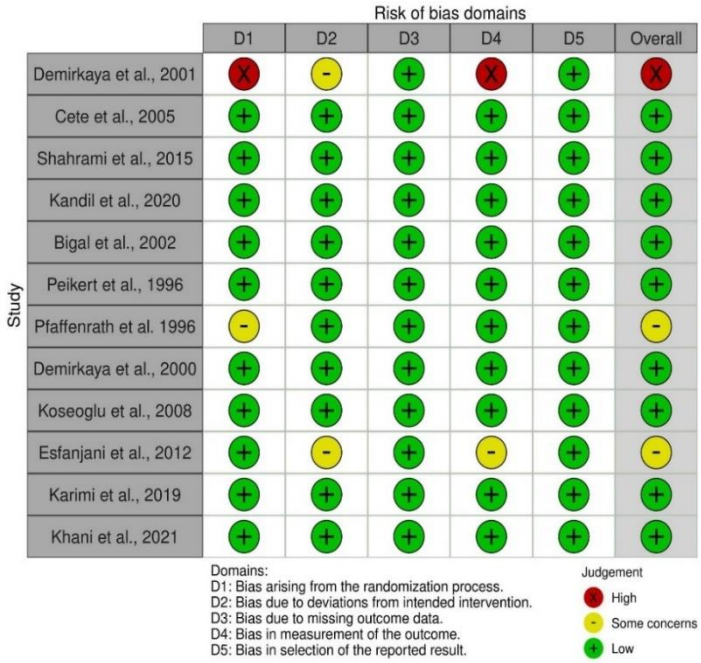

Figure 2. Risk of Bias Assessment.

The figure displays a comprehensive risk of bias assessment for 13 included studies across 5 domains: bias arising from the randomization process (D1), bias due to deviations from intended interventions (D2), bias due to missing outcome data (D3), bias in measurement of the outcome (D4), and bias in selection of the reported result (D5). The assessment uses a color-coded system where green circles indicate low risk, yellow circles indicate some concerns, and red circles indicate high risk of bias. The majority of studies demonstrate low risk of bias across most domains, with only a few studies showing some concerns or high risk in specific areas.

Table 1. Summary of Study Characteristics: IV Magnesium Studies.

First Author, Year	Country	Population (N, Age, Aura)	IV Magnesium Dose	Comparator	Outcome		Time Points
					Efficacy	Safety	
Demirkaya et al., 2001[6]	Turkey	30, 35±8.9 yrs, both	1g over 15 min	Placebo	Pain-free: 86.6% (13/15) vs 0% (0/15), p<0.0001 Symptom-free: 100% (15/15) vs 20% (3/15), p<0.0001	Mild: 86.6% (26/30) flushing/burning; 4/30 BP drop; no severe AEs	Immediate, 30 min, 24h
Cete et al., 2005[7]	Turkey	113, 40±12 yrs, both	2g over 10 min	Metoclopramide + Saline	No overall group difference at 15 & 30 min (p=0.619) In migraine with aura: VAS reduction at 15 min, p=0.03 (vs metoclopramide), p=0.04 (vs placebo)	Flushing: 8% (3/36, Mg); dystonia: 3% (1/37, Metoclopramide); none (placebo)	15 min, 30 min, 24h
Shahrami et al., 2015[8]	United States	70, 37 ± 11.87 yrs, both	1g over 15 min	Dexamethasone + Metoclopramide	20 Min Numeric Rating Scale (NRS) (mean ± SD) Magnesium: 5.2 ± 1.7 Comparator: 7.4 ± 1.4 60 Min NRS (mean ± SD) Magnesium: 2.3 ± 1.9 Comparator: 6.0 ± 2.4 120 Min NRS (mean ± SD) Magnesium: 0.66 ± 1.3 Comparator: 2.5 ± 2.9	Nausea: - Magnesium: 4/35 (11.4%) - Comparator: 4/35 (11.4%) Vomiting: - Magnesium: 0/35 (0%) - Comparator: 1/35 (2.9%) Vertigo: - Magnesium: 0/35 (0%) - Comparator: 1/35 (2.9%) Lethargy: - Magnesium: 0/35 (0%) - Comparator: 1/35 (2.9%)	Baseline, 20, 60, 120 min
Kandil et al., 2021[9]	United States	36 years (median), 157 patients, both	2g in 50 mL D5W	Metoclopramide/ Prochlorperazine	Primary Outcome: Change in Pain Score at 30 Minutes - Magnesium: 0.75 ± 2.41 - Metoclopramide: 0.67 ± 2.22 - Prochlorperazine: 1.00 ± 2.96 - p-value = 0.71 (not statistically significant) Secondary Outcomes: Change in Pain Score at 60 Minutes - Magnesium: 1.33 ± 2.96 - Metoclopramide: 1.33 ± 2.22	Adverse Events - Magnesium: 3/61 (5%) - Metoclopramide: 2/44 (4.5%) - Prochlorperazine: 6/52 (11.5%) - p-value = 0.51 (not statistically significant) The most commonly reported adverse effects were Dizziness, Akathisia (specifically noted in the	30, 60, and 120 minutes

