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Research Article

Effectiveness of combination therapy of magnesium, vitamin B2 and Co-enzyme 10 supplementation on vestibular migraine: a retrospective cohort study

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Abstract

Vestibular migraine (VM) has conventionally been treated through acute migraine-aborting therapeutic interventions and prevention to reduce migraines' occurrence, length and intensity. There is growing attention to the development of non-pharmaceutical prophylactic interventions for migraines in the search for effective treatments, such as through mineral, vitamin and other supplementation. This research aims to examine the effectiveness of magnesium, vitamin B_2 and Co-enzyme 10 supplementation to decrease vestibular migraines' frequency, duration and severity. Method: This retrospective cohort study was conducted in a Jordanian context over 57- VM patients, each patient attending the outpatient dizziness clinic between August 2022 and February 2023. Patients were treated for six months with a combined supplementation of magnesium, vitamin B_2, and Co-enzyme Q10. Assessments were made of three measures of VM attack, namely frequency, duration and severity, both before and after intervention. Result: Supplements administration demonstrated a significant reduction (by 81.1%) in VM-symptoms frequency ($p < 0.001$). Moreover, reductions in symptom duration in minutes occurred progressively as the treatment period continued and showed statistical significance, with impacts upon over 80% of the sample and a reduction from 763.9 minutes to 122.5 minutes ($p < 0.001$). The mean of pre-intervention severity was 7.2/10, with a significant decrease shown following treatment, at 2.1/10, and very positive results for over 71% of the sample ($p < \mathbf{0.001}$). Conclusion: The preliminary findings of this study showed a promising potential for such supplements in the treatment and prevention of VM; however, more research and a prospective trial are recommended.

Keywords

Vestibular Migraine (VM), Vitamin B_2 (Riboflavin), Magnesium, Co-enzyme Q10

Introduction

Vestibular migraine (VM) is the most frequent and second most frequent causal factor, respectively, in spontaneous episodic vertigo and vertigo (Shen and Qi 2022). Under the International Classification of Headache Disorders (ICHD), VM is a unified term referring to combined migraine-related and vestibular symptom sets (Smyth et al.

2022). VM is growing more frequent as a causal diagnosis in episodic vertigo but is thought to remain underdiagnosed. Vertigo and migraines have been associated with neurology since the nineteenth century (Liveing 1873).

VM diagnoses are made based on clinical patient histories. The condition presents diagnostic challenge based on the absence of agreed biomarkers or diagnostic testing to confirm the diagnosis (Nowaczewska 2020), as well as the fact that certain VM symptoms are shared by a range of disorders, including Ménière's disease, classic migraines, migraines with brainstem aura, posterior circulatory ischemia, benign paroxysmal positional vertigo, vestibular paroxysmia, vestibular neuritis, multiple lacunar infarctions, type two episodic ataxia and travel sickness. Patients suffering from classical migraines can occasionally report vestibular disturbance: however, this is insufficient to be diagnosed as VM (Shen and Qi 2022; Webster 2023). Based on the above, there is a pressing need for diagnostic criteria in order to increase VM diagnosis rates while reducing misdiagnoses of the condition. According to Shen and Qi (2022), VM diagnosis is reliant upon the symptom set, severity, length and frequency of vestibular attacks, as well as migraine history and co-occurrence of vestibular and migraine symptoms in half or more of occurrences, in addition to discounting other potential causes of symptoms.

Neuhauser et al. (2001) originally put forward the diagnostic criteria currently in place with the subsequent approval of the International Headache Society. Moreover, the Bárány Society's Committee for the International Classification of Vestibular Disorders (ICVD) (Lempert et al. 2012) specifies that patient histories include migraine with overlapping vestibular symptoms for a minimum of 50% of attacks while considering the potential for probable VM (Table 1). As VM does not have a gold standard or objective criteria for diagnosis, it is significant that the criteria described have demonstrated reliability in multiple evaluations across nine years (Radtke et al. 2011).

Pathophysiological processes in VM remain poorly understood. However, these probably have similarities to classical migraines. In both diagnoses, females are significantly more highly represented, lacking a detailed explanation (Arnold 2018). It is thought that genetics and environment are each significant in VM (Özçelik et al. 2022).

