DOI: *http://dx.doi.org/10.18502/cjn.v23i4.18763*

Current Journal of Neurology

Original Paper

Curr J Neurol 2024; 23(4): 208-16

Podcast

Improving migraine headache characteristics with high dose of thiamine: A randomized double-blind controlled trial

Received: 08 June 2024
Accepted: 10 Aug. 2024

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Keywords
Thiamine; Migraine; Headache; Episodic Migraine

Abstract

Background: Migraine, a prevalent neurological condition, is recognized as the sixth leading cause of global disability. The proposed mechanism involves a combination of diminished energy reserves and heightened sensory stimulation activating the trigeminovascular system. Thiamine, essential for energy generation in various tissues including the nervous system, is hypothesized to be involved. This study aims to examine the effects of administering a high dose of thiamine to women with episodic migraine.

Methods: A randomized, controlled clinical trial was conducted involving 40 women with episodic migraine. Participants were divided into two groups: one receiving 990 milligrams of thiamine three times daily, and the other receiving 990 milligrams of maltodextrin over 12 weeks. Headache frequency, duration, severity, and disability were evaluated through questionnaires. Initial and final measurements of serum calcitonin gene-related peptide (CGRP) were taken.

How to cite this article: Ghods M, Togha M, Jafari E, Noormohammadi M, Salami Z, Nilghaz M, et al. Improving migraine headache characteristics with high dose of thiamine: A randomized double-blind controlled trial. Curr J Neurol 2024; 23(4): 208-16.

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Results: Thiamine supplementation resulted in a significant reduction in Migraine Disability Assessment (MIDAS) scores, migraine frequency, duration, and intensity compared to the placebo group. However, both groups experienced a decline in serum CGRP levels, with no significant difference between them.
Conclusion: This study suggests that high-dose thiamine supplementation may offer a beneficial adjunctive treatment for episodic migraine. Further investigations with prolonged intervention periods are necessary to validate these findings.

Introduction

Migraine headache is a neurovascular disorder manifested by a unilateral pulsating, throbbing, and disturbing head pain.[1] For the productive age group of 15-49 years, migraine headache is the major reason of partial disability. It significantly impacts their physical and mental well-being, as well as their quality of day-to-day life and socioeconomic status.[2] As a result, the prevention and treatment of migraine have become global concerns.[3]

One theory for the migraine pain is a short vasoconstriction followed by vasodilatation of intra- and extra-cranial blood vessels, which stimulate the cerebral blood flow causing extravasation of pro-inflammatory neuromodulators like nitric oxide (NO), substance P, calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase activating polypeptide (PACAP), vasoactive intestinal polypeptide (VIP), neurokinin A, and serotonin. Another theory considered cortical spreading depression (CSD) as the main cause of migraine pain. In this theory, the CSD triggers the trigeminal nervous system and initiates migraine. CSD is a depolarization self-propagating wave of neuronal and glial cells that presents its effect through the cerebral cortex leading to a long-lasting withholding of neuronal activity. There is a vast influx of ions (Ca2+, Na+) in the depolarization phase. Then both theories were merged into the neurovascular theory. Furthermore, as CSD can aggravate mitochondrial damage in the brain, they have been connected to the disruption of oxidative capacities of mitochondria besides hindering of the normal functioning of the nervous system. This impairment disrupts mitochondrial membrane potential and respiratory function resulting in less efficient adenosine triphosphate (ATP) synthesis and the production of reactive oxygen species (ROS), hence, affecting migraine pain.[4]

The biologically active form of thiamine, known as vitamin B1, functions as a cofactor for four major enzymes in the mitochondrial respiratory chain and the tricarboxylic acid cycle (TCA) enzyme. Thus, thiamine can regulate the energy metabolism of neurons by controlling the TCA, oxidative phosphorylation reactions, electron transport chain (ETC), ATP synthesis, and ion homeostasis.[2] Additionally, a deficiency in vitamin B1 significantly impacts energy synthesis and release in various tissues, including the nervous system.[5] Moreover, research has indicated that individuals with migraines receive lower levels of thiamine through their diet compared to non-migraineurs.[6] Furthermore, previous studies have suggested that thiamine supplementation may lead to improvements in migraine headaches in individuals with Wernicke-Korsakoff syndrome.[7]

Therefore, in this double-blind, placebo-controlled, randomized trial, we aimed to investigate the impact of high-dose oral supplementation of vitamin B1 on episodic migraines in premenopausal women.