First Author, Year	Country	Population (N, Age, Aura)	IV Magnesium Dose	Comparator	Outcome		Time Points
					Efficacy	Safety	
					- Prochlorperazine: 1.50 ± 3.70 - p-value = 0.27 (not statistically significant) Change in Pain Score at 120 Minutes - Magnesium: 1.75 ± 3.52 - Metoclopramide: 1.75 ± 3.89 - Prochlorperazine: 2.58 ± 3.52 - p-value = 0.66 (not statistically significant) Need for Rescue Analgesia - Magnesium: 26/61 (43%) - Metoclopramide: 15/44 (34%) - Prochlorperazine: 17/52 (33%) - p-value = 0.50 (not statistically significant)	prochlorperazine group), Anxiety	
Bigal et al., 2002[10]	Brazil	27.6 years (median), 60 patients, both	1g	Placebo	10 point Verbal-Analogical Scale Migraine without Aura (MO) Initial: MgSO4 8.2 vs Placebo 7.8 T30: MgSO4 6.8 vs Placebo 6.0 T60: MgSO4 5.0 vs Placebo 5.5 Migraine with Aura (MA) Initial: MgSO4 7.5 vs Placebo 8.0 T30: MgSO4 5.0 vs Placebo 6.5 T60: MgSO4 4.0 vs Placebo 6.3 ($p<0.05$) Use of Rescue Medication (n/N, %) Migraine without Aura (MO) MgSO4: 12/30 (40%) vs Placebo: 15/30 (50%) Migraine with Aura (MA) MgSO4: 6/30 (20%) vs Placebo: 12/30 (40%)	N/A	30 minutes, 60 minutes, 24 h

Table 2. Summary of Study Characteristics: Oral Magnesium Studies.

First Author, Year	Country	Subject (Age, N, with/without Aura)	Number of migraine/ month	Intervention, (duration, total dose)	Comparator	Outcome		Observational Time Points
						Efficacy	Safety	
Peikert et al, 1996[11]	Germany	Mg group: 43.8 ± 10.7 years Placebo group: 47.6 ± 10.0 years, 81 patient Both	3.6 per month (mean attack frequency)	Oral magnesium (trimagnesium dicitrate) 600 mg/day, 12 weeks, 7200 mg	Magnesium-free placebo powder	**Attack Frequency Reduction** Magnesium group: 1.51 ± 2.07 attacks Placebo group: 0.58 ± 2.30 attacks **Days with Migraine Reduction** Magnesium group: 2.49 ± 3.05 days Placebo group: 1.16 ± 3.89 days **Pain Intensity Reduction (VAS)** Magnesium group: 2.06 ± 2.77 Placebo group: 1.25 ± 2.29	**Diarrhea/soft stool** - Magnesium: 8/43 (18.6%) - Placebo: 2/38 (5.3%) **Gastric irritation** - Magnesium: 2/43 (4.7%) - Placebo: 0/38 (0%)	4 weeks baseline 12 weeks treatment Total 16 weeks follow-up
Pfaffenrath et al. 1996[12]	Multi center, multi national	40.5 ± 12.4 years 69 patient without aura	2-6 migrains per month	Oral magnesium -u-aspartate-hydrochloride-trihydrate 243mg twice per day, 12 weeks, 40,824 mg	Placebo (unspecified)	**Primary endpoint (≥50% reduction in migraine duration/intensity)** - Magnesium: 10/35 (28.6%) - Placebo: 10/34 (29.4%) **≥50% reduction in migraine duration only** - Magnesium: 7/35 (20.0%) - Placebo: 8/34 (23.5%) **≥50% reduction in migraine intensity only** - Magnesium: 7/35 (20.0%) - Placebo: 5/34 (14.7%)	**Adverse events:** Magnesium: 16/35 (45.7%) Placebo: 8/34 (23.5%) Main adverse events in Magnesium group: Soft stools: 5/35 Diarrhea: 5/35 Palpitations: 3/35	Baseline, 4 weeks, 8 weeks, 12 weeks
Demirkaya et al., 2000[13]	Turkey	32.67 ± 7.1 years 92 patients Both	3 or more migraine attacks per month	1830 mg magnesium citrate per day in 3 equal doses, 12 weeks, 1164700mg	10 mg flunarizine per day once every evening; 10 mg amitriptyline per day once every night; placebo three times a day	**Migraine Frequency** **Month 1** Mg: 3.52±1.38 Flunarizine: 3.55±1.26 Amitriptyline: 3.70±1.13 Placebo: 4.05±1.05 **Month 2** Mg: 2.22±1.91 Flunarizine: 2.59±1.01	N/A	Baseline, 1 month, 2 month, 3 month