VM management can include lifestyle changes, exercises to improve spatial orientation perception, modified diet, medication, and vestibular physical therapy (Paz-Tamayo et al. 2020). Currently, medication-based intervention for VM includes prophylaxis as well as interventions for acute episodes. Many of these treatments have been developed from commonly applied treatments for classical migraines (Huang et al. 2020). Various medications are available to treat acute migraines, such as paracetamol, antiemetic drugs, triptans and non-steroidal anti-inflammatory drugs (NSAIDs) (Webster et al. 2022).

Guidance issued by the European Federation of Neurological Societies suggests that prophylaxis may be appropriate if the patient has a significantly limited quality of life, if they suffer more than one acute migraine per month, if migraines are unresponsive to acute interventions, or where auras are frequently-occurring, lengthy or cause discomfort (Ryliškienė and Jokubaitis 2022). Current medications used as prophylaxis are the beta-blockers propranolol and metoprolol; flunarizine and other calcium channel blockers; antidepressant medications such as amitriptyline, nortriptyline and venlafaxine; antiepileptics, e.g. topiramate and sodium valproate; antiserotonergics, including pizotifen; antihypertensive drugs, i.e. candesartan and lisinopril; calcitonin gene-related peptides (CGRPs); monoclonal antibody therapies, such as erenumab, fremanezumab and galcanezumab; and supplementation with vitamins (Ahmed et al. 2019).

In spite of this wide range of interventions, patient dissatisfaction remains high, as conventional medications are costly and ideal control is frequently not attained. Moreover, the large, randomized placebo-based control trials required to verify the effectiveness of the interventions have not been carried out (Huang et al. 2020). In addition, several drugs currently used for this purpose have negative side-effects which are not acceptable (Pittler and Ernst 2004). Among these, Propranolol can trigger bronchoconstriction and is linked to exacerbation of depressive illness, as well as to impotence, while Flunarizine can lead to patients gaining weight, and cause nausea and drowsiness (Evers et al. 2009). Topiramate can also present adverse effects, including dysfunctional cognition, paresthesias and drowsiness, and Amitriptyline is linked

Table 1. Bárány Society/International Headache Society VM criteria (10).

Vestibular Migraine	Probable Vestibular Migraine
A. Minimum of five episodes including moderate or severe vestibular symptoms, of duration between five minutes and 72 hours.	**A.** Minimum of five episodes including moderate or severe vestibular symptoms, of duration between five minutes and 72 hours.
B. Currently or previously experiencing migraine, which may or may not have an aura, following the International Classification of Headache Disorders (ICHD)	**B.** A single criterion from VM criteria B and C is met: either history of migraines or migraine characteristics in the episodes, but not both.
C. Single or multiple migrainous symptoms alongside a minimum of half of vestibular episodes: • Headache accompanied by 2 or more of the symptoms listed: located on a single side of the head, feeling of pulsation, pain is from moderate to high severity, exacerbated when carrying out normal physical activities • Phono- and photo-phobia • Aura (experienced visually)	**C.** Symptoms cannot be more satisfactorily explained by other vestibular/ICHD diagnoses.
D. Symptoms cannot be more satisfactorily explained by other vestibular/ICHD diagnoses.	

to sedative, constipating, conduction blocking and weight gain effects (Salviz et al. 2016).

Thus, the growing attention to developing alternative options to pharmaceuticals in prophylactic treatment of migraine is partially underpinned by the requirements for efficacy with a lower adverse effects burden, and this has led to assessments of vitamin and mineral supplements, as well as herbal medicines (Brevern and Lempert 2020).

The current article reports on a study applying six-month supplementation with Vitamin B_2, Co-enzyme 10, and magnesium as a prophylactic for preventing acute VM. Here, efficacy is examined for this regimen in reductions in the rate of occurrence, length and intensity of attacks.

Materials and methods

The research was developed following a retrospective analytical observational design and carried out in Jordan at Royal Medical Services Hospital, at the outpatient dizziness clinic within the Department of Otolaryngology. The clinic is at a tertiary facility and patients are referred from secondary and primary care contexts.

Patients

This retrospective cohort study had a patient sample of 57 individuals enrolling in the period August 2022 to February 2023. Each patient was examined for neurological, ear, nose and throat issues, and then an audio vestibular investigations done were, PTA (Pure Tone Audiometry), VNG (Video Nystagmo Gram), c+o-VEMP(cervical and ocular Vestibular Myogenic Evoked Potentials), the imaging method was Brain MRI. The sample was selected in line with specific criteria and patients were included in the study group if they met all these criteria (Table 2).