Materials and Methods

Design: This investigation was structured as a double-blind, randomized, placebo-controlled clinical trial. Every individual took part in a combined total of two appointments, comprising an initial screening session and a final screening session at the conclusion of the study.

Participants: In this randomized, double-blind, controlled clinical trial, we recruited 40 premenopausal women with episodic migraines aged 18-45 years. These women had a clinical diagnosis of migraine according to the International Classification of Headache Disorders, 3rd edition (ICHD-3), and experienced three or more migraine attacks per month for at least three months. The participants had a body mass index (BMI) of 18.5-30 kg/m^2 and had not made any changes to their migraine prophylactic drugs in the three months before the study. We recruited these participants from 25/01/2022 to 24/07/2023 from a headache clinic in Sina Hospital, Tehran City, Iran. We excluded individuals with diabetes, gastrointestinal disorders [such as malabsorption and inflammatory bowel disease (IBS)], kidney disorders, liver disorders (cirrhosis and hepatitis), hypertension (HTN), congestive heart failure (CHF), cancer, those who had consumed vitamin B1 or any B1-containing multivitamins in the three months preceding the study, individuals using

antipsychotic medications, and pregnant or lactating women. Additional exclusion criteria included smoking, the occurrence of any potential side effects during the study, consumption of less than 10% of thiamine supplements, and pregnancy during the study.

The study received ethical approval from the Research Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, at 22/01/2023 (approval code: IR.SBMU.nnftri.Rec.1401.068) and was registered with the Iranian Registry for Clinical Trials at 11/03/2023 (Registration No. IRCT20140804018677N24, available at www.irct.ir). All methods were performed in accordance with the relevant guidelines and regulations of the Research Ethics Committee of Shahid Beheshti University of Medical Sciences.

Intervention: All participants were thoroughly briefed on the study's objectives and procedures, and written consent was obtained from each individual. Subsequently, participants were randomly divided into intervention or placebo groups using a blocked randomization technique. Randomization was executed via the randomization tool on www.sealedenvelope.com, considering the number of intervention groups, sample size, and block size (which was set at 4 for this study). The resulting allocation list was utilized for patient assignment. The website allowed for flexible allocation across groups. For the study's required sample size of 40 patients (20 in the intervention group and 20 in the control group), 10 blocks of four were randomly selected using software, generating various block sequences such as BAAB, ABBA, AABB, BBAA, and ABAB. Subsequently, 40 pockets were created, each containing either group A or B. A neutral individual, not affiliated with the research team, arranged the pockets according to the predetermined block list. Upon admission, each patient received a pocket, determining their assignment to either group A (intervention) or B (control). Sampling continued sequentially until the target sample size was reached. Medication bottles were coded by an impartial investigator not involved in intervention or data collection to maintain blinding. The research team, including the principal investigator, data collectors, and outcome assessors, remained blinded until the completion of the data analysis. Each participant was given two bottles every 6 weeks and instructed to consume 3 capsules daily (every 8 hours) for a duration of 12 weeks. Each capsule contained 330 mg of thiamine (intervention group) or maltodextrin (placebo group). The placebo capsules were made to resemble the vitamin capsules in terms of shape, weight, size, and color. Follow-ups with the participants were conducted through telephone calls and text messages every 2 weeks to monitor their adherence to the intervention. The patients were instructed not to alter their prophylactic treatment during the study and to take a similar abortive medication to the one taken before entering the study at the time of a headache attack. The participants were also asked to inform the researcher of any potential side effects or changes in the type or dosage of prophylactic treatments. Additionally, the participants were requested to return the capsule bottles to the researchers at the end of the study. In this particular study, the assessment of patients' adherence to B1 supplement intake involved determining the number of remaining B1 capsules at the end of the 12th week. If a participant had consumed less than 10% of their prescribed capsules, they were subsequently excluded from the study.

Anthropometric measurements: The measurement of body weight was carried out using a Seca scale with a precision of 100 grams while the participants were wearing light clothing. The height of the individuals was assessed with a tape measure, recording to the closest 0.5 cm. BMI was computed by dividing the weight in kilograms by the square of the height in meters.

Blood samples and biochemical analysis: In the present study, a venous blood sample of 5 ml was collected from all participants before and after the intervention. Subsequently, the blood samples were centrifuged at room temperature (20-25 Celsius) at 4000 rpm for a duration of 10 minutes. Afterwards, serum and red blood cell (RBC) samples were divided into micro-tubes and stored at -80 °C until further biochemical analyses. The enzyme-linked immunosorbent assay (ELISA) method by ZellBio kits (GmbH, Germany) was utilized to measure the concentrations of serum CGRP, the serum level of vitamin B1, and the activity level of erythrocyte transketolase.