						Amitriptyline: 2.70±0.92 Placebo: 4.00±1.27 **Month 3** Mg: 1.52±1.34 Flunarizine: 1.73±1.42 Amitriptyline: 1.90±0.97 Placebo: 3.81±1.4		
Köseoglu et al. 2008[14]	Turkey	Mg group: 36.6 ± 9.3 years. Placebo group: 43.5 years (median) 40 patients without aura	Mg group: 2.5 attacks per month (mean) Placebo group: 3.5 attacks per month (median)	Oral magnesium citrate 300 mg water soluble granulate sachet twice per day, 12 weeks, 7200 mg	Placebo (unspecified)	**Migraine Attack Frequency Reduction** - Magnesium group: - Before treatment: 3.25 ± 0.75 - After treatment: 1.75 ± 0.75 - Placebo group: - Before treatment: 3.5 ± 0.75 - After treatment: 3.25 ± 0.75 **Pain Intensity Reduction (VAS Score)** - Magnesium group (as reported in the study): - Before treatment: 7.57 ± 0.86 - After treatment: 4.00 ± 1.53 - Placebo group (estimated values): - Before treatment: 7.00 ± 0.50 - After treatment: 6.75 ± 0.75	Magnesium group (n=40): **Diarrhea/soft stools**: 4/40 (10%) **Gastric irritation**: 2/40 (5%) Total AEs: 6/40 Placebo group (n=10): No adverse events reported (0/10)	4 weeks before the beginning of treatment 12 weeks treatment Total 16 weeks followup
Esfanjani et al., 2012[15]	Iran	Mg group: 31.94 ± 1.76 Years L-Carnitine group: 34.09 ± 1.70 years Mg-L-carnitine group: 32.37 ± 1.74 years	Magnesium oxide group: 6.97 ± 0.97 L-Carnitine group: 7.06 ± 0.75 Mg-L-Carnitine group: 6.08 ± 0.63	Magnesium oxide 500 mg/day, 12 weeks, 42000 mg	L-Carnitine 500 mg/d L-carnitine 500 mg/d + MgO 500 mg/d Control: cconventional/routine treatments not specifically detailed in the	**Migraine Attacks per Month:** Magnesium: 6.97±0.97 → 2.33±0.27 L-Carnitine: 7.06±0.75 → 4.01±0.59 Mg-L-carnitine: 6.08±0.63 → 2.63±0.24 Control: 7.01±0.80 → 6.88±0.68 **Days with Migraine per Month:** Magnesium: 6.09±1.13 → 1.50±0.37 L-Carnitine: 6.05±1.10 → 1.41±0.45 Mg-L-carnitine: 8.19±1.70 → 1.57±0.49 Control: 8.02±1.70 → 5.48±1.50	**Withdrawal due to adverse events:** - Magnesium group: 4/37 (gastrointestinal discomfort) - L-Carnitine group: 0/35 - Mg-L-carnitine group: 2/32 (gastrointestinal discomfort) - Control group: 0/35	12 weeks

