Review Article

The effect of riboflavin on the mean attack frequency, severity, and duration of migraine headaches: A systematic review and dose–response meta-analysis of clinical trials

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Background: Due to the anti-inflammatory and antioxidant effects of riboflavin, this vitamin can be effective in improving migraine. However, due to conflicting results in previous studies, the present study aimed to determine the effectiveness of riboflavin in improving migraine in a systematic review and dose–response meta-analysis. **Methods:** Scopus, ISI Web of Science, and PubMed databases, as well as Google Scholar, were searched up to March 15, 2025 to find trials, published in the English language, that investigated the effect of riboflavin on migraine. Quality assessment of trial studies was done using the Cochrane Collaboration tool. STATA software was used to analyze the data. **Results:** The present study included 12 trials with a total sample size 749. The dose–response meta-analysis revealed a significant linear relationship, showing that increasing riboflavin intake up to 400 mg/day was associated with greater reductions in migraine frequency and duration, without evidence of a threshold effect ($P < 0.001$). Riboflavin had a significant effect on frequency (weighted mean difference [WMD]: −1.39, 95%CI: −2.52 to −0.25; $I^2 = 91.7\%$, $P < 0.001$) and duration of migraine (WMD: −1.36, 95% CI: −2.69 to −0.03; $I^2 = 90.4\%$, $P < 0.001$) in comparison to the control. In terms of methodological approach, eight trials had a good and four had a fair quality. **Conclusion:** Riboflavin exhibits promising effects in reducing the frequency and duration of migraine. The limitations of the present study include the absence of a control group and the small sample size in some included studies.

Key words: Headache, meta-analysis, migraine disorders, riboflavin

How to cite this article: Amini S, Heidari Z, Clark CC, Bagherniya M. The effect of riboflavin on the mean attack frequency, severity, and duration of migraine headaches: A systematic review and dose–response meta-analysis of clinical trials. J Res Med Sci 2026;31:1.

INTRODUCTION

Migraine is a neurological disorder that is accompanied by debilitating headache attacks.[1] Migraine headaches have a relatively high global prevalence (about 12%–14%).[2,3] Due to the frequent need for rest and concern about subsequent recurrent painful headache attacks, these conditions significantly affect quality of life, in such a way that impairs the patient's individual and social functioning.[4-6]

One of the most important disorders leading to migraine headache attacks is impaired brain energy metabolism, resulting in impaired nerve function.[7] Mitochondrial dysfunction may be associated with decreased energy production through oxidative metabolism in the brain, which can cause an overreaction to stimuli by altering the threshold for migraine attacks and increasing nerve excitability.[8-10] Several studies have suggested a significant effect of oxidative stress and its complications on migraine pathogenesis.[11-13] Furthermore, neuroinflammation, caused by an increase

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_547_24

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Submitted: 24-Sep-2024; **Revised:** 24-Sep-2025; **Accepted:** 01-Dec-2025; **Published:** 31-Jan-2026

in pro-inflammatory cytokines in neurons, can exacerbate migraines.[14,15]

Riboflavin (Vitamin B_2), in the coenzyme form of flavin mononucleotide (FMN) and flavin adenosine dinucleotide (FAD), is effective in a wide range of oxidative reactions in the mitochondria.[16] According to a recent review, riboflavin can improve migraines due to its anti-inflammatory and antioxidant effects.[17] The results of a recent systematic review showed that riboflavin is an effective and safe strategy for migraines. Moreover, most of the trial studies included in the review by Thompson and Saluja reported moderate improvement in headaches after riboflavin supplementation.[18]

According to various articles that evaluated the effect of different doses of riboflavin in migraine, and their discrepant results, there might be a dose–response relationship between riboflavin intake and frequency, duration, and severity of migraine,[19-23] however, there is no dose–response meta-analysis available in the literature, so this study aimed to summarize the evidence on the effect of riboflavin on the mean attack frequency, duration, and severity of migraine headaches in the form of a dose–response meta-analysis.

METHODS

This systematic review and meta-analysis were designed and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24]

Search strategy

The Scopus, ISI Web of Science, PubMed databases, as well as Google Scholar, were searched up to March 15, 2025, to identify studies evaluating the effect of riboflavin on the mean attack frequency, severity, and duration of migraine headaches. The following keywords were used in the search: ("chronic migraine" OR "chronic daily headache" OR "chronic tension-type headache" OR "frequent headache" OR "chronic frequent headache" OR "transformed migraine" OR "transformed headache" OR "medication overuse headache" OR "frequent daily headache" OR "frequent migraine" OR "analgesic overuse headache" OR "rebound headache" OR "misuse of headache medication") AND ("riboflavin" OR "vitamin b2" OR "vitamin b 2" OR "vitamin g" OR "vitamin b.complex" OR "vitamin b complex" OR "vitamin b-complex" OR "water-soluble B-vitamins" OR "flavin mononucleotide" OR "FMN" OR "flavin adenine dinucleotide" OR "FAD" OR "flavoproteins" OR "diflavin" OR "7,8-dimethyl-(N-10-ribityl) isoalloxazine" OR "Flavin nucleotides" OR "riboflavin deficiency" OR "riboflavin 5′-phosphate"). In addition, Medical Subject Headings (MESH) were used where needed.

Study selection

After importing the search results into EndNote software (version X8; Thomson Reuters; https://endnote.com/) and removing duplicate entries, two independent researchers (S.A. and M.B.) evaluated the titles and abstracts of the remaining articles. When necessary, the full texts of the studies were reviewed. Studies that did not meet the inclusion criteria were excluded. In cases of disagreement regarding the inclusion or exclusion of specific studies, the researchers discussed and reached a consensus. Ultimately, parallel and crossover clinical trials examining the effects of riboflavin supplementation on the mean attack frequency, severity, and duration of migraine headaches were included in the review.

Inclusion criteria

The following inclusion criteria were considered in finding articles: (1) trial design (2) riboflavin intervention, (3) published in the English language, (4) patients with migraine headaches, and (5) assessing mean attack frequency, severity, and duration of migraine headaches.

Exclusion criteria

Exclusion criteria were as follows: (1) *in vivo* or *in vitro* studies, (2) animal studies, (3) meeting abstracts, reviews, letters, study protocol, editorial articles, or case reports, (4) Insufficient reported information, and (5) duplicate studies.

Data extraction

After screening and selecting appropriate articles, the information of studies, including the first author, date of publication, place of study, target population, sample size, gender, mean age (year), intervention (treatment), control, the dose of riboflavin supplementation, study design, duration of intervention for trials, and the mean changes in the frequency, severity, and duration of migraine headaches, were extracted by two independent researchers (S.A. and M.B.).

