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Original Article

A PROSPECTIVE OPEN-LABEL STUDY TO COMPARE THE EFFICACY AND SAFETY OF TOPIRAMATE ALONE VERSUS TOPIRAMATE WITH VITAMIN D IN PROPHYLACTIC TREATMENT OF PATIENTS WITH MIGRAINE

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ABSTRACT

Objective: Migraine affects 10% of the global population, especially women aged 25-55, causing severe headaches with light and sound sensitivity. While acute treatments are common, preventive therapies are underutilized. Recent studies suggest combining vitamin D with Topiramate, an anticonvulsant, could enhance prevention, reducing both attack frequency and duration. Therefore, the present study compares the safety and efficacy of Topiramate alone versus topiramate with Vitamin D.

Methods: A study was conducted on 100 migraine patients to compare the effect of topiramate alone versus topiramate with vitamin D. Pain severity and disability were measured using a Visual Analog Scale (VAS), Migraine Disability Assessment Score (MIDAS), and Migraine Severity (MIGSEV) scores over 12 w, excluding patients with other medical conditions.

Results: Both the Topiramate and Topiramate with Vitamin D groups showed significant reduction in VAS, MIDAS, and MIGSEV scores after 12 weeks. Migraine without aura was more common in both groups. The Topiramate with Vitamin D group also experienced increased serum calcium and Vitamin D levels. Both groups showed significant improvements in pain and disability, with the Topiramate with Vitamin D group showing better results.

Conclusion: Combining topiramate with vitamin D effectively reduces migraine frequency and disability.

Keywords: Pain severity, Migraine disability assessment score

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INTRODUCTION

The word "migraine" is from the Greek ἡμικρανία (hemikrania), "a pain on one side of the head," from ἡμι-(hemi-), "half," and κρανίον (kranion), "skull" [1]. Migraine and tension headaches are the most common primary headache disorders that affect 80% of people all over the world [2]. A global estimation of migraine headache prevalence showed that migraine affects 1 in 10 people worldwide [3]. Migraine is a disabling headache disorder characterized by unilateral pulsating headaches associated with photophobia, phonophobia, nausea, and occasionally transient neurological symptoms [4]. In contrast to trigeminal autonomic cephalalgias, where the headache is generally side-locked, a common characteristic of migraine is that the headache may switch sides from attack to attack. Migraines are self-limiting, usually associated with autonomic symptoms [1]. Migraine without aura is more common in women than migraine with aura [5].

Recurrent migraines are commonly diagnosed in people around the ages of 25 and 55 worldwide, affecting 6% of men and 18% of women [5]. Most migraine patients have been prescribed or treat themselves with acute attack/rescue medication. Unfortunately, prophylactic migraine treatment is not much more common. Numerous global recommendations have been released about drug selection, treatment objectives, and indications. While there is considerable variation among these guidelines, it is generally agreed upon that a thorough discussion with the patient should precede the initiation of preventive medication. The reasonable objectives for preventive therapy include reduced attack frequency, severity, and length; enhanced response to acute attack treatment; and enhanced quality of life [6].

Today, physicians are interested in using alternative medicine and non-pharmacological remedies for migraine prevention, and many nutraceuticals, such as magnesium, coenzyme Q10, riboflavin, butterbur, feverfew, melatonin, etc., are utilized for the prophylaxis of migraine in children and adults [7]. Much concern was directed toward the presence of a possible relationship between vitamin D and migraine.

Vitamin D was found to have a role in the pathways involved in the pathogenesis of migraine, including pain sensitization, inflammation, and immune dysfunction [8]. The brain has an abundance of vitamin D receptors, and there is evidence of a non-skeletal role of vitamin D in inflammation, immunity, and the metabolism of neurotransmitters [9, 10]. An association between the dysfunction of transporter proteins of vitamin D3 metabolites and migraine attacks was observed in a study by Nagata *et al.* [11], which concluded that higher levels of vitamin D3 might reduce the risk of migraine headaches.