		Control: 36.54 ± 1.54 years 133 patients Both	Control group 7.01 ± 0.80		paper			
Karimi et al., 2019[16]	Iran	36.78 ± 8.85 years 70 patients Both	≥2 attacks but not more than 15 days	Magnesium oxide 500 mg twice daily **Baseline (4 Weeks)** Daily 1000 mg dose, total 28,000 mg. **First Treatment (8 Weeks)** Magnesium oxide or sodium valproate, total 56,000 mg. **Washout (4 Weeks)** No medication to clear residual effects. **Second Treatment (8 Weeks)** Switch to the other medication, total 56,000 mg.	Sodium valproate 400 mg twice daily	**Pain Severity (VAS)** - Baseline: 9.11 ± 0.83 (Group 1) and 9.05 ± 0.72 (Group 2) - First period: 4.65 ± 2.41 (Magnesium) vs. 4.83 ± 2.40 (Valproate) - Second period: 5.56 ± 2.22 (Magnesium) vs. 4.75 ± 2.70 (Valproate) - Result: Both groups showed significant improvement (P < 0.001) **Headache Impact (HIT-6)** - Baseline: 65.92 ± 5.59 (Group 1) and 64.74 ± 7.32 (Group 2) - First period: 49.81 ± 8.98 (Magnesium) vs. 49.87 ± 10.26 (Valproate) - Second period: 51.61 ± 8.62 (Magnesium) vs. 49.70 ± 9.80 (Valproate) - Result: Significant reduction in both groups (P < 0.001) **Disability Assessment (MIDAS)** - Baseline: 24.22 ± 7.37 (Group 1) and 22.48 ± 6.68 (Group 2) - First period: 6.78 ± 6.45 (Magnesium) vs. 6.25 ± 6.28 (Valproate) - Second period: 8.01 ± 6.14 (Magnesium) vs. 7.20 ± 7.30 (Valproate) - Result: Significant improvement in both groups	No significant adverse effects were reported in either the magnesium oxide or valproate sodium groups - Both treatments appeared to be well-tolerated by patients who completed the study	Baseline (4 weeks) End of first treatment period (8 weeks) After washout (4 weeks) End of second treatment period (8 weeks) Phone follow-up every 2 weeks Neurologist assessment every 4 weeks

						(P < 0.001) **Headache Parameters:** **Duration (hours)** - Baseline: 48.65 ± 21.10 (Group 1) and 43.54 ± 23.29 (Group 2) - First period: 15.53 ± 21.84 (Magnesium) vs. 13.38 ± 14.10 (Valproate) - Second period: 17.62 ± 14.27 (Magnesium) vs. 14.00 ± 12.75 (Valproate) **Number of Attacks** - Baseline: 5.17 ± 2.21 (Group 1) and 5.34 ± 2.01 (Group 2) - First period: 1.72 ± 1.82 (Magnesium) vs. 1.27 ± 1.27 (Valproate) - Second period: 1.75 ± 1.21 (Magnesium) vs. 1.90 ± 1.93 (Valproate) **Migraine Days** - Baseline: 9.57 ± 4.44 (Group 1) and 8.28 ± 4.49 (Group 2) - First period: 2.09 ± 1.70 (Magnesium) vs. 2.22 ± 1.96 (Valproate) - Second period: 2.62 ± 2.35 (Magnesium) vs. 2.51 ± 2.96 (Valproate)		
Khani et al., 2021[17]	Iran	Group A (Sodium valproate + Placebo): 35.16 ± 8.21 years Group B (Sodium	at least four monthly attacks but not higher than 15	Magnesium Oxide tablet 500mg/day, 12 weeks, 42000 mg	Sodium valproate tablet and placebo tablet (unspecified)	**Migraine attacks:** **Baseline**: 6.65 ± 1.65 (Group A) and 6.89 ± 1.52 (Group B) and 7.06 ± 1.54 (Group C) **After 1 month:** 4.09 ± 0.99 (Group A) and 4.04 ± 0.93 (Group B) and 5.49 ± 1.45 (Group C) **After 2 months:** 2.83 ± 0.73 (Group A) and 2.47 ± 0.71 (Group B) and 4.21 ± 0.08 (Group C) **After 3 months:** 1.60 ± 0.76 (Group A) and 1.40 ± 0.75 (Group B) and 3.91 ± 0.86 (Group C)	N/A	Patients followed monthly