Data collection and questionnaires: To collect data and questionnaires, demographic information such as age, years of migraine onset, medication or supplement usage, the mean sleep duration over a 24-hour period, and the mean daytime computer usage was obtained from the patients. The dietary

intake was assessed by conducting a 24-hour recall questionnaire for three days (2 regular weekdays and 1 day of the weekend) through interviews before and after the intervention.

Furthermore, the participants' levels of physical activity were assessed using the International Physical Activity Questionnaire (IPAQ) both at the beginning and end of the study. The validity and reliability of this questionnaire have been confirmed in a study conducted by Vasheghani-Farahani et al. in Iran.[8]

All patients completed headache diaries created by Prof. M.T. prior to enrolling in the study.[7] These diaries gathered information on headache characteristics, including the frequency (number of attacks per month), severity, and duration of migraine attacks. Participants were also instructed to document their headache features throughout the study using a new form.

The impact of headaches on employment, household chores, and social activities in the past three months was assessed using the Migraine Disability Assessment (MIDAS) questionnaire at the beginning and end of the intervention. The validity and reliability of this questionnaire have been confirmed in a study conducted by Zandifar et al. in Iran.[9]

Sample size and statistical analysis: Given that a comprehensive study of this nature has not yet been undertaken about patients with migraine, due to constraints within current research, prior studies have been referenced wherein a combination of B6 + B1 + B12 was examined instead of B1. Consequently, the standard deviation (SD) for the number of headache days per month within the supplement and placebo groups stands at 4.5 and 7 days, respectively.[10] The determination of the sample size for this particular study hinged upon the selection of an adequate number of samples to detect a statistically significant difference in the mean number of headache days per month between the supplement and placebo groups, set at a minimum of 6 days, with a 95% confidence level ($\alpha = 0.05$) and 90% power ($\beta = 20\%$). Herein, a sample size of 16 patients was projected for each group, factoring in an approximate dropout rate of 25%, resulting in a total of 20 samples allocated to each group.

For the statistical analysis, SPSS software (version 26, IBM Corporation, Armonk, NY, USA) was employed. All hypothesis tests were two-tailed, with a significance level below 0.05. The normal distribution of quantitative variables was evaluated using diverse methods including skewness, histogram chart, Q-Q plot, leaf and stem, box plot, and Shapiro-Wilk test. Quantitative variables exhibiting a normal distribution were presented as mean ± SD, while those with non-normal distribution were presented as median (Q1-Q3). Qualitative variables were displayed as numbers (percentages). Independent samples t-test was utilized to compare quantitative variables with a normal distribution between the two groups receiving vitamin B1 and the placebo group at both the commencement and conclusion of the study. The chi-square test was applied for qualitative variables. The comparison of quantitative variables after the study, in contrast to the baseline in each group, was assessed using the paired-samples t-test. The study results were adjusted through analysis of covariance (ANCOVA) test for variables that showed significant differences at the beginning of the study.

Results

Among the 20 participants in each group, one individual from the intervention group was unable to continue due to the presence of facial blisters, while another participant experienced heart pain, severe dizziness, and nausea. Additionally, an additional participant from the intervention group was excluded from the study due to an increase in appetite and obesity. Finally, one participant from the intervention group was excluded due to a lack of willingness to cooperate. In the placebo group, three individuals were excluded due to their unwillingness to cooperate, and one participant was excluded due to pregnancy. As a result, the final count for the intervention group was 16 participants, and the placebo group also consisted of 16 individuals (Figure 1). At the beginning of the study, there were no significant differences observed in terms of age and the age of onset of headache between the two groups (Table 1).

In terms of energy consumption, macronutrients, and micronutrient intake, there were no noticeable differences between the two groups at both the start and end of the study. Furthermore, there were no significant changes observed at the end of the study compared to the beginning (Table 2).

No significant differences in physical activity levels were found between the two groups at either the beginning or the end of the study. Physical activity findings are presented in table 3.