Sufficient levels of circulating vitamin D are mandatory for the absorption of several minerals, particularly calcium, but also phosphorus and magnesium [12]. There are two major forms of vitamin D: D2 and D3. The first one is acquired from ultraviolet (UV) irradiation of the yeast sterol, ergosterol, while vitamin D3 is produced from 7-dehydrocholesterol in the skin after exposure to UV radiation [13]. Vitamin D3 deficiency (serum 25-OH vitamin D3 level<20 ng/ml) and insufficiency (25-OH vitamin D3<30 ng/ml) are also connected with pain disorders, including fibromyalgia and headaches [13, 14]. It is also a potent antioxidant, thus contributing to the vascular health of the brain.

Furthermore, vitamin D and its metabolites (as a steroid hormone) can influence many neurotransmitters, including dopamine, acetylcholine, and serotonin [14]. Vitamin D also reduces the production of nitric oxide (NO) by inhibiting the expression of NO synthase. NO is an important biological regulator that affects neurotransmission and vasodilation and is considered a key mediator in migraine [15]. During headache attacks, NO levels in jugular venous plasma increase; there is also evidence that NO synthase inhibitors are effective in treating migraine [16].

Current evidence suggests that the antiepileptic drug Topiramate is best in context to safety and efficacy for prophylactic treatment of migraine. Several studies show that prophylactic treatment of topiramate in migraine reduces the frequency of attacks and has fewer side effects. It has been observed that patients with migraine are suffering from vitamin D deficiency. Vitamin D in combination with antiepileptic drugs for prophylaxis of migraine has shown a significant reduction in the frequency and duration of attacks. Just 12.4% reported current use of daily preventive migraine medication [17]. This indicates that preventive treatment is still severely underutilized. With this background, the present study aims to compare the efficacy and safety of topiramate alone versus topiramate with vitamin D in episodic and chronic migraine patients.

MATERIALS AND METHODS

A study involving 100 migraine patients was conducted in the Uttar Pradesh University of Medical Sciences, Saifai Etawah, U. P. Department of Pharmacology, in collaboration with the Neurology Department. The patients were identified as having episodic, chronic migraine with aura and migraine without aura. Patients with a history of traumatic brain injury, chronic liver/kidney disease, hypertension, psychiatric disorders, significant CNS disorders, epilepsy or seizure history, and pregnant or lactating women were excluded. Patients were divided into two groups: those receiving topiramate 25/50 mg daily and those receiving vitamin D3 8000 IU along with topiramate 25/50 mg daily. The lowest dose of either medication was used for all patients, and their medical and dietary history along with sociodemographic details was recorded. The degree of pain intensity was assessed using a Visual Analog Scale [(VAS)-0 to 10 rating scale] at 0, 4, 8, and 12 w. To determine the pain severity, a 12 w Migraine Disability Assessment Score (MIDAS) measuring the impact of headaches on migraineurs life and Migraine Severity (MIGSEV) scale for diagnosis and management of migraineurs were evaluated at baseline and after 3 mo.

Ethical approval: The study was approved by the Institutional Ethics Committee (193/2020-21)

Statistical analysis

All the patients were assessed on the intention-to-treat principle. The primary and secondary efficacies, as well as the quantitative and qualitative data, were compared. Primary efficacy was evaluated by the percentage change in VAS and secondary efficacy by the percentage changes in MIDAS and MIGSEV scores at the end of the study. The quantitative data was evaluated using the student t-test and the qualitative data using the chi-square test. A P-value less than 0.05 was considered significant.

RESULTS

In the Topiramate group, the majority of patients, 16 (32%), were aged 25 years or younger, while at least 4 (8%) were aged 55 years or older. The mean age of patients was 35.3 years. In the Topiramate+Vitamin D Group, the majority of patients, 26 (52%), were between 26 and 40 years old, with 3 (6%) patients aged over 55. The mean age of patients in this group was 33.9 years. The distribution of patients in different age categories in both groups was found to be statistically non-significant, and the mean age of patients in all groups was also non-significant (P>0.05).

The majority of patients in all groups were married, and the correlation of patients' marital status in both groups was found to be statistically non-significant (p>0.05). Out of a total of 100 patients, 36 in the Topiramate group and 40 in the Topiramate+Vitamin D group had a positive family history of migraine. Based on the type of migraine, patients from both groups were categorized, and it was observed that migraine without aura was more common overall, covering more than 50% of patients in each group. The correlation between the type of migraine and the distribution of patients in both groups was found to be statistically non-significant (p>0.05) as depicted in table 1.