Data was gathered concerning VM in terms of length, severity and rate of occurrence, with each of these factors being measured prior and post-supplementation.

Supplements

Patients were given six months' combined supplements consisting of 200 mg Vitamin B_2 tablet (once daily), 300 mg Magnesium tablet (once daily) and 100 mg Co-enzyme 10 tablets (three times daily). For the study patients, no other medicines were prescribed to treat VM.

Evaluation criteria

Criteria used to evaluate effectiveness included: frequency of VM, expressed as days with attacks each month; severity, the scaling of dizziness severity used is NDS (Numeric Dizziness scale), from (0–10); which is a subjective individual rating scale designed to quantify dizziness intensity; in which 0 refers to no dizziness and 10 to the worst imaginable dizziness (Rice et al. 2018). and duration, in which the length of an attack is measured in minutes. These criteria were assessed over the 6-month supplementation period.

Statistical analysis

The collected data was analyzed using the Statistical Package for Social Sciences (SPSS), 24th Edition, applying mean, standard deviation (SD) and percentage frequency to analyze category and continuous variables. Between-group variations in VM length, intensity and frequency were evaluated pre- and post-intervention, using paired-t tests. Findings with p-values of 0.05 and below were assessed as statistically significant.

Ethical approvals

This research followed the ethical standards set out by Royal Medical Services in their Medical Committee's declaration.

Results

Overall, 57 patients took part in the research undergoing assessments prior to and following dietary supplementation with Vitamin B_2 (1 × 200 mg daily), Co-enzyme 10 (3 × 100 mg daily) and magnesium (1 × 300 mg daily). The sample had a mean age of 43.5±16.8, and 75% of individuals (n = 43) were females (see Table 3).

Table 2. The specific criteria, which was used to select the sample to study.

Inclusion criteria Patients were included in the study group if they met all these criteria	Exclusion criteria
Males and females attending the outpatient clinic	Any VM patient with further neurological or vestibular diagnoses were excluded
Aged between 17–85 years	Any VM patient who taking further medications to treat migraines; B-blockers, Ca-Channel blockers, Tricyclic Antidepressants, anti-epileptic drugs
Had a primary VM diagnosis*	Any VM patient who discontinued treatment before the planned duration had finished
	Women who were pregnant or breastfeeding

* VM patients diagnosed by using Barany Society criteria, after doing audio vestibular and imaging investigations to exclude other neurological or vestibular disorders and using NDS to scale the dizziness severity.

Table 3. Participant Demographics (n = 57).

Variables		
• Age (mean ± STD)	43.5±16.8	
Gender	**N**	**%**
• Females	43	75.4
• Males	14	24.6

Table 4. The duration, frequency and severity of VM symptoms were assessed pre- and post-supplementation (n = 57).

Measured variables	Pre		Post		Mean reduction (%)	T	*p-value**
	Mean	STD	Mean	STD			
Symptom duration (in minutes)	763.9	131.40	122.5	57.87	641.4(81.7)	4.0	**<0.001**
Symptom severity (scored 0–10)	7.2	1.7	2.1	2.2	5.1(71.9)	17.2	**<0.001**
Frequency (per month)	13.0	12.5	2.9	5.9	10.1(81.1)	6.9	**<0.001**

* Statistically significant findings set at $p < 0.05$, shown in bold. STD: Standard deviation.

Table 5. The mean reduction in duration, frequency and severity of VM symptoms were assessed after supplementation per Gender (n = 57).

Measured variables	Female		Male		*p-value**
	Mean Reduction	STD	Mean Reduction	STD	
• Duration of symptoms (min)	722.9	130.3	390.9	79.9	**0.044**
• Frequency (per month)	11.1	11.9	7.1	7.9	0.055
• Severity of symptoms (Scale 0–10)	5.4	1.9	4.3	2.8	0.116

* Statistically significant findings set at $p < 0.05$, shown in bold. STD: Standard deviation.

Before supplementation, the average length of an attack was 763.9 minutes, while the mean occurrence was 13.0 times per month. A significant reduction of over 80% was identified following the provision of the supplements, as shown in Table 4. Findings for symptom severity mirrored this change closely, with supplements being linked to a decrease of approximately 71.9% in mean scores, which dropped from 7.2/10 to 2.1/10. Table 5 shows the mean reduction in duration, frequency and severity of VM symptoms were assessed after supplementation per Gender. There was a significant difference between female and male in terms of duration of symptoms; hence, the mean reduction in female was 722.2 min (±130.0), while for male 390.0 min (±79.9). On the other hand, there was not a significant difference between them in terms of frequency and severity of symptoms.