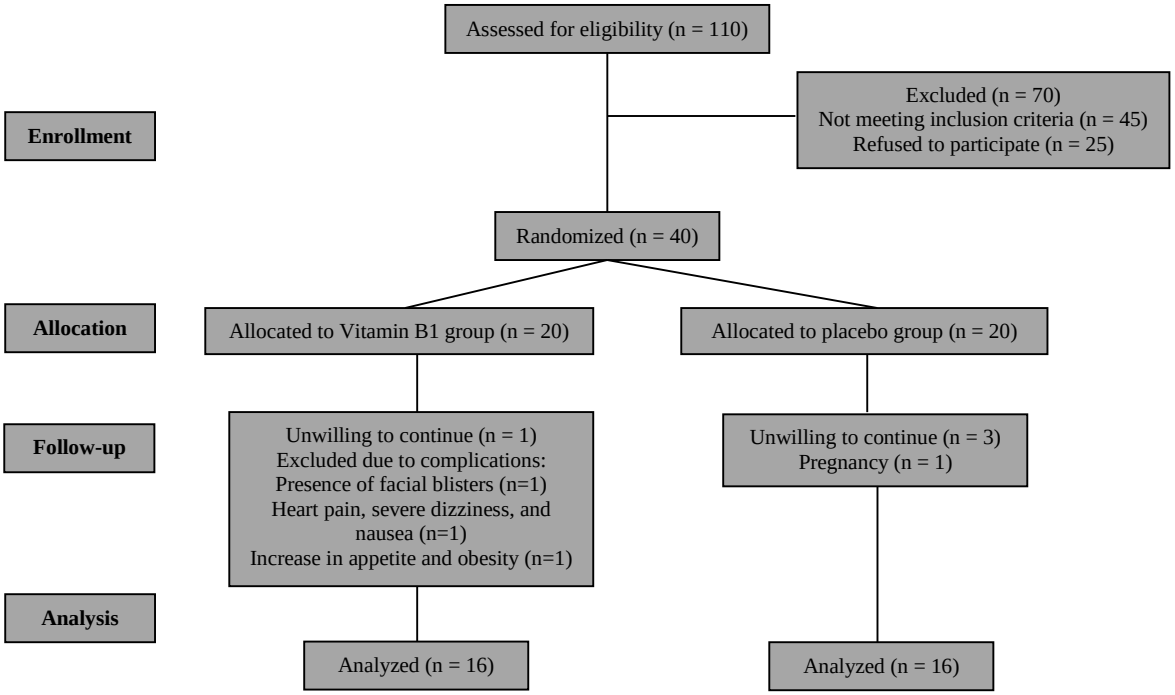

Figure 1. Flowchart of studied participants

Supplementation with thiamine resulted in a decrease in CGRP level from 54.94 ± 20.24 to 54.13 ± 16.61 (P = 0.753). CGRP levels also decreased in the placebo group from 48.50 ± 17.97 to 47.63 ± 18.87 (P = 0.694). No significant changes were observed within or between the groups.

The intervention group showed a significant reduction in the MIDAS score (P = 0.002), frequency of migraine headaches (P < 0.001), and duration of migraine headaches (P = 0.001). However, there was no significant difference between the two groups at the end of the study. Both groups experienced a significant decrease in headache severity at the end of the study, with the intervention group showing a significantly greater reduction.

After adjusting for sleep hours, computer work hours, and baseline values, a significant difference was observed between the intervention and control groups in terms of severity (4.56 ± 2.34 vs. 6.25 ± 2.02, P = 0.019), frequency (3.00 ± 2.71 vs. 4.19 ± 1.68, P = 0.012), and duration of migraine headaches (4.00 ± 3.03 vs. 8.25 ± 15.30, P = 0.004) which was significantly lower in the intervention group (Table 4). Changes in frequency, severity, and duration are shown in figure 2.

Discussion

Daily oral supplementation with 990 mg of thiamin for 12 weeks significantly reduced the severity, frequency, and duration of migraine attacks, and also decreased the MIDAS score. In the placebo group, except for severity, other parameters of migraine characteristics did not show significant changes. Thiamine supplementation resulted in a significantly greater reduction in the severity of migraine headaches compared to placebo.

Studies examining the supplementation of vitamin B1 for the management of migraine headaches are rare. Consistent with our findings, Prakash et al. conducted a case report on the impact of vitamin B1 on reducing pain intensity in chronic migraine.[5]

Table 1. General characteristics, serum levels of thiamine, and transketolase in patients with migraine headaches in the vitamin B1 intervention group and the placebo group

Variable	Intervention (n = 16)	Control (n = 16)	P*
Age (year)	30.75 ± 9.34	34.75 ± 8.25	0.209
Headache onset (years)	8.81 ± 5.52	12.34 ± 9.24	0.202
Thiamine (ng/ml)	34.01 ± 13.43	31.11 ± 14.07	0.555
Transketolase (ng/ml)	0.98 ± 0.13	1.07 ± 0.19	0.113