Table 1: Distribution of patients with migraine based on age, gender, and marital status

Age in years	Topiramate (n = 50)	Topiramate+Vitamin D (n =50)	P-value
≤ 25	16 (32%)	13 (26%)	0.231
26-40	15 (30%)	26 (52%)	
40 – 55	15 (30%)	8 (16%)	
>55	4 (8%)	3 (6%)	
mean Age	35.3±12.5	33.9±10.9	0.346
Male	18 (36%)	22 (46%)	0.563
Female	32 (64%)	28 (54%)	
Married	36 (72%)	41 (82%)	0.068
Unmarried	14 (28%)	9 (18%)	
Migraine with Aura	17 (34%)	18 (36%)	0.818
Migraine without Aura	33 (66%)	32 (64%)	

The VAS scores of patients in both groups were measured, and it was observed that the VAS score significantly reduced in both groups from 0 w to the 12th w (P<0.05). The MIDAS score was also significantly reduced in both the groups from 0 w to the 12th w (p<0.05). In comparison to the baseline, the MIDAS score in both groups was found to be non-significant at the end of the study, whereas it was significant at the 12th w with a p-value less than 0.05. The MIGSEV score was significantly reduced in both groups from 0 w to 12th ws (p<0.05) but was found to be non-significant at 0 w, whereas it was statistically significant in both the groups at 12th w (P<0.05) compared to the baseline, as depicted in table 2.

Table 2: Comparison of different scores in patients with migraine in different groups

Patients	VAS score		MIDAS score		MIGSEV score	
	0 W	12 W	0 W	12 W	0 W	12 W
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Topiramate	7.3±0.9	5.3±0.6*	30.9±2.6	25.1±3.7*	3.0±0.0	2.5±0.5*
Topiramate+Vitamin D	8.1±0.8	3.3±0.6*	30.5±2.2	20.1±1.5$^{*\#}$	3.0±0.0	1.3±0.4$^{*\#}$

*Denotes P<0.001; Significant values at 12th w in corresponding groups as compared to 0 w, $^{\#}$Denotes P<0.001; Topiramate alone versus topiramate and vitamin D at 12th w.

Additionally, as depicted in table 3, the serum calcium and Vitamin D levels were observed to have increased significantly in the Topiramate along with Vitamin D group from 0 w (9.6±1.0 and 9.8±2.9, respectively) to the 12th w (11.0±0.1 and 15.5±2.7, respectively) (p<0.001).

Table 3: Comparison of serum vitamin D and serum calcium among patients with migraine in different groups at 0 d and the end of the 12th w

Patients	Serum calcium		Vitamin D	
	0 W	12 W	0 W	12 W
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Topiramate (n=50)	8.1±1.4	9.6±1.0*	10.2±3.7	9.8±2.9*
Topiramate+Vitamin D (n=50)	10.0±1.0	11.0±0.1*	10.6±2.9	15.5±2.7*

Denotes P<0.001; Significant values at 12th w in corresponding groups as compared to 0 w {Reference Normal Values:* Serum vitamin D: (30-50 ng/ml)*;* Serum calcium: (8.5-11 mg/dl)}

DISCUSSION

In the present study, a total of 100 individuals diagnosed with migraine were enrolled and evenly distributed into two categories: one receiving only Topiramate and the other receiving a combination of Topiramate and Vitamin D. Within the group receiving Topiramate with Vitamin D, a majority (more than 50%) of the patients fell within the 26-40 y age range, showing a higher prevalence among females. Our findings align with Theeler BJ *et al.* [18], who noted a higher occurrence of migraine in females compared to males. Various studies have reported migraine prevalence rates ranging from 5% to 8% in males and 11% to 16% in females [5, 19], potentially linked to hormonal fluctuations during the menstrual cycle, as proposed in the "Estrogen withdrawal hypothesis of Somerville." Similar results were noted by Victor *et al.* [20] in a national health survey in the United States. According to a recent systematic analysis for the Global Burden of Disease Study 2016, the age-standardized prevalence rate of migraine worldwide was estimated to be 14%, with a significantly higher prevalence in females (19%) compared to males (10%) [21].