PICO items include the population of patients with migraine, intervention with riboflavin, and comparison with control, and the investigated results include frequency, severity, and duration of migraine, respectively [Table 1].

Quality assessment

The quality of the studies was evaluated by two separate researchers (S.A. and M.B.), using the Cochrane Collaboration tool.[25] This tool has seven domains: 1 – random sequence generation, 2 – allocation concealment method, 3 – selective reporting, 4 – incomplete outcome data, 5 – blinding of participants and staff, 6 – blinding the evaluation of the

Table 1: Detailed information about population, intervention, comparator, and outcome

PICO items	Definition
Population	Migraine patients
Intervention	Riboflavin
Comparison	Placebo or other compounds or without control group
Outcome	Mean attack frequency, severity, and duration of migraine

PICO=Population, intervention, comparator, and outcome

result, and 7 – other risk of bias. Each of these can have one of three scores of low, unclear, or high risk of bias. Finally, if a study had more than two low-risk cases, it was considered to have good methodological quality; if two low risks were present, it was considered relatively good quality, and less than two low risks were present, it was considered a study with low methodological quality.[25]

Statistical analysis

All statistical analyses were conducted using STATA software version 13 (Stata Corporation, College Station, TX, USA). P <0.05 was considered statistically significant. Effect sizes were calculated based on the mean and standard deviation (SD) of migraine frequency, severity, and duration in the intervention group. For studies reporting standard errors (SE), SD was estimated using the formula: SD = SE × $\sqrt{N}$. When only the 95% confidence interval (CI) was available, SD was derived using the formula: SD = $\sqrt{N}$ × (upper limit – lower limit) ÷3.92, as previously described by Wan *et al*.[26]

Meta-analyses were performed using the metan command. A fixed-effect model was applied when heterogeneity was low (P > 0.1), and a random-effects model was used in the presence of significant heterogeneity, following the DerSimonian and Laird method.[27]

Sensitivity analyses were conducted by sequentially excluding individual studies to assess their influence on the pooled effect size. Additional sensitivity tests were performed based on study quality (risk of bias), dosage variations (low vs. high dose), intervention duration (3 vs. 4 months), and participant age (<18 vs. >18 years). Robustness was evaluated by monitoring changes in overall estimates and heterogeneity (I^2) following each exclusion, in accordance with Cochrane recommendations.[28]

Publication bias was assessed through visual inspection of funnel plots, complemented by Begg's rank correlation test[29] and Egger's regression asymmetry test.[30] The overall effect size was reported as weighted mean difference (WMD) for migraine frequency and duration, and as standardized mean difference (SMD) for migraine severity due to differences in measurement units across studies. Dose–response relationships and multivariate synthesis were explored using advanced meta-analytic techniques, based on the frameworks proposed by Crippa and Orsini[31] and Schmid *et al*.,[32] allowing for more nuanced modeling of effect modifiers. All statistical procedures and reporting standards were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (version 6.5)[28] and the PRISMA 2020 guidelines,[24] ensuring methodological rigor and transparency.

For dose–response meta-analysis, we used restricted cubic splines with three knots, which is a commonly recommended approach to allow sufficient flexibility while avoiding overfitting. The number of knots was selected based on standard guidelines for dose–response modeling in meta-analyses, typically placing them at the 10th, 50th, and 90th percentiles of the exposure distribution.[31] We fitted both linear and non-linear models (including quadratic trends) and compared their performance using the Akaike Information Criterion (AIC). The model with the lowest AIC was selected as the best-fitting model, balancing goodness-of-fit and model complexity.[33] To evaluate the significance of non-linear trends, we conducted Wald tests. These tests assess whether the coefficients of the spline terms differ significantly from zero. In our analysis, Wald test results indicated that nonlinear models were not statistically significant (Wald test P > 0.05), and therefore, linear models were retained for final interpretation.[34]

Heterogeneity assessment

Between-study heterogeneity was assessed using the I^2 statistic, which quantifies the proportion of total variation attributable to heterogeneity rather than chance. Interpretation of I^2 followed established guidelines: 0%–40%: low heterogeneity, 30%–60%: moderate heterogeneity, 50%–90%: substantial heterogeneity, and 75%–100%: considerable heterogeneity. These thresholds were originally proposed by Higgins *et al*.[35] and further elaborated by Viechtbauer,[36] who provided a broader framework for modeling heterogeneity in random-effects meta-analysis. In cases where substantial heterogeneity remained unresolved, subgroup analyses were conducted based on study duration (3 vs. 4 months) and participant age (<18 vs. >18 years) to explore potential sources of heterogeneity.

RESULTS

Search results and study selection

The total number of studies obtained in the initial search was 1251 (PubMed; 210, Scopus; 1008, Web of Sciences; 33). The first 100 references of Google Scholar were also searched. After the elimination of duplicate studies, 1115 studies remained. Then, 737 articles were removed due to irrelevant titles and abstracts. The full

texts of the remaining articles were carefully reviewed, and 366 studies were omitted for the following reasons: review papers (n = 174), animal articles (n = 187), case–control (n = 3), and cosupplementation of riboflavin with other compounds (n = 2). Although the search extended to March 2025, several recent studies – particularly in pediatric populations – were excluded due to methodological limitations such as retrospective design.[37] Finally, 12 trial studies were included in this study [Figure 1].

All studies that met the inclusion and exclusion criteria were included in the study, and no study was subsequently excluded.

Characteristics of the included studies

This review study consisted of 12 articles published from 1994 to 2018[19-23,38-44] [Table 2]. The total sample size of all studies was 749. In terms of age range, 5 studies were performed on participants under 18 years,[20,21,23,41,43] and 6 studies were performed on over 18 years of age,[19,22,39,40,42,44] and one study did not report the age range of patients.[38] Oral riboflavin was used in all studies, and no study used a plant-based compound or other vitamin in combination with riboflavin in the intervention group. In 7 studies, the riboflavin dose was 400 mg/day,[19,38-40,42-44] one study had a dose of 200 or 400 mg/day,[41] and 4 studies had a dose less than or equal to 200 mg/day.[20-23] In 9 studies, the duration of riboflavin supplementation was 12 wee ks,[19,20,22,23,38,40,41,43,44] and in 3 studies, it was 16 weeks.[21,39,42] Among the 12 clinical trials included in this review, 3 did not have a control group,[40-42] in 3 studies, a placebo was used as a control group, but the type of placebo was not mentioned.[20,23,43] One study compared 400 mg of riboflavin plus 75 mg of aspirin with 400 mg of riboflavin.[38] In two studies, carotene,[19,21] in one study, propranolol,[22] in one study, sodium valproate,[44] and in one study, β-blockers[39] were used as a control group. It was a cross-over study[21] that, due to its heterogeneity compared to other studies, was only included in the systematic review section of the present study and was not included in the statistical analysis.