	valproate + Magnesium oxide): 37.11 ± 6.56 years Group C (Magnesium oxide + Placebo): 34.41 ± 6.19 years	**Headache Severity:** **Baseline**: 5.33 ± 0.67 (Group A) and 5.27 ± 0.79 (Group B) and 5.16 ± 1.02 (Group C) **After 1 month:** 3.68 ± 0.81 (Group A) and 3.69 ± 0.73 (Group B) and 3.93 ± 1.24 (Group C) **After 2 months**: 2.51 ± 0.68 (Group A) and 2.16 ± 0.67 (Group B) and 3.32 ± 0.78 (Group C) **After 3 months**: 1.71 ± 0.55 (Group A) and 1.26 ± 0.59 (Group B) and 2.41 ± 1.15 (Group C) **Headache Duration (hour):** **Baseline**: 11.56 ± 3.53 (Group A) and 11.96 ± 1.73 (Group B) and 10.99 ± 2.49 (Group C) **After 1 month:** 10.39 ± 2.8 (Group A) and 9.95 ± 1.80 (Group B) and 10.64 ± 1.96 (Group C) **After 2 months**: 8.19 ± 2.76 (Group A) and 7.22 ± 1.66 (Group B) and 9.30 ± 1.84 (Group C) **After 3 months:** 7.06 ± 2.53 (Group A) and 6.08 ± 1.75 (Group B) and 8.15 ± 1.83 (Group C) **MIDAS**: **Group A**: 21.74 ± 4.44 (pre-intervention) → 17.11 ± 4.06 (post-intervention) **Group B**: 21.68 ± 3.72 (pre-intervention) → 16.11 ± 3.87 (post-intervention) **Group C**: 22.13 ± 1.88 (pre-intervention) → 18.81 ± 1.76 (post-intervention) **HIT-6:** **Group A**: 56.72 ± 4.59 (pre-intervention) → 49.91 ± 4.58 (post-intervention) **Group B:** 56.89 ± 3.84 (pre-intervention) → 50.50 ± 3.27 (post-intervention) **Group C:** 57.54 ± 2.13 (pre-intervention) → 53.03 ± 1.88 (post-intervention)

Efficacy of IV Magnesium

Reduction in Pain Intensity Measured by Numeric Rating Scale *(NRS) at Different Time Points*

IV magnesium reduced pain intensity compared to active comparators at various time points, though with varying significance. At 30 and 60 minutes, the reduction was non-significant (MD = -0.81, p = 0.29; MD = -1.30, p = 0.30) with high to very high heterogeneity. At 120 minutes, there was a trend towards significance (MD = -0.98, p = 0.07) with moderate heterogeneity. Overall, IV magnesium showed a significant pain reduction (MD = -1.01, p = 0.03) with considerable heterogeneity (I^2 = 86%). No significant differences were observed between time points (p = 0.94, I^2 = 0%), indicating a consistent effect across measurements.

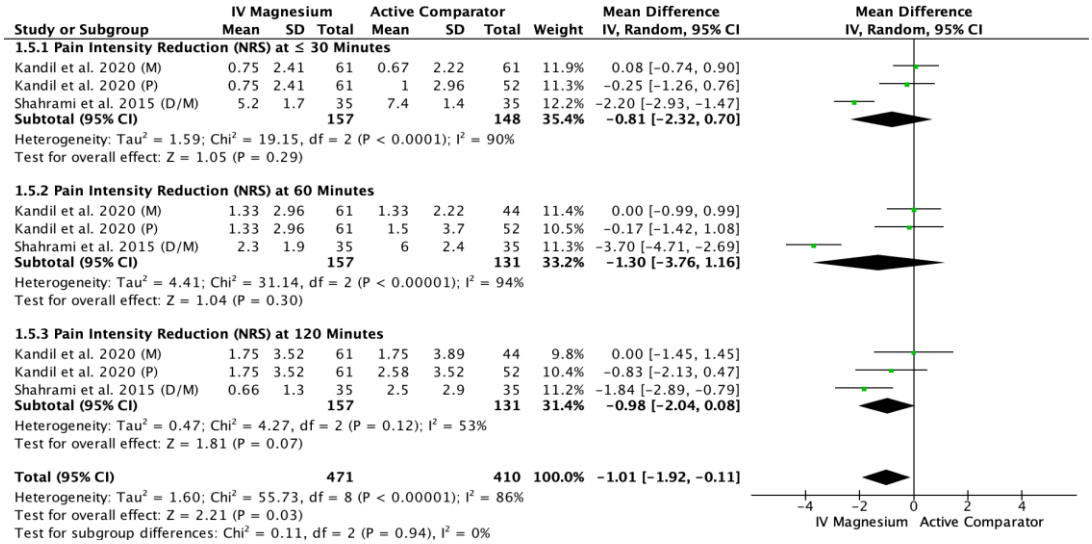

Figure 3. Forest plot of mean difference in pain intensity reduction (NRS) between IV magnesium and active comparators (metoclopramide, prochlorperazine, dexamethasone/metoclopramide) at ≤30, 60, and 120 minutes. Negative values favor IV magnesium.
D/M: dexamethasone/metoclopramide, M: metoclopramide, P: prochlorperazine.

Need for Rescue Analgesia Compared to Placebo

Patients receiving IV magnesium were significantly less likely to require rescue analgesia compared to those receiving placebo (RR = 0.66, 95% CI [0.46, 0.95], p = 0.02), suggesting effective pain relief in acute migraine attacks. The forest plot showed minimal heterogeneity, indicating consistency in the treatment effect across studies.