Data are presented as mean ± standard deviation (SD)
*Independent samples t-test

Table 2. The daily intake of energy, macronutrients, and micronutrients in patients with migraine headaches in the vitamin B1 intervention group and placebo group, at the beginning and end of the study

		Intervention (n = 16)	Control (n = 16)	P*
Energy (kcal)	Before	1374.96 ± 338.75	1664.42 ± 516.30	0.071
	After	1374.75 ± 378.23	1565.06 ± 479.74	0.222
P**		0.998	0.280	
Carbohydrates (g)	Before	154.63 ± 56.11	186.74 ± 81.92	0.206
	After	153.84 ± 53.75	174.69 ± 84.03	0.410
P**		0.960	0.204	
Protein (g)	Before	60.33 ± 17.59	68.94 ± 18.94	0.193
	After	51.87 ± 15.07	64.66 ± 21.97	0.064
P**		0.110	0.424	
Fat (g)	Before	58.45 ± 16.92	65.22 ± 24.93	0.376
	After	61.77 ± 21.42	67.79 ± 27.30	0.493
P**		0.588	0.468	
Thiamin (mg)	Before	0.95 ± 0.34	1.04 ± 0.60	0.598
	After	0.81 ± 0.29	1.00 ± 0.63	0.280
P**		0.143	0.558	
Riboflavin (mg)	Before	1.12 ± 0.50	1.39 ± 0.55	0.158
	After	0.98 ± 0.41	1.35 ± 0.64	0.065
P**		0.261	0.672	
Pyridoxine (mg)	Before	1.34 ± 0.51	1.28 ± 0.65	0.767
	After	1.11 ± 0.38	1.23 ± 0.41	0.389
P**		0.194	0.743	
Cobalamin (µg)	Before	2.43 ± 2.00	3.03 ± 1.67	0.367
	After	2.47 ± 2.16	2.93 ± 1.27	0.463
P**		0.954	0.855	
Folic (mg)	Before	268.13 ± 126.60	268.49 ± 161.78	0.994
	After	244.59 ± 133.39	302.31 ± 154.13	0.266
P**		0.580	0.101	
Vitamin D3 (µg)	Before	8.84 ± 11.88	23.77 ± 29.81	0.078
	After	13.74 ± 25.03	18.59 ± 20.75	0.555
P**		0.513	0.482	
Fiber (g)	Before	11.93 ± 4.45	16.74 ± 8.57	0.058
	After	12.95 ± 7.86	16.00 ± 9.19	0.321
P**		0.615	0.597	

Data are presented as mean ± standard deviation (SD)
*Independent samples t-test, **Paired samples t-test

In this study, two individuals suffering from chronic migraines were administered 500 mg of thiamine through intravenous (IV) means over three days. Following this regimen, the dosage was reduced to 200 mg of injectable thiamine on the fourth day.[5]

Subsequently, the patients underwent a transition to oral therapy, wherein they were prescribed 100 mg of thiamine to be taken twice daily. Prakash et al. observed promising results from IV thiamine supplementation on migraine headache intensity and frequency.[5]

Table 3. Physical activity of patients with migraine headaches in the vitamin B1 intervention group and placebo group, at the beginning and end of the study

		Before			After		
		Intervention	Control	Total	Intervention	Control	Total
IPAQ	Sedentary	9 (56.3)	5 (31.3)	14 (43.8)	10 (62.5)	4 (25.0)	14 (43.8)
	Moderate	3 (18.8)	6 (37.5)	9 (28.1)	3 (18.8)	6 (37.5)	9 (28.1)
	Severe	4 (25.0)	5 (31.3)	9 (28.1)	3 (18.8)	6 (37.5)	9 (28.1)
	P*		0.324			0.102	

Data are presented as number (%)
*Chi-square test
IPAQ: International Physical Activity Questionnaire

Table 4. Body mass index (BMI), serum calcitonin gene-related peptide (CGRP), Migraine Disability Assessment (MIDAS) score, severity, duration, and frequency of migraine headaches in patients with migraine headaches in the vitamin B1 intervention group and placebo group, at the beginning and end of the study