Quality of the included studies

Among 12 trials, 8 records had good quality,[19-23,41,43,44] and 4 studies were relatively good[39-40,42] [Table 3].

Comparison between baseline and postintervention with riboflavin supplementation

Frequency of migraine

Ten studies with 11 intervention arms comparing baseline and post values of migraine frequency after intervention in the riboflavin-supplemented group were included.[19,20,22,23,39-44] As shown in Figure 2, a significant reduction in migraine frequency levels was observed after intervention with riboflavin (WMD: −2.42, 95% CI: [−2.99 to −1.86]; I^2 = 90.8%, P < 0.001). No publication bias was observed in these studies (Begg's test P = 0.102; Egger's test P = 0.117). In the sensitivity analysis of these articles, the omission of any of the studies did not significantly change the overall effect size. A subgroup analysis based on age (age group under 18 or over 18 years) showed a significant reduction in migraine frequency in the riboflavin group in both age ranges (age >18; WMD: −1.87, 95% CI: [−2.40 to −1.34];

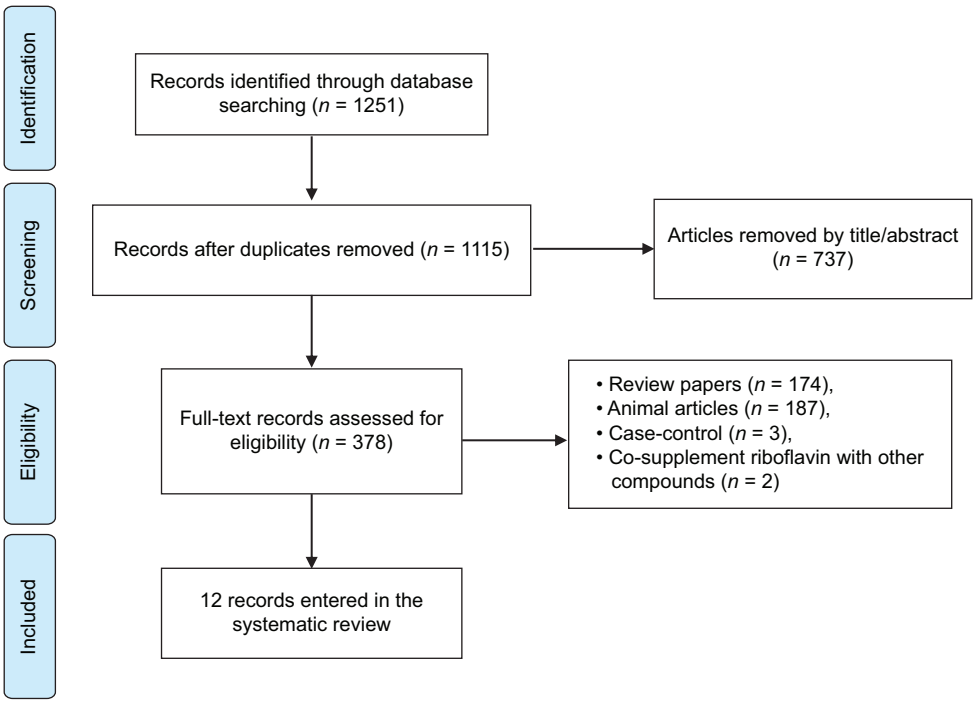

Figure 1: Flow diagram of the literature selection process

Table 2: The characteristics of included randomized trials (arranged alphabetically by year of publication)

ID	First author (publication year)	Country	Sample size (male/female)	Mean age (or range of age)	Study design	Population	Duration	Riboflavin dose in the intervention group	Control group	Frequency (number of migraine attacks/month)	Duration (h/month)	Severity
1	Schoenen (1994)[1]	Belgium	44 (NM)	NM	Clinical trial-an open pilot study	Migraine patients	12 weeks	400 mg/day	400 mg riboflavin plus 75 mg aspirin	NM	NM	↔ (↓ in both groups)
2	Schoenen (1998)[2]	Belgium	54 (12/42)	18–65	RCT	Migraine patients	12 weeks	400 mg/day	Avicel (850 mg) + carotene (0.473 mg)	↓	↓	↓
3	Sándor (2000)[3]	Belgium	26 (5/20)	30.9±14.4	Clinical trial	Migraine patients	16 weeks	400 mg/day	β-blockers	↔	NM	↔
4	Boehnke (2004)[4]	Germany	23 (4/19)	52.09±10.05 (20–65)	Clinical trial	Migraine patients	12 weeks	400 mg/day	No control group	↓	↔	↔
5	MacLennan (2008)[5]	Australia	48 (24/24)	5–15	RCT	Migraine patients	12 weeks	200 mg/day	Placebo (type: NM)	↔	↔	↔
6	Condò (2009)[6]	Italy	40 (16/25)	8 years, 11 months–18 years, 10 months	Clinical trial	Migraine patients	12 weeks	200 OR 400 mg/day	No control	↓	NM	↓
7	Di Lorenzo (2009)[7]	Italy	64 (NM)	18.81±8.9	Clinical trial	Migraine patients	16 weeks	400 mg/day	No control	↓	↔	NM
8	Bruijn (2010)[8]	Netherland	42 (NM)	6–13	RCT-Cross-over	Migraine patients	16 weeks	50 mg/day	Carotene 100 mg	↔*	↔	↔
9	Nambiar (2011)[9]	India	100 (45/55)	18–65 (31.5±7.6)	Open-label RCT	Migraine patients	12 weeks	100 mg/day	Propranolol 80 mg/day	↔	↔	↓
10	Athaillah (2012)[10]	North Sumatera	98 (27/71)	12–19 (mean: 14)	Randomized, double-blind, controlled trial	Migraine patients	12 weeks	400 mg/day	Placebo (type: NM)	↓	↓	NM
11	Rahimdel (2015)[11]	Iran	90 (18/78)	15–55	RCT	Migraine patients	12 weeks	400 mg/day	Sodium valproate (500 mg/day)	↔	↔	↔
12a	Talebian (2018)[12]	Iran	60 (NM)	5–13	Randomized, double-blind, placebo-controlled trial	Migraine patients	12 weeks	100 mg/day	Placebo (type: NM)	↔	↔	↔
12b	Talebian (2018)[12]	Iran	60 (NM)	5–13	Randomized, double-blind, placebo-controlled trial	Migraine patients	12 weeks	200 mg/day	Placebo (type: NM)	↓	↓	↔

*No significant difference in the reduction of mean attack frequency of migraine attacks in the last month of treatment was found between placebo and riboflavin (P=0.44). However, a significant difference in the reduction of the mean attack frequency of headaches with a tension-type phenotype was found in the riboflavin treatment (P=0.04). ↓=Decreasing effect; ↑=Increasing effect; ↔=No significant effect; RCT=Randomized controlled trial; NM=Not mentioned