Migraine, whether with or without aura, exhibits distinct familial patterns and modes of inheritance, suggesting different etiologies [22]. Migraine with aura is linked to an increased risk of ischemic stroke, whereas this increased risk is not associated with migraine without aura, and other disorders are also connected to migraine with aura, but not to migraine without aura [23]. In our study, migraine without aura was more prevalent, comprising over 50% of the patients in the groups. Silberstein SD *et al.* [24] reported that 35.5% of subjects in the intention-to-treat population experienced migraine with aura. Russell MB *et al.* [22],in a comparison of clinical characteristics in 484 migraineurs from the general population, found a prevalence of 14.7% for migraine without aura, in contrast to 7.9% for migraine with aura.

To assess the efficacy of Topiramate alone versus Topiramate with Vitamin D, a comparison of VAS, MIDAS, and MIGSEV scores was done at 0 w and the end of the 12th w after administering the drugs to the respective groups. In this study, the VAS scores for pain measurement were calculated at 0 w and 12 w intervals for both the groups and the differences were statistically significant for both groups (p<0.05). At the end of the 12th w, the results showed statistical significance with P<0.001 in the VAS score when compared to the baseline.

The baseline MIDAS score at 0 w between patients of Topiramate and those of Topiramate with Vitamin D was insignificant (P<0.408). However, at the end of the 12th w, the MIDAS score exhibited statistical significance (P<0.001). To assess the drug efficacy in each group, the Migraine Disability Assessment (MIDAS) questionnaire was employed. High mean scores were observed at the treatment initiation among the groups (30.9±2.6 in the Topiramate group and 30.5±2.2 in the Topiramate and Vitamin D group). After 12 w of treatment, significant differences were observed in scores among the groups (p<0.05), with values of 25.1±3.7 and 20.1±1.5, respectively. The Topiramate and Vitamin D medication demonstrated the lowest score.

Similar results were reported by Moras K [25], where patients subjected to migraine prophylaxis with amitriptyline exhibited a mean MIDAS score reduction from 11.6 to 9.4 after treatment. Dwajani. S. *et al.* [26] observed a reduction in MIDAS score from 22.70±13.68 at enrollment to 10.44±4.25 after 3 mo of treatment with Topiramate. Similarly, Laghari Jamil M. *et al.*[27] reported significant reductions in headache frequency and MIDAS total score with topiramate treatment.

At baseline, the MIGSEV score at 0 w between patients of Topiramate and those of Topiramate with Vitamin D was insignificant. MIGSEV scores were significantly reduced in both groups from 0 w to the 12th w (p<0.05). The correlation of MIGSEV scores in both groups was non-significant at 0 w but came out to be statistically significant at the 12th w (p<0.05). El Hasnaoui A. *et al.* [28] stated that the MIGSEV questionnaire is proposed as a simple measure of severity for the diagnosis and management of migraineurs, suitable for use by both physicians and patients. The limitations of the present study were the lack of a placebo, the single-centered open-label study, and the lack of follow-up after discontinuation.

CONCLUSION

The present study concludes that the combination of topiramate and vitamin D3 proved more efficacious than topiramate alone in reducing both weekly frequency and disability scores in patients associated with migraine. Moreover, the use of vitamin D3 therapy emerges as a potentially safe and effective approach for prophylaxis against both episodic and chronic migraines. To establish the optimal dosage of vitamin D3 for migraine prevention, additional clinical trials with larger sample sizes, altitude control, and consideration of seasonal variations are warranted.

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AUTHORS CONTRIBUTIONS

All the authors Dr. Alok Dixit, Dr. Manik Brahemi, Dr. Nasreen Fatma Khan, Dr. Ramakant Yadav, and Dr. C. V. Singh, have equally made a substantial contribution to the conception, acquisition of data, and interpretation of data and drafting the article and agreed to be held accountable for all aspects of the work.

CONFLICTS OF INTERESTS

The researchers received no financial support from any pharmaceutical companies. The authors declared no conflicts of interest.

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