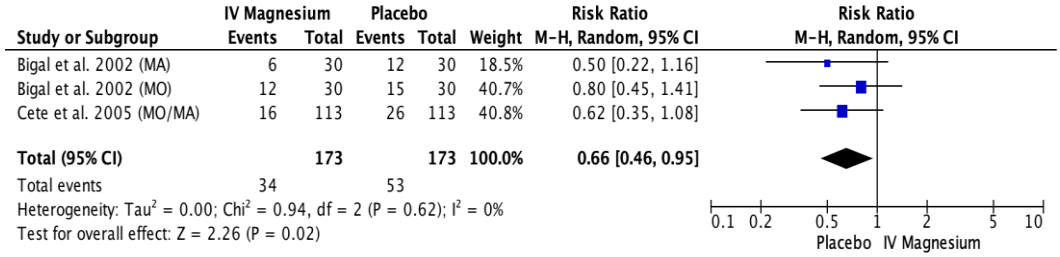

Figure 4. Forest plot of the risk ratio for the need for rescue analgesia with IV magnesium versus placebo in patients with migraine, with and without aura. Squares represent individual studies; the diamond indicates the pooled estimate. MA: migraine with aura, MO: migraine without aura.

Safety of IV Magnesium

Any Adverse Event after IV Magnesium Compared to Active Comparator

The incidence of adverse events with IV magnesium was similar to that of active comparators (RR = 0.76, 95% CI [0.34, 1.66], p = 0.48). Common adverse events included dizziness, akathisia (noted in the prochlorperazine group), anxiety, dystonic reactions, nausea, burning sensation in the face/neck, and flushing.

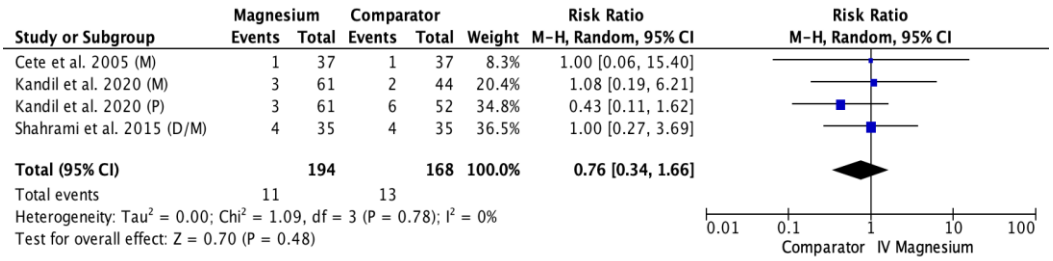

Figure 5. Forest plot of risk ratio for any adverse event after IV magnesium compared to active comparators (metoclopramide, prochlorperazine, dexamethasone/metoclopramide). Squares indicate individual studies; the diamond shows the pooled estimate. M: metoclopramide, P: prochlorperazine, D/M: dexamethasone/metoclopramide

Efficacy of Oral Magnesium

Migraine Duration (Hours) between Oral Magnesium and Sodium Valproate

Analysis of migraine duration measured in hours between oral magnesium supplementation and sodium valproate showed non-significant effects (MD = 0.28, 95% CI [-0.48, 1.03], p = 0.47).

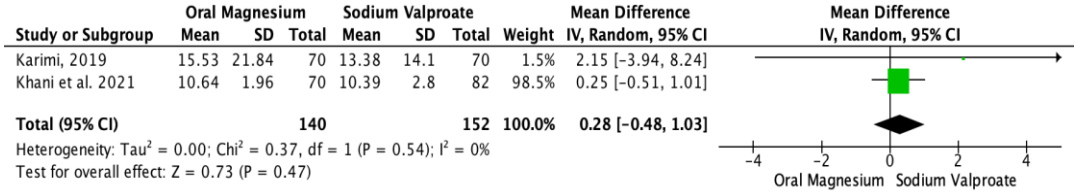

Figure 6. Forest plot of mean difference in migraine duration in hours between oral magnesium and sodium valproate. Squares represent individual studies; the diamond indicates the pooled estimate.

HIT-6 Scores between Oral Magnesium and Sodium Valproate

There was no significant difference in Headache Impact Test-6 (HIT-6) scores between oral magnesium and sodium valproate groups (MD = 1.90, 95% CI [-1.13, 4.93], p = 0.22), indicating comparable efficacy in improving headache-related quality of life. The forest plot showed minimal heterogeneity, suggesting consistency in treatment effects across studies. Both treatments similarly reduced the impact of migraines on daily functioning, as measured by the HIT-6.