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Table 3: Risk of bias assessment for included randomized clinical trials

ID	First author (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other risks of bias	Total quality
1	Schoenen (1994)[1]	H	H	H	H	U	L	L	Relatively good
2	Schoenen (1998)[2]	L	L	L	L	L	L	L	Good
3	Sándor (2000)[3]	H	H	H	H	H	L	L	Relatively good
4	Boehnke (2004)[4]	H	H	H	H	U	L	L	Relatively good
5	MacLennan (2008)[5]	L	L	L	L	L	L	L	Good
6	Condò (2009)[6]	U	U	H	H	L	L	L	Good
7	Di Lorenzo (2009)[7]	U	U	H	U	U	L	L	Relatively good
8	Bruijn (2010)[8]	L	L	L	L	L	L	L	Good
9	Nambiar (2011)[9]	L	L	H	H	U	L	L	Good
10	Athaillah (2012)[10]	U	U	U	U	L	L	L	Good
11	Rahimdel (2015)[11]	L	L	U	H	L	L	L	Good
12	Talebian (2018)[12]	L	L	L	L	L	L	L	Good

L=Low risk of bias

H=High risk of bias

U=Unclear risk of bias

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I^2 = 89.5%, P < 0.001), (age < 18; WMD: −3.54, 95% CI:[−5.43 to −1.65]; I^2 = 90%, P < 0.001). In another subgroup analysis based on the period of riboflavin supplementation (3 or 4 months), a significant reduction in migraine frequency was observed in the riboflavin group in both intervention periods – 3 months (WMD: −2.62, 95% CI: [−3.27 to −1.98]; I^2 = 92.6%, P < 0.001) and 4 months (WMD: −1.60, 95% CI: [−2.33 to − 0.087]; I^2 = 0.0%, P = 0.512).

Among the studies that investigated the frequency of migraine, 7 studies had a control group[19,20,22,23,39,43,44] and 3 studies had no control.[40-42] In subgroup analysis based on control, a significant decrease in migraine frequency was observed in both the results of studies with control (WMD: −2.65, 95% CI: [−3.56 to −1.73]; I^2 = 93%, P < 0.001) and studies without control (WMD: −2.39, 95% CI: [−3.87 to −0.92]; I^2 = 76.1%, P = 0.015).

Duration of migraine

Four studies, with 5 intervention arms, that compared baseline and post values of migraine duration in the riboflavin-supplemented group,[19,22,23,44] showed a significant reduction (WMD: −3.36, 95% CI: [−5.25 to −1.47]; I^2 = 97.5%, P < 0.001) [Figure 3]. No publication bias was observed in the Egger's test (P = 0.106), but in the Begg's test (P = 0.014), publication bias was observed. Also, by examining the funnel plot, publication bias was observed in these studies. In the sensitivity analysis of these articles, the omission of any of the studies did not significantly change the overall effect size. In the subgroup analysis based on age, a significant decrease in duration of migraine was observed in the age group over 18 years (WMD: −4.46, 95% CI: [−8.35 to −0.58]; I^2 = 98.5%, P < 0.001), but this decrease was not statistically significant in the under 18 years age group (WMD: −2.04, 95% CI: [−5.79 to 1.71]; I^2 = 96.7%, P < 0.001).

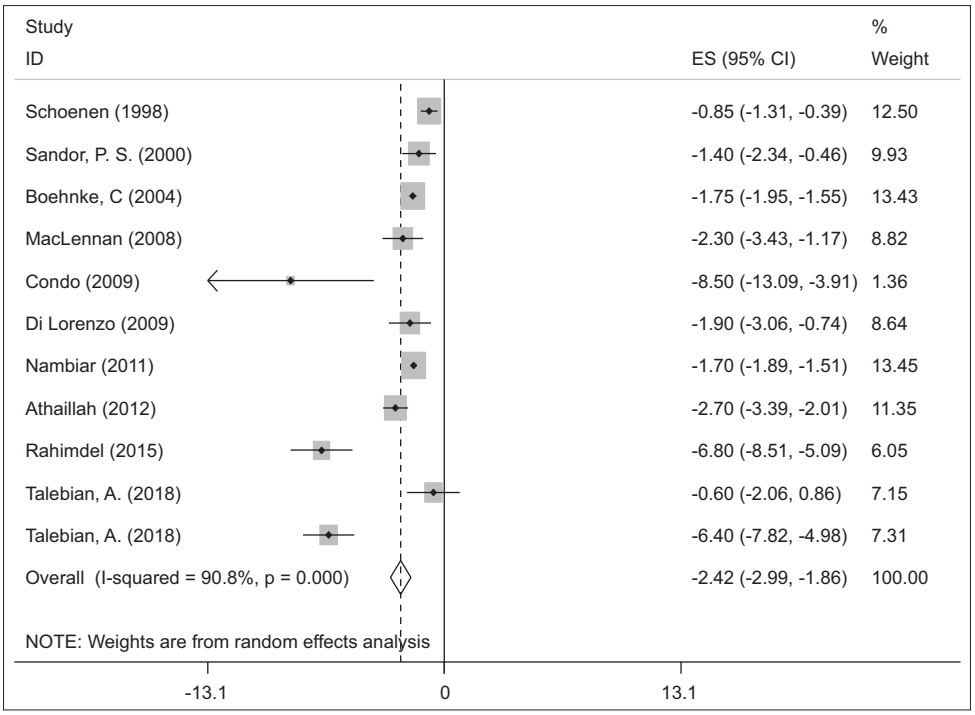

Figure 2: Comparison of migraine frequency before and after intervention with riboflavin supplement in all studies that reported migraine frequency

Severity of migraine

Five trial studies, with 6 intervention arms, evaluated the effect of riboflavin on migraine severity.[19,22,23,38,39] Unexpectedly, an increase in migraine severity was observed after riboflavin supplementation compared to baseline (WMD: 0.68, 95% CI: [0.39 to 0.98]; I^2 = 86.8%, P < 0.001) [Figure 4].

No publication bias was observed by Egger's (P = 0.091) and Begg's test (P = 0.558). Furthermore, publication bias was not observed in the funnel plots. In the sensitivity analysis of these articles, the omission of any of the studies did not significantly change the overall effect size.

Subgroup analysis based on age (age >18; 95% CI: 0.94 [0.43 to 1.45]; I^2 = 85.9%, P < 0.001), (age < 18; WMD: 0.43, 95% CI: [0.29 to 0.56]; I^2 = 32.5%, P = 0.224) and duration of use (3 months; WMD: 0.70, 95% CI: [0.36 to 1.03]; I^2 = 89.2%, P < 0.001), (4 months; WMD: 0.68, 95% CI: [0.34 to 1.02]; I^2 = 0.0%, P = 0.0) also showed an increase in migraine severity after riboflavin supplementation.