		Intervention (n = 16)	Control (n = 16)	P*	P**
BMI (kg/m^2)	Before	23.91 ± 3.30	23.72 ± 3.52	0.871	0.705¥
	After	23.93 ± 3.53	23.65 ± 3.48	0.819	0.846#
	Change	0.02 ± 0.69	-0.07 ± 0.71	0.720	0.846#
	P***	0.903	0.707		
CGRP (pg/ml)	Before	54.94 ± 20.24	48.50 ± 17.97	0.349	0.759¥
	After	54.13 ± 16.61	47.63 ± 18.87	0.309	0.781#
	Change	-0.81 ± 10.16	-0.87 ± 8.73	0.985	0.781#
	P***	0.753	0.694		
MIDAS	Before	12.19 ± 8.32	15.19 ± 13.19	0.448	0.582¥
	After	4.81 ± 5.10	9.50 ± 11.24	0.199	0.291#
	Change	-7.38 ± 7.71	-1.92 ± 11.60	0.146	0.291#
	P***	0.002	0.578		
Frequency (attacks per month)	Before	7.00 ± 3.14	5.00 ± 2.78	0.066	0.105¥
	After	3.00 ± 2.71	4.19 ± 1.68	0.147	0.012#
	Change	-4.00 ± 3.37	-0.81 ± 2.40	0.004	0.012#
	P***	< 0.001	0.196		
Severity	Before	6.31 ± 1.45	6.69 ± 2.09	0.559	0.231¥
	After	4.56 ± 2.34	6.25 ± 2.02	0.037	0.019#
	Change	-1.75 ± 1.69	-0.44 ± 0.63	0.007	0.019#
	P***	0.001	0.014		
Duration	Before	6.38 ± 2.68	9.13 ± 17.58	0.545	0.738¥
	After	4.00 ± 3.03	8.25 ± 15.30	0.292	0.004#
	Change	-2.38 ± 2.39	-0.88 ± 2.48	0.092	0.004#
	P***	0.001	0.179		
Hours of sleep in the day	Before	7.44 ± 1.21	6.75 ± 1.18	0.115	0.097¥
	After	7.81 ± 1.05	6.69 ± 1.20	0.008	0.026#
	Change	0.38 ± 0.89	-0.06 ± 0.44	0.091	0.026#
	P***	0.111	0.580		
Computer	Before	1.63 ± 3.14	7.31 ± 5.11	0.001	0.373¥
	After	1.44 ± 2.16	7.19 ± 4.53	< 0.001	0.051#
	Change	-0.19 ± 2.04	-0.13 ± 0.96	0.912	0.051#
	P***	0.718	0.609		

Data are presented as mean ± standard deviation (SD)
*Independent samples t-test, **Analysis of covariance (ANCOVA), ***Paired samples t-test, ¥Adjusted for sleep and computer hours at the end of study, #Additionally adjusted for baseline values
BMI: Body mass index; CGRP: Calcitonin gene-related peptide; MIDAS: Migraine Disability Assessment

In our previous study, we compared the effects of supplementing with B1 (300 mg/day), B6 (80 mg/day), and B12 (500 mcg/day) on migraine headaches.

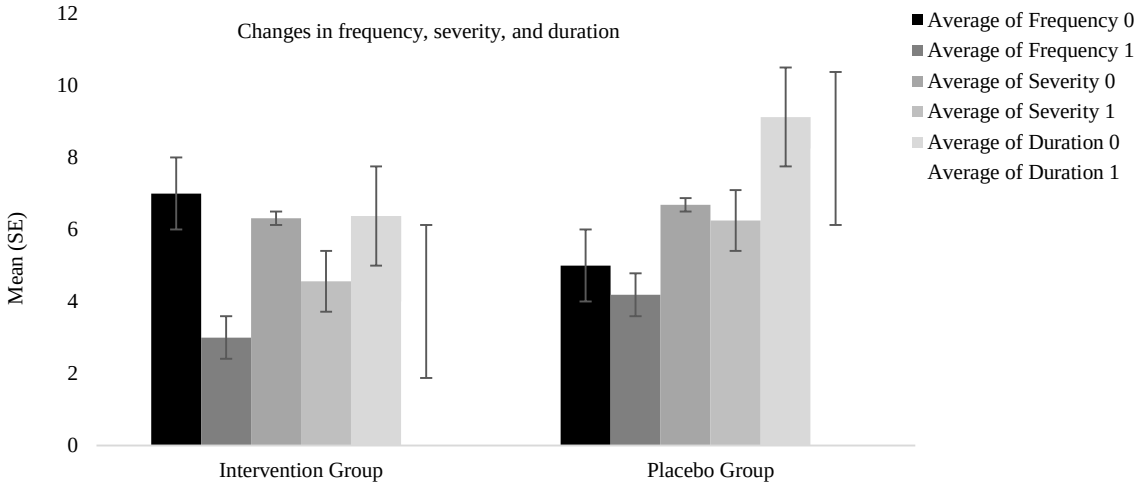

Figure 2. Changes in frequency, severity, and duration at time points T0 and T1, separated by groups