The results shown in Figs 1–3 illustrate this supplementation regimen's potential to lead to reduced duration, frequency and severity of VM attacks. Over 40% of patients in the study stated that they had experienced a complete absence of VM symptoms (i.e., 100% remission of symptoms) as measured through frequency (n = 24, 42%), severity (n = 24, 42%) and duration (n = 27, 47%). In addition to this, over one third of participants reported a partial reduction (i.e., 50–99% remission of symptoms) in term of duration (n = 24, 42%), frequency (n = 29, 51%) and severity (n = 19, 33%). While others in the sample reported a reduction of under 50% in the measured variables.

Discussion

VM is the most frequent causal factor in recurring spontaneous vertigo, affecting approximately 1% of people and 10% of those suffering migraines. Moreover, females are

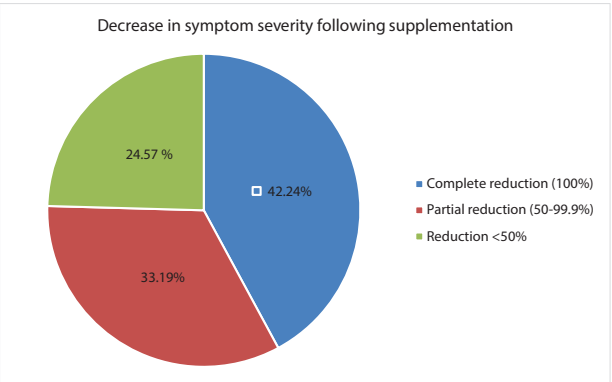

Figure 2. Decrease in severity of vestibular migraine following supplementation (n = 57).

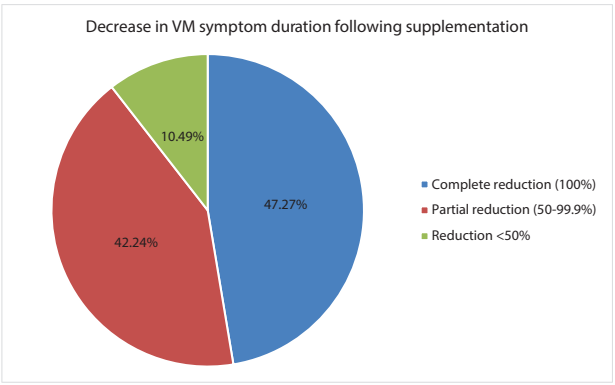

Figure 1. Decrease in vestibular migraine symptom duration following supplementation (n = 57).

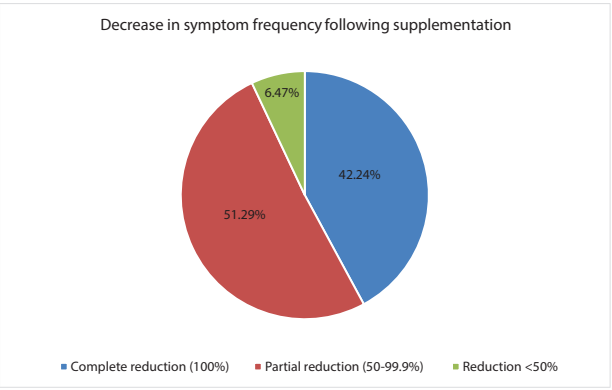

Figure 3. Decrease in frequency of vestibular migraines following supplementation (n = 57).

disproportionately affected by VM, at a ratio of 3:1 compared to males (Guilbot et al. 2017). However, the precise pathophysiology for VM has not yet been elucidated, with theoretical models of the mechanisms for VM being similar to migraines generally, with no fully detailed hypothesized process for pathogenesis (Shen et al. 2020).