Comparison between riboflavin supplementation and control

Frequency of migraine

We analyzed 7 studies with 8 intervention arms that evaluated the effect of riboflavin supplementation, compared with control, on migraine frequency.[19,20,22,23,39,43,44] In general, riboflavin had a statistically significant effect on migraine frequency compared with control (WMD: −1.39, 95% CI: [−2.52 to −0.25]; I^2 = 91.7%, P < 0.001) [Figure 5]. Publication bias was not observed in these studies (Begg's test P = 0.322; Egger's test P = 0.146), also in the sensitivity analysis of these articles, with the omission of any of the studies, the overall effect size did not change significantly. Subgroup analysis of riboflavin intake period showed that 3-month intake of this supplement was associated with a significant reduction in migraine frequency (WMD: −1.61, 95% CI: [−2.88 to − 0.34]; I^2 = 92.9%, P < 0.001), but 4-month intake did not show a significant change (WMD: 0.1, 95% CI: [−1.19 to 1.39]; I^2 = 0%, P < 0.001). Although it is interesting to note that only one study reported the effect of riboflavin on migraine frequency over 4 months, more studies are needed to evaluate this more accurately.

Duration of migraine

Meta-analysis of 4 studies, with 5 intervention arms, comparing the effect of riboflavin with control on the duration of migraine showed a statistically significant reduction[19,22,23,44] (WMD: −1.36, 95% CI: [−2.69 to −0.03]; I^2 = 90.4%, P < 0.001) [Figure 6]. Publication bias was not observed in these studies (Begg's test P = 0.327; Egger's test P = 0.092), also in the sensitivity analysis of these articles, with the omission of any of the studies, the overall effect size did not change significantly.

Severity of migraine

In the intergroup intensity meta-analysis, 4 studies with 5 intervention arms were included.[19,22,23,39] Riboflavin generally reduced the severity of migraines, but this reduction was not statistically significant compared with control (SMD: −0.09, 95% CI: [−0.5 to 0.32]; I^2 = 66.7%,

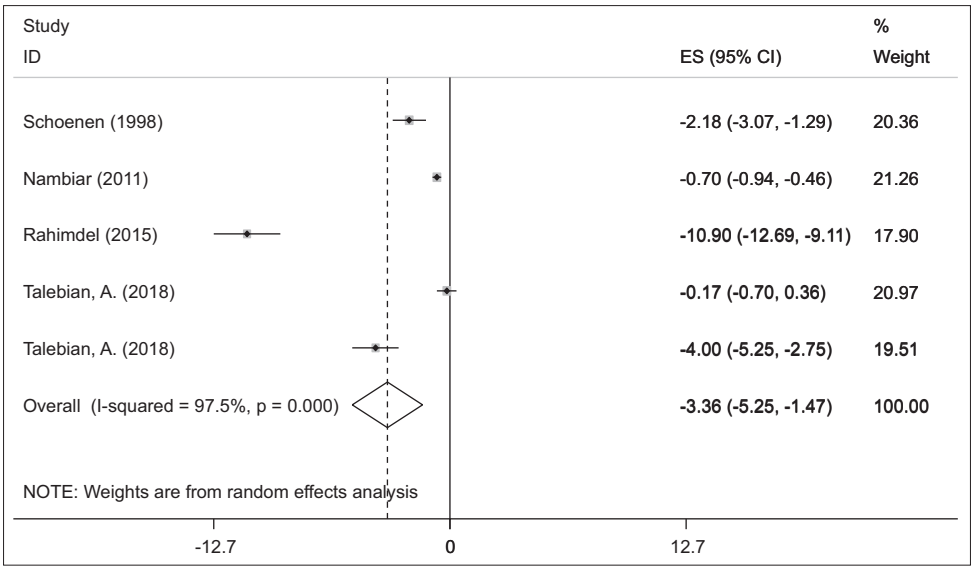

Figure 3: Comparison of migraine duration before and after intervention with riboflavin supplement in all studies that reported migraine duration

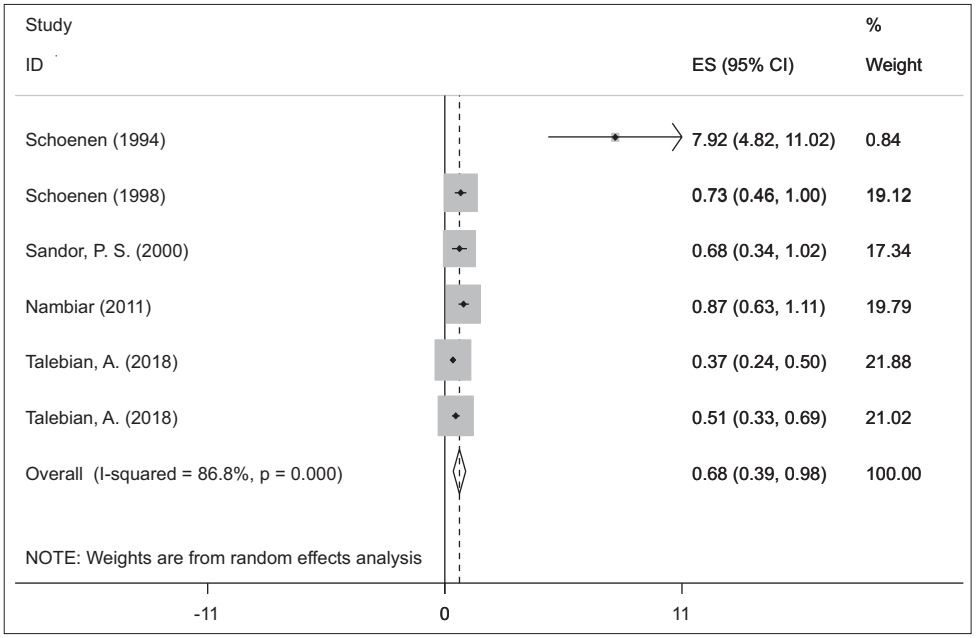

Figure 4: Comparison of migraine severity before and after intervention with riboflavin supplement in all studies that reported migraine severity

$P = 0.017$) [Figure 7]. Publication bias was not observed in these studies (Begg's test $P = 0.624$; Egger's test $P = 0.707$), also in the sensitivity analysis of these articles, with the omission of any of the studies, the overall effect size did not change significantly. In the subgroup analysis based on age (age group under 18 or over 18 years), a decrease in migraine severity was observed in the intervention group compared to control, however this was not statistically significant (>18; SMD: −0.07, 95% CI: [−0.87 to 0.72]; $I^2 = 83.1\%$, $P = 0.003$), (<18; SMD: −0.07, 95% CI: [−0.43 to 0.29]; $I^2 = 0\%$, $P = 0.796$). In subgroup analysis based on the duration of intervention, with 3-month riboflavin intervention, a decrease in migraine severity was observed, but this reduction was not statistically significant (SMD: −0.22, 95% CI: [−0.6 to 0.15]; $I^2 = 57.2\%$, $P = 0.072$).