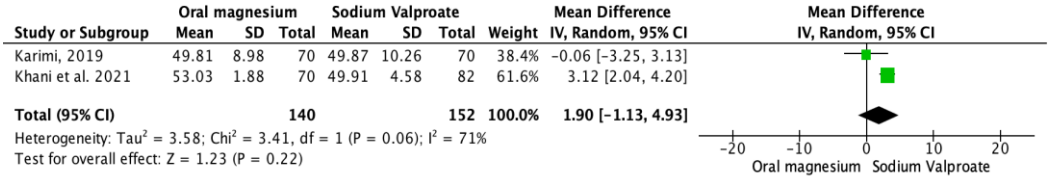

Figure 7. Forest plot of mean difference in HIT-6 scores between oral magnesium and sodium valproate. Squares represent individual studies; the diamond indicates the pooled mean difference with 95% confidence interval.

MIDAS Scores between Oral Magnesium and Sodium Valproate

Migraine Disability Assessment (MIDAS) scores showed a statistically significant difference favoring sodium valproate over oral magnesium (MD = 1.30, 95% CI [0.03, 2.56], p = 0.04), indicating superior efficacy of sodium valproate in reducing migraine-related disability. The forest plot demonstrated minimal heterogeneity, suggesting consistency in the treatment effect across studies.

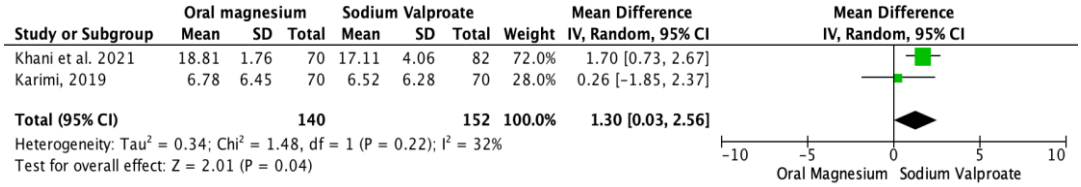

Figure 8. Forest plot of mean difference in MIDAS scores between oral magnesium and sodium valproate. Squares represent individual studies; the diamond indicates the pooled mean difference with 95% confidence interval. Positive values favor sodium valproate.

Safety of Oral Magnesium

Risk of Gastrointestinal Adverse Events (Diarrhea/Soft Stool) with Oral Magnesium vs Placebo

Gastrointestinal adverse events, particularly diarrhea and soft stool, were significantly more common with oral magnesium compared to placebo (RR = 4.54, 95% CI [1.38, 14.97], p = 0.01). These side effects were generally mild to moderate in severity.

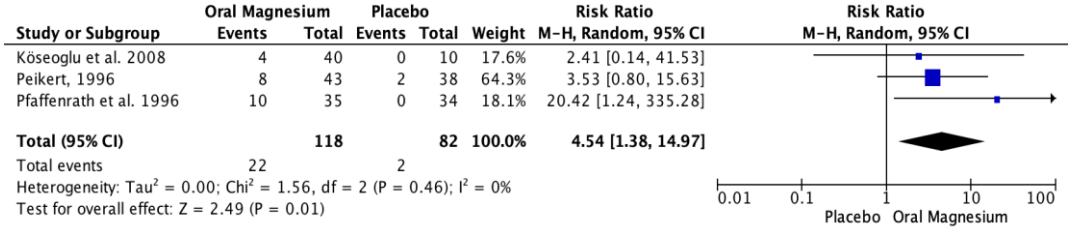

Figure 9. Forest plot of risk ratio for gastrointestinal adverse events (diarrhea/soft stool) comparing oral magnesium to placebo. Squares represent individual studies; the diamond indicates the pooled risk ratio with 95% confidence interval.