We noticed that supplementation with B1 had the most significant effect on migraine intensity, resulting in a decrease in the Visual Analog Scale (VAS) score of -1.63 ± 1.67. Furthermore, it led to a reduction in the number of headache days per month by -2.38 ± 3.58 and a decrease in the MIDAS by -3.53 ± 3.48.[11] The results of our current study are consistent with our previous findings. By increasing the dosage of thiamin from 300 mg/day to 990 mg/day, beside improvements in headache frequency, intensity, and disability score, attacks duration decreased significantly.

We did not notice any significant change in CGRP level by consuming thiamine supplement. If the mitochondrial dysfunction is considered as a downstream event of the neuroinflammation, it can be concluded that vitamin B1 affects migraine characteristics by preserving mitochondrial function including bioenergetics. Damage to mitochondria in any part of the brain can lead to a deficiency in mitochondrial energy and a subsequent increase in ROS levels. Migraine headaches often arise from either brain energy deficiency or excessive oxidative stress surpassing the antioxidant capacity.[12,13] Studies suggest that CSD can trigger ROS formation in the cerebral cortex, meninges, and trigeminal ganglia. ROS may contribute to central and peripheral sensitization by influencing protein kinase activity, modifying glutamatergic nerve signaling, promoting neurogenic inflammation, and regulating ion channels like the transient receptor potential channel V1 (TRPV1).[14] Inhibiting ROS and deactivating transient receptor potential A1 (TRPA1) channels could potentially offer therapeutic advantages in preventing stress-induced migraines via CGRP pathways.[15]

Thiamine acts as a cofactor for numerous enzymes, many of which are localized in the mitochondria.[16] Several of these enzymes are involved in the energy metabolism of the citric acid cycle and the ETC.[17] Additionally, some thiamine-dependent enzymes are part of the antioxidant system.[16] Thiamine is also crucial for maintaining the integrity of mitochondria.[18] Thiamine deficiency can lead to disturbances in mitochondrial integrity, reduced energy production, and subsequent elevation of ROS levels.[17] Therefore, maintaining adequate levels of this vitamin is essential for optimal mitochondrial function and the deactivation of TRPA1 channels.

Moreover, research has shown that during CSD, there is an elevation in intracellular calcium levels within astrocytes, leading to vasoconstriction, a process mediated by phospholipase A2.[19] This rise in intracellular calcium concentration is associated with heightened peripheral pain, whereas a decrease inhibits it.[20] Mitochondria play a crucial role in regulating intracellular calcium levels, and any dysfunction in mitochondrial function can result in increased pain sensitivity.[20] Therefore, thiamine may also contribute to raising the pain threshold by influencing mitochondrial function.

The research boasts several robust features, such as its forward-looking, randomized, and blinded approach, the innovative use of vitamin B1 in a therapeutic capacity for those with episodic migraines, the specialized headache neurologist's diagnosis, and the migraine validation based on ICHD standards (ICHD-3). Nonetheless, it is important to acknowledge a few shortcomings. One of the primary limitations of this study was the relatively small sample size. To assess whether this sample size was adequate for detecting meaningful differences and to ascertain the generalizability of our findings to larger populations, we calculated the statistical power for the study variables that changed significantly using SPSS software. The statistical power for the variable "frequency" was determined to be 0.985, while for the "MIDAS score", it was 0.936. Additionally, the statistical power for "headache severity" was 0.986, and for "duration of migraine attacks", it was found to be 1. Consequently, we can assert that with a sample size of 16 participants in each group, the statistical power was sufficiently robust to detect significant differences, thus supporting the generalizability of our results to a larger population. Moreover, verification of non-deficient thiamine levels and erythrocyte transketolase activity was only performed initially. Additionally, we did not examine markers associated with migraine mechanisms. The focus of study was solely on female episodic migraine sufferers, omitting the potential thiamine effects on men with migraines. Finally, it is suggested that future studies with extended durations and a meta-analytical approach especially on different consequences of mitochondrial involvement be conducted to fully ascertain thiamine's influence on episodic migraine.