Dose–response meta-analysis

Frequency of migraine

For dose–response meta-analysis of the frequency of migraine, 7 studies with 8 intervention arms were included.[19,20,22,23,39,43,44] We used restricted cubic splines with three knots and models with linear and quadratic trends. According to the results of the Wald statistic, none of the nonlinear models were significant. After fitting the models, the linear dose–response model-1 had the lowest AIC (69.41). By visual examination of the chart, it was

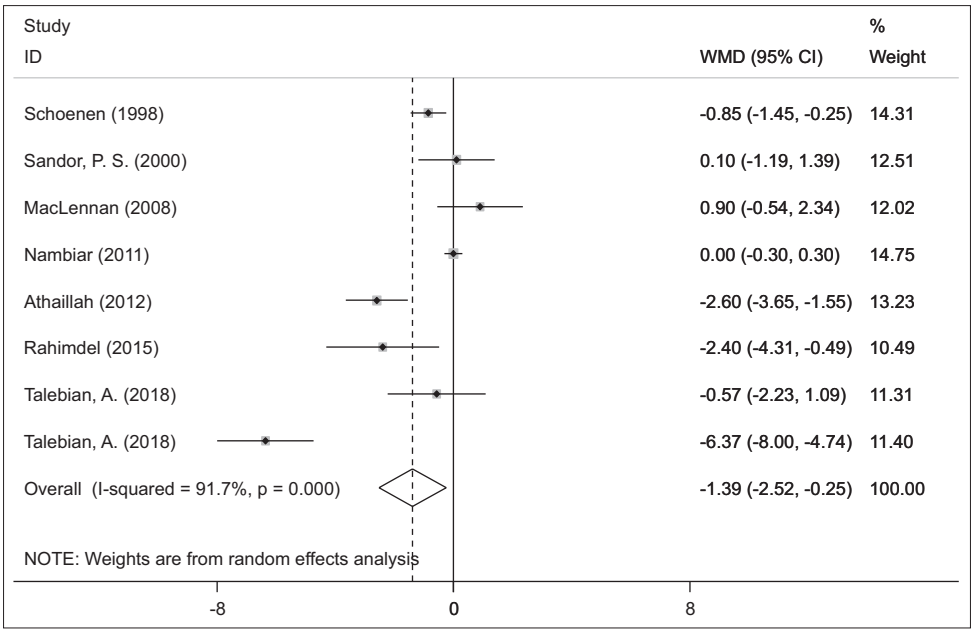

Figure 5: Effect of riboflavin supplementation on migraine frequency compared to control in all studies that reported migraine frequency

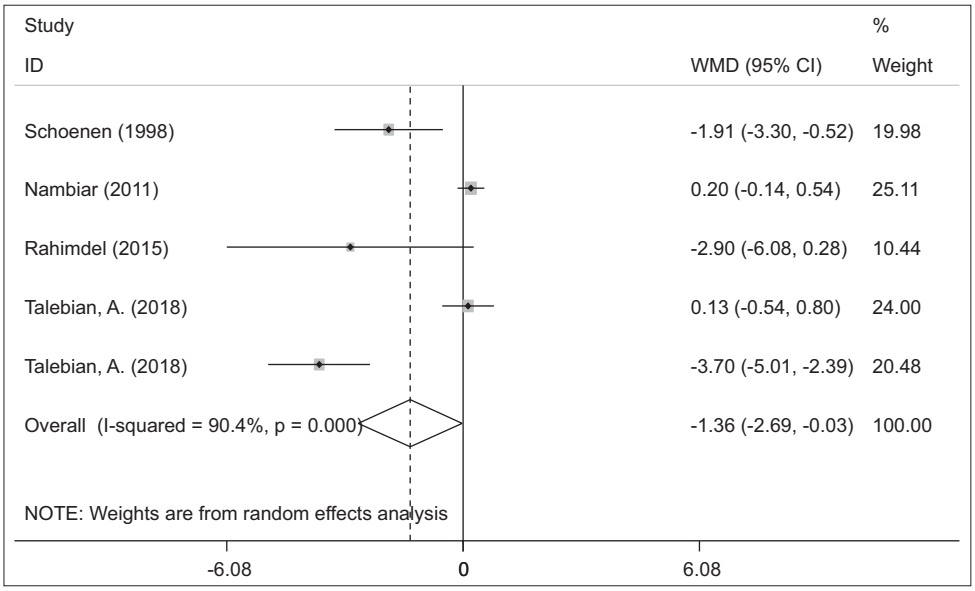

Figure 6: Effect of riboflavin supplementation on migraine duration compared to control in all studies that reported migraine duration

observed that with increasing riboflavin consumption from 0 to 400 mg/day, the migraine frequency decreased with a significant linear slope ($P < 0.001$) [Figure 8].

Duration of migraine

Four studies with 5 intervention arms were included in the dose–response meta-analysis of the duration of migraine.[19,22,23,44] We used restricted cubic splines with three knots and models with linear and quadratic trends. According to the results of the Wald statistic, none of the non-linear models were significant. After fitting the models, the linear dose–response model-1 had the lowest AIC (17.71). Significant results were observed in reducing the duration of migraine by increasing the intake of riboflavin from zero to 400 mg/day. The resulting graph was linear with a steady and significant slope ($P < 0.001$) [Figure 9].