Clinically, the underuse of drugs to prevent migraines has been identified, and preventive treatment approaches and principles are a significant factor in enhancing compliance, reducing adverse effects, and optimizing patient outcomes (Furman et al. 2003). Baier et al. (2009) demonstrates that many medications which used for prophylactic may be effective for treating vestibular migraine and its associated with reducing symptoms (Silberstein 2015). The efficacy of medicines such as metoprolol, propranolol, flunarizine, valproic acid and topiramate as prophylaxis for the reduction of symptoms of episodic migraine has been demonstrated through clinical trials (Linde and Rossnagel 2004; Silberstein 2015). Despite this, a significant proportion of patients show poor responses to such treatment or are severely affected by side effects (Linde and Rossnagel 2004). Moreover, several patients do not comply with the medication regime based on dissatisfaction with their effectiveness, tolerance or safety problems, or questions of safety over the longer term (Linde et al. 2013). This has recently led to differing migraine prevention approaches, utilizing interventions with a lower frequency or severity of adverse events. These include onabotulinum toxin-A, monoclonal antibody therapy, external neurostimulation (Silberstein et al. 2004; Lipton and Silberstein 2015) and nutraceutical approaches. This last involves treatment with substances which are not pharmaceuticals, such as vitamin or mineral supplements and herbal treatments (Hepp et al. 2015).

According to Wells et al. (2019), vitamin B_2, co-enzyme Q10 and Magnesium each assist in preventing migraine, possibly due to effects on the pathophysiological mechanisms causing migraines to arise while presenting negligible safety concerns. Within this, magnesium acts to block glutamate receptors, as well as modulate ATP generation and metabolism of glucose metabolism. This means that supplementing with magnesium in high doses can cause reductions in cortical spreading depression as activated through glutamate. Similarly, supplements of vitamin B_2 and co-enzyme Q10 could enhance mitochondrial complex activities, preventing dysfunctions in the mitochondria (Daniel and Mauskop 2016).

The findings of this retrospective cohort study illustrate that the sample improved significantly across the measures used, which were duration, rate of occurrence and severity when evaluated following six months' treatment with magnesium, vitamin B2, and co-enzyme Q10 supplements. Frequency (number of days/month) with vestibular migraine decreased from 13.0 to 2.9, statistically significant, with a p-value of $p < 0.001$. Moreover, over 80% of the sample stated that they experienced significant decreases in VM attack length ($p < 0.001$). Severity in vestibular migraine as assessed through the vertigo analogue showed a mean value of 7.2/10 prior to treating with supplements, and 2.1/10 following six months' treatment, which represents a significant decrease, with good results found for over 71% of the sample ($p < 0.001$). Although, there was a significant difference between female and male in terms of duration of symptoms; hence, the mean reduction in female was 722.2 min, while for male 390.0 min. There was not a significant difference between them in terms of frequency and severity of symptoms

Although a range of previous nutraceutical research and reviews has been conducted to assess supplementation and its effect on migraine symptom reduction (Tepper et al. 2006), this study is original in investigating the effectiveness of a combined supplement regimen including magnesium, vitamin B_2, and co-enzyme Q10 for preventing vestibular migraine through measuring occurrence rate, duration and intensity. Over 4 in 10 of the patients taking part in the study stated that their vestibular migraine symptoms entirely remitted when measured through rate of occurrence (42%), intensity (42%) and duration (47%). Further, over a third of participants reported that the duration (42%), frequency (51%) and intensity (33%) of symptoms had lessened to a significant extent, while others in the sample reported a reduction of under 50% in the measured variables.

The final major finding in this study is that the participants did not report any severe adverse events during the supplementation period. The adverse events reported in the study were mild, limited to two reports of urine discoloring orange and a single report of mild diarrhea. However, two participants withdrew and were then excluded from the study, as they stopped taking the treatment before the end of the period because of adverse events, with one reporting anxiety while the other stated that their headaches had increased. These two events are not linked to the use of the supplements provided (Vikelis et al. 2020). In sum, the findings of the current research support those of an earlier study that trialed proprietary supplementation with co-enzyme Q10, Magnesium and feverfew (Guilbot et al. 2017).

Our current study found that supplementing with these constituents offered good tolerance and efficacy as a complementary therapy for preventing vestibular migraine. On the other hand, the study had a small sample and used a limited duration of follow-up, with the comparatively high cost of this approach against different prophylaxis. This restricted the participant numbers and significantly limited the study.

Author Contributions

AA was the study's principal investigator and SA the project manager. MB undertook data analysis, and RA and HK were responsible for data collection. AA contributed to writing this article, with all authors reading and approving the finished manuscript.

Data Availability Statement

All data and materials are available on request.

Conclusion

The study reported here supports the potential effectiveness of proprietary dietary supplementation with Vitamin B_2, Co-enzyme 10 and Magnesium, as well as the low level and mostly non-severe nature of adverse reactions to this treatment. The findings point to the need for continued research and a prospective trial.

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