Conclusion

We observed the clinical benefits of vitamin B1 supplementation in episodic migraine. However,

further studies are needed to determine the probable mechanism of the effect of vitamin B1.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

We would like to express our gratitude to the participants of this study. Additionally, we extend our utmost appreciation to Mrs. Moslehi, Mrs. Darjani, and the staff of Sina Hospital for their kind cooperation. Furthermore, we thank the Endocrine and Metabolism Research Center of Shahid Beheshti University of Medical Sciences for conducting the biochemical analyses. This study was conducted as part of a master's thesis at Shahid Beheshti University of Medical Sciences.

References

1. Steiner TJ, Stovner LJ. Global epidemiology of migraine and its implications for public health and health policy. Nat Rev Neurol 2023; 19(2): 109-17.
2. Wang Y, Wang Y, Yue G, Zhao Y. Energy metabolism disturbance in migraine: From a mitochondrial point of view. Front Physiol 2023; 14: 1133528.
3. Raggi A, Leonardi M, Bussone G, D'Amico D. A 3-month analysis of disability, quality of life, and disease course in patients with migraine. Headache 2013; 53(2): 297-309.
4. Olesen J. The role of nitric oxide (NO) in migraine, tension-type headache and cluster headache. Pharmacol Ther 2008; 120(2): 157-71.
5. Prakash S, Kumar Singh A, Rathore C. Chronic Migraine Responding to Intravenous Thiamine: A Report of Two Cases. Headache 2016; 56(7): 1204-9.
6. Faraji H, Paknahad Z, Chitsaz A. Dietary Intake of Thiamine in Migraine Patients and Healthy Subjects: a Case-Control Study. Clin Nutr Res 2018; 7(1): 40-7.
7. Antonio C, Massimo T, Gianpaolo Z, Immacolata PM, Erika T. Oral High-Dose Thiamine Improves the Symptoms of Chronic Cluster Headache. Case Rep Neurol Med 2018; 2018: 3901619.
8. Vasheghani-Farahani A, Tahmasbi M, Asheri H, Ashraf H, Nedjat S, Kordi R. The Persian, last 7-day, long form of the International Physical Activity Questionnaire: translation and validation study. Asian J Sports Med 2011; 2(2): 106-16.
9. Zandifar A, Asgari F, Haghdoost F, Masjedi SS, Manouchehri N, Banihashemi M, et al. Reliability and validity of the migraine disability assessment scale among migraine and tension type headache in Iranian patients. Biomed Res Int 2014; 2014: 978064.
10. Togha M, Rahmanzadeh R, Nematgorgani S, Yari Z, Jahromi SR, Refaeian F. Suppression of menstrual-related migraine attack severity using pyridoxine, thiamine, and cyanocobalamin: a quasi-experimental within-subject design. Arch Neurosci 2020; 7(3): e93103.
11. Nematgorgani S, Razeghi-Jahromi S, Jafari E, Togha M, Rafiee P, Ghorbani Z, et al. B vitamins and their combination could reduce migraine headaches: A randomized double-blind controlled trial. Curr J Neurol 2022; 21(2): 105-18.
12. Fila M, Pawłowska E, Blasiak J. Mitochondria in migraine pathophysiology - does epigenetics play a role? Arch Med Sci 2019; 15(4): 944-56.
13. Gross EC, Lisicki M, Fischer D, Sándor PS, Schoenen J. The metabolic face of migraine - from pathophysiology to treatment. Nat Rev Neurol 15 2019; 15(11): 627-43.
14. Meents JE, Neeb L, Reuter U. TRPV1 in migraine pathophysiology. Trends Mol Med 2010; 16(4): 153-9.
15. Jiang L, Ma D, Grubb BD, Wang M. ROS/TRPA1/CGRP signaling mediates cortical spreading depression. J Headache Pain 2019; 20(1): 25.
16. Dhir S, Tarasenko M, Napoli E, Giulivi C. Neurological, Psychiatric, and Biochemical Aspects of Thiamine Deficiency in Children and Adults. Front Psychiatry 2019; 10: 207.
17. Mrowicka M, Mrowicki J, Dragan G, Majsterek I. The importance of thiamine (vitamin B1) in humans. Biosci Rep 2023; 43(10).
18. Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. Chem Biol Interact 2006; 163(1-2): 94-112.
19. Metea MR, Newman EA. Glial cells dilate and constrict blood vessels: a mechanism of neurovascular coupling. J Neurosci 2006; 26(11): 2862-70.
20. Xu S, Cheng X, Wu L, Zheng J, Wang X, Wu J, et al. Capsaicin induces mitochondrial dysfunction and apoptosis in anaplastic thyroid carcinoma cells via TRPV1-mediated mitochondrial calcium overload. Cell Signal 2020; 75: 109733.