Severity of migraine

We included 4 studies with 5 intervention arms for dose–response meta-analysis of the severity of migraine.[19,22,23,39] We used restricted cubic splines with three knots and models with linear and quadratic trends. According to the results of the Wald statistic, none of the non-linear models were significant. After fitting the models, the linear

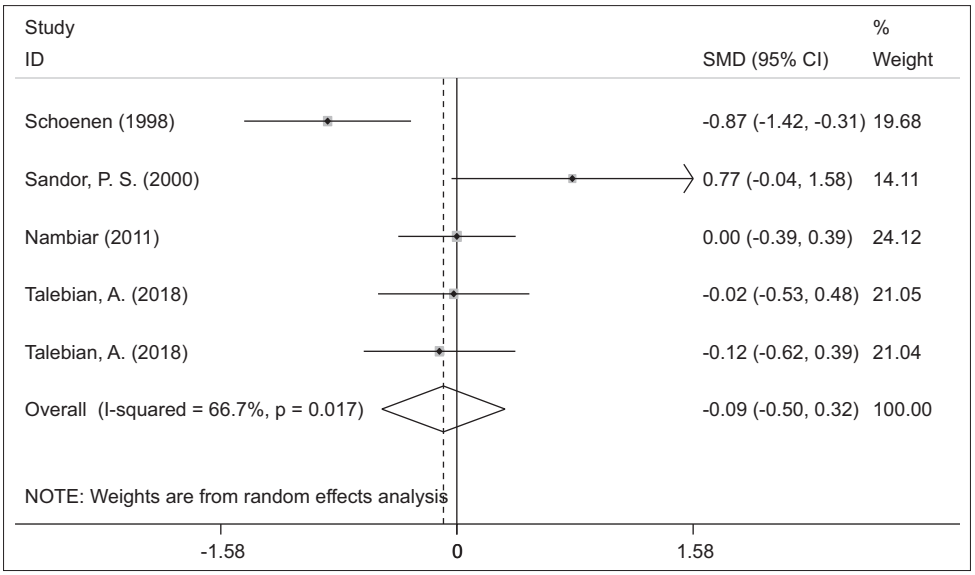

Figure 7: Effect of riboflavin supplementation on migraine severity compared to control in all studies that reported migraine severity

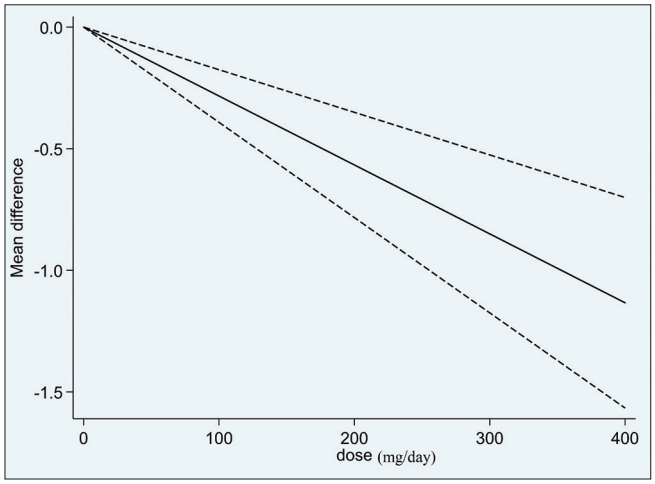

Figure 8: Dose-response meta-analysis of frequency of migraine

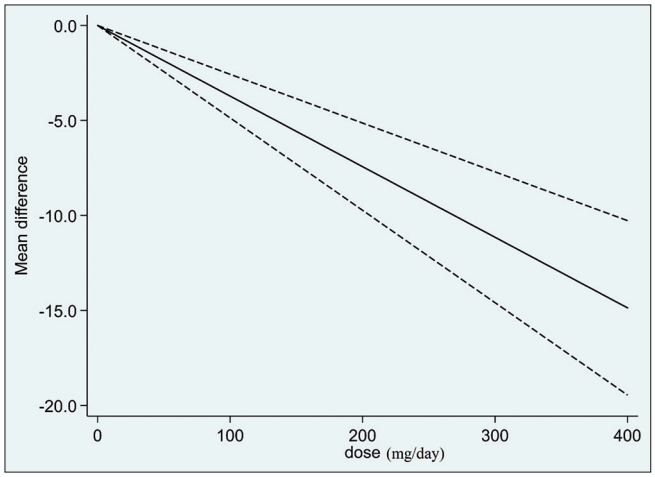

Figure 9: Dose-response meta-analysis of the duration of migraine

dose–response model-1 had the lowest AIC (7.05). By visual examination of the resulting graph, with increasing riboflavin consumption from 0 to 400 mg/day, a very slow decline in migraine severity was observed, but it was not statistically significant ($P = 0.577$) [Figure 10].

DISCUSSION

The aim of this study was to systematically review and dose–response meta-analyze the effect of riboflavin on the mean attack frequency, duration, and severity of migraine headaches. The current study includes 12 clinical trial studies with 13 study arms.[19-23,38-44] The investigated factors included the frequency, duration, and severity of migraine.

The findings of this study reinforce the potential role of riboflavin as a therapeutic intervention for migraine management, particularly in reducing migraine frequency and duration. The observed improvements across various age groups highlight the importance of considering riboflavin supplementation as a non-pharmacological treatment option. Given the significant reduction in migraine frequency following 3 months of supplementation ($P < 0.001$), clinicians may consider recommending riboflavin as part of a preventative strategy for migraine sufferers.

However, the absence of statistically significant results for migraine duration in individuals under 18 years of age ($P > 0.05$) suggests the need for further research before definitive clinical guidelines can be established for younger patients. Since only one study has examined this aspect, future clinical trials should focus on assessing the efficacy of riboflavin supplementation in patients under 18 years of age with more robust study designs.[23]

In the subgroup analysis based on the duration of the riboflavin supplementation period, a significant decrease

in the frequency of migraine was observed following 3 months of riboflavin supplementation ($P < 0.001$), but the frequency changes in 4 months compared with control were not significant ($P > 0.05$). An important point in this regard is that only one study investigated the effect of riboflavin supplementation compared with control on migraine frequency over 4 months, and this study did not observe a significant effect of this supplementation on migraine frequency.[39] Therefore, considering that the result of one study cannot be considered as a comprehensive reference, it is recommended that more studies evaluate 4 months.

Riboflavin generally reduced the severity of migraines, but this reduction was not statistically significant compared with control ($P > 0.05$). Among these studies, only one study had an ineffective control group.[23] Therefore, due to the lack of a suitable control group, the results may have uncorrectable bias, so it is suggested that future studies investigate the effect of riboflavin on migraine severity in better-controlled clinical trial studies.

In the results of the dose–response analysis, a significant linear relationship was observed based on the one-stage fixed-effect dose–response model-1 between riboflavin intervention with the frequency and duration of migraine. Significant results were observed in reducing the frequency and duration of migraine by increasing the intake of riboflavin from zero to 400 mg per day ($P < 0.001$). However, no significant results were obtained in the dose–response analysis of migraine severity ($P = 0.577$), which may be related to the lack of a suitable control group in most studies investigating the effect of riboflavin on migraine severity.

Publication bias was not reported in most parts of the study. Of course, in the comparison of the duration of migraine with the baseline, no publication bias was observed in the Egger's test ($P = 0.106$), but in the Begg's test ($P = 0.014$), publication bias was observed. Furthermore, by examining the funnel plot, publication bias was observed in these studies. These findings highlight the presence of publication bias in some aspects of the analysis, which may have affected the estimated effect size and overall interpretation of the results. The discrepancy between Egger's and Begg's tests suggests that different statistical approaches may yield varying assessments of publication bias. The asymmetry observed in the funnel plot further supports this notion, indicating that smaller studies with nonsignificant results may be underrepresented.