DISCUSSION

Migraine pathophysiology involves activation of the trigeminovascular nociceptive pathways, causing meningeal vasodilation and neurogenic inflammation. The 2024 International Headache Society (IHS) guidelines recommend triptans, selective serotonin receptor agonists, as first-line treatment for severe migraines. Triptans act by inducing vasoconstriction through 5-hydroxytryptamine receptor 1B (5-HT1B) receptors and inhibiting nociceptive peptide release via 5-HT1D receptors, thus reducing pain signaling.[18]

Magnesium plays a key role in maintaining calcium homeostasis and regulating N-methyl-D-aspartate (NMDA) receptor activity, both of which are critical for neuronal excitability. Its anti-migraine effect is primarily due to its action as a

natural calcium channel blocker, which reduces excitatory neurotransmitter release. By stabilizing central sensitization following nociceptive stimulation, magnesium helps protect neurons from excitotoxicity and oxidative stress.[5]

Our study showed that IV and oral magnesium supplementation significantly improved migraine management. IV magnesium reduced acute migraine severity, both with and without aura, with meta-analyses demonstrating a significant overall reduction in pain intensity compared to active comparators ($p = 0.03$), with consistent effects across 30, 60, and 120 minutes ($p = 0.94$). Although the effect was not statistically significant at each individual time point, the pooled analysis confirmed the clinical benefit of IV magnesium (figure 6). Our results align with Chiu et al.'s findings, further supporting the analgesic role of IV magnesium in migraine management.[19] Shahrami et al. found IV magnesium more effective than a dexamethasone-metoclopramide combination, while Kandil et al. and Cete et al. reported comparable effects to standard antiemetics.[8-9]

Our analysis showed that patients receiving IV magnesium were significantly less likely to require rescue analgesia compared to placebo ($p = 0.02$), indicating improved symptom control in acute migraine attacks (figure 7). Despite concerns about adverse effects, the incidence was not significantly different from that of active comparators ($p = 0.48$), and events such as flushing, warmth, and nausea were generally mild and transient.[6–9]

Our meta-analysis found no significant difference in migraine duration between oral magnesium supplementation and sodium valproate ($p = 0.47$), suggesting that both treatments have comparable efficacy in reducing migraine duration (figure 6), as also reported by Karimi and Khani et al.[16,17] Similarly, HIT-6 scores showed no statistically significant difference between the two groups ($p = 0.22$) (figure 7). In line with this, Both Karimi and Khani et al. reported reductions in HIT-6 scores after treatment with either oral magnesium

or sodium valproate, indicating comparable improvements in migraine-related quality of life. However, results for MIDAS scores were mixed. Karimi et al. reported no difference, whereas Khani et al. found a significant benefit of sodium valproate.[16,17] In contrast, our meta-analysis revealed a statistically significant difference favoring sodium valproate over oral magnesium in reducing MIDAS scores ($p = 0.04$), suggesting its superior efficacy in alleviating migraine-related disability (figure 8).

Gastrointestinal adverse events, particularly diarrhea and soft stool, were significantly more frequent in patients receiving oral magnesium compared to placebo ($p = 0.01$) (figure 9). This aligns with previous studies, including Pfaffenrath et al. who reported a 45.7% incidence of side effects such as diarrhea, soft stools, and palpitations.[12] Similar findings were reported by Koseoglu et al., Esfanjani et al., and Peikert et al., all noting a higher prevalence of gastrointestinal issues in magnesium-treated groups. These disturbances are likely due to the osmotic gradient created by magnesium in the intestinal lumen, drawing fluid into the lumen and causing symptoms like bloating, nausea, and diarrhea.[11,14,15]

Our meta-analysis suggests that IV magnesium is a safe and effective treatment for acute migraine attacks, particularly in emergency department settings. Oral magnesium may be a viable option for prophylaxis, especially for patients who cannot tolerate other medications. Healthcare providers should consider individual patient factors and preferences when weighing the benefits and risks of magnesium therapy. Further studies are needed to define the optimal use of magnesium in migraine management, including different formulations, dosages, and patient subgroups. Patients prescribed oral magnesium should be informed about the potential for gastrointestinal side effects.

CONCLUSION

IV magnesium is an effective acute treatment for migraine, significantly improving headache response, reducing pain intensity, and lowering the need for rescue medication with a

favorable safety profile. Oral magnesium shows potential for prophylaxis, demonstrating efficacy comparable to sodium valproate, though its benefits over placebo remain uncertain. However, its use is limited by gastrointestinal side effects. IV magnesium is a well-supported option for acute migraine attacks, while oral magnesium may be considered for prophylaxis in patients intolerant to first-line preventive therapies. However, further research is needed to standardize magnesium-based treatment protocols for migraine, establish optimal dosing strategies for both acute and preventive therapy, and enhance patient outcomes.

ACKNOWLEDGEMENT

The authors would like to thank the Faculty of Medicine and Health Science, Atma Jaya Catholic University of Indonesia, and Prof. Dr. W.Z. Johannes Regional Public Hospital, Kupang, for their support. We also extend our appreciation to all colleagues and mentors who provided valuable input during the preparation of this manuscript.

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