To mitigate the impact of publication bias, future research should prioritize comprehensive reporting, including unpublished studies and registered trials, to enhance the robustness of meta-analytic findings. In addition, alternative statistical techniques, such as the "trim and fill" method, may provide adjusted estimates that account for the influence of missing studies. Despite these limitations, the primary conclusions of this study remain relevant, though they should be interpreted with caution, considering the potential effect of publication bias on the reported results.

Migraine attacks are usually caused by a disorder in the brain's energy metabolism.[7] In the case of mitochondrial dysfunction, which plays an important role in the electron transport chain and oxidative metabolism, can reduce the threshold for migraine attacks by reducing energy production.[10] Oxidative stress and neuroinflammation are influential factors in the pathogenesis of migraine.[12,14]

Riboflavin (Vitamin B_2) is effective in providing adequate energy to brain neurons and improving the threshold for migraine attacks due to its important role in mitochondrial oxidative metabolism[16,18] [Figure 11]. This vitamin can exhibit antioxidant effects by acting on the redox cycle of glutathione and its effect on enzymes that reduce oxidative

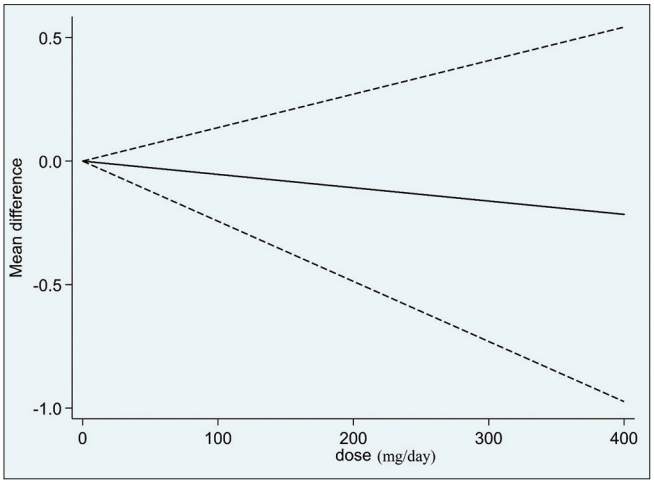

Figure 10: Dose-response meta-analysis of severity of migraine

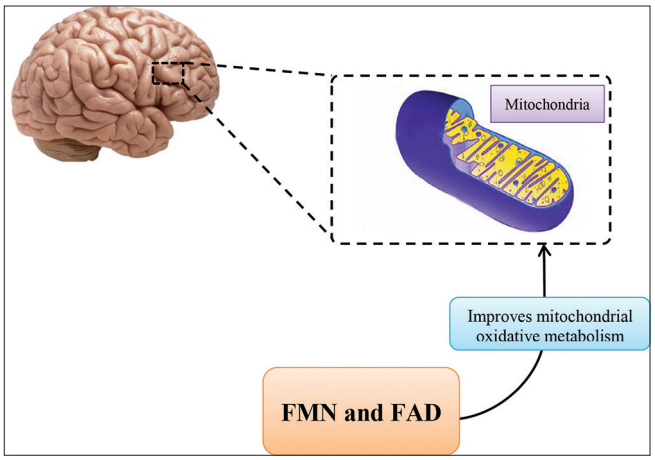

Figure 11: Possible mechanism of riboflavin effect (precursor of flavin mononucleotide and flavin adenosine dinucleotide) on improving oxidative metabolism of mitochondria in the brain

stress. It also exerts anti-inflammatory effects by suppressing nuclear factor kappa and tumor necrosis factor-alpha.[17] A recent systematic review identified riboflavin as an effective and safe strategy for migraines.[18]

A recent meta-analysis was conducted to assess the effectiveness of riboflavin in the treatment and management of migraines.[45] This study reviewed multiple trial articles and included a total of nine studies. However, two of these studies investigated the impact of riboflavin in combination with other substances rather than as a standalone intervention. While these findings contributed valuable insights, they did not fully isolate the effects of riboflavin alone.

In contrast, the present study provides a more comprehensive and detailed analysis by including 12 clinical trial studies with 13 intervention arms. One of the key distinctions of this research is its exclusive focus on riboflavin as an independent intervention. By analyzing its effects separately, this study aims to offer a clearer and more precise evaluation of riboflavin's role in migraine management without the potential confounding influence of other substances.

In addition, the present study incorporates a dose–response meta-analysis, which enables a thorough examination of the relationship between varying dosages of riboflavin and their impact on migraine symptoms. This methodological approach enhances the depth of the analysis by determining whether different dosages contribute to varying levels of effectiveness.

Overall, this study expands upon previous research by presenting more complete and comprehensive findings compared to the earlier meta-analysis. Through a focused investigation of riboflavin alone and the inclusion of a dose–response analysis, this study provides valuable insights that can better inform future clinical applications and recommendations regarding riboflavin's potential benefits in migraine treatment.

The current study, although novel, has some limitations. First, some of the studies included in this review did not have a control group, or the control group was itself an intervention and not an ineffective control. In addition, some studies had a small sample size. We are unable to control these limitations, so it is advisable to interpret the results of the present study with extreme caution. Although recent observational studies suggest potential benefits of riboflavin in pediatric migraine,[37] their exclusion from this meta-analysis due to methodological constraints may limit the generalizability of our findings. Future randomized controlled trials are needed to address this gap. According to these limitations, conducting future clinical trial studies with a higher sample size and well-defined control groups is strongly advocated to permit elucidation of the true effect.

CONCLUSION

The results of the present review showed that riboflavin supplementation, as an inexpensive, readily available, and safe supplement, can improve the frequency and duration of migraine. However, no beneficial effect on migraine severity was observed. Riboflavin caused a significant decrease in the frequency of migraine in all ages and a decrease in the duration of migraine in those over 18 years old compared to the baseline. A reduction in migraine severity compared to controls was also observed in all ages, but this was nonsignificant ($P > 0.05$). Notwithstanding the tentatively positive findings, further studies are needed for a more accurate assessment of this issue, so it is suggested that more clinical trial studies, based on dose, duration of use, and other factors, are conducted.

Acknowledgments

All authors were fully responsible for the validity and reliability of the data, analysis, and writing of the article.

Isfahan University of Medical Sciences has approved and founded this study with grant number 299247 and ethical code IR.MUI.RESEARCH.REC.1399.736.

Financial support and sponsorship

Isfahan University of Medical Sciences has funded this study with grant number 299247 and ethical code IR.MUI.RESEARCH.REC.1399.736.

Conflicts of interest

There are no conflicts of interest.

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