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Comparison between the effectiveness of three prophylactic drugs for vestibular migraine; cinnarizine, propranolol, and topiramate: prospective study

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Abstract

Background Vestibular migraine (VM) is considered one of the most common causes of episodic vertigo. Acute attacks may interfere or hinder daily activities, and hence decrease the quality of life. Accordingly, this study was designed to evaluate and compare the effectiveness of Cinnarizine, Propranolol, and Topiramate as prophylactic treatment for vestibular migraine, in order to decrease the occurrence of acute attacks. Several medications have been proposed as a prophylactic treatment, but their benefit is still a vast field of study.

Methods Forty-five subjects were diagnosed with vestibular migraine. They were divided into 3 groups; each group either received Cinnarzine, Propranolol, or Topiramate. All patients were submitted to thorough history taking for headache and vertiginous attacks, Dizziness Handicap Inventory questionnaire (DHI) -Arabic version, visual analog scale**,** videonystagmography, and computerized dynamic posturography (CDP) before and after receiving the treatment by 3 months.

Results Topiramate was significantly superior in reducing the frequency and severity of headache attacks. The three drugs showed improvement but with no significant difference as regards duration and frequency of vertiginous attacks, DHI scores, and CDP. Only 5 patients had non-serious temporary side effects.

Conclusions The three drugs were effective for ameliorating vertiginous attacks in vestibular migraine patients, but Topiramate was better in the 25 mg twice daily dose.

Keywords Vestibular migraine, Prophylactic, Cinnarizine, Propranolol, Topiramate

Background

Vestibular migraine (VM) is considered one of the most common causes of episodic vertigo. VM may occur at an average age of about 40 years, with a male-to-female ratio of 1.5–5 to 1. Familial occurrence is not uncommon, probably based on an autosomal dominant pattern of inheritance [1].

The International Headache Society approved VM as a diagnostic entity, and the diagnostic criteria for VM appear in the appendix for International Classification of Headache Disorders (ICHD) (3rd version), this

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classification includes only definite VM, but the Barany Society classification includes probable VM [2].

Treatment of VM includes two situations: treatment of acute attacks and prophylactic treatment. Triptans and non-steroidal anti-inflammatory medications are utilized during acute episodes. While B-blockers, calcium channel blockers, anticonvulsants, and antidepressants and other non-pharmacologic methods (lifestyle and dietary modifications besides vestibular rehabilitation) are prescribed in prophylactic treatment [3].

Cinnarizine (CIN) is a selective calcium channel blocker that has been used in the treatment of vertigo. It also has anti-serotonergic and antihistaminic action and directly inhibits vestibular hair cell stimulation [4].

Beta-blockers (BBs) as propranolol act by preventing central hypersensitivity by inhibiting norepinephrine release, antagonizing serotonin (5-HT) receptors, and inhibiting nitric oxide (NO) synthesis. Since Serotonin plays an important role in the pathophysiology of VM, this could contribute to the prophylactic action of B-blockers [5].

Topiramate is an antiepileptic drug that reduces neural hyper-excitability [6]. Through multiple mechanisms including state-dependent inhibition of voltage-activated calcium channels, inhibition of glutamate-mediated neurotransmission, modulate trigemino-vascular signaling, which could affect migraine pathogenesis [7].

Daily activities may be hampered or interfered with by acute attacks. Consequently, the goal of this study was to evaluate the effectiveness of prophylactic therapy in VM patients in reducing the frequency and severity of attacks of VM and reliving the symptoms.

Methods

The present study comprised of 45 patients diagnosed with VM selected according to the following criteria: Age ranged from 18–50 years old Patients with definite vestibular migraine (VM) according to International Classification of Headache Disorders (ICHD) 3rd edition and Barany Society [2]. Patients excluded were subjects with other vestibular or neurological disorders other than vestibular migraine, pregnant or lactating women.

The study was conducted at the vestibular unit and neurology department (headache clinic), Ain-Shams University hospitals.

All patients were instructed to follow lifestyle and dietary modifications (cessation of caffeine, chocolate, old cheese, etc.), besides the medical treatment. Patients were randomly divided into three groups according to the drug received, taking into consideration cases with diabetes mellitus, bronchial asthma, and bradycardia, who must not receive propranolol (no cases in our study had the previous conditions).

Cinnarizine group received a calcium channel blocker (Cinnarzine® 75 mg twice daily). Propranolol group received a beta-blocker (Inderal® 40 mg twice daily). Topiramate group received anticonvulsant (Topamax® 25 mg twice daily). Follow-up was done for all patients after 3 months.

All patients underwent the following before and after treatment by 3 months:

History taking

Detailed history of migraine attacks

Duration of migraine, frequency per month, duration, and intensity (measured by visual analog scale) of each attack. Migraine characteristics (pulsatile or throbbing), location (unilateral or bilateral), associations (photophobia, phonophobia, nausea or vomiting), aggravating factors (physical activity), precipitating factor or triggers (stress, sleep disturbance, etc.), presence of visual aura, and family history.

Detailed history of vertigo attacks

Duration, frequency per month, each attack duration, number of attacks per day, last attack, temporal relation to migraine, and the character of dizziness (sense of self-rotation, rotation of surroundings, sense of imbalance, light headedness), also associated auditory symptoms (aural fullness, tinnitus, hearing loss, earache) or neurological symptom as (diplopia, dysarthria, limb weakness, numbness, and dysphagia). History of motion sickness (what is the trigger, onset since childhood or recent or was present at childhood but disappeared now). History of neurological diseases, any chronic diseases, and any medical treatment received.

Fulfillment of the Dizziness Handicap Inventory (DHI) (Arabic version) [8]

The questionnaire is formed from 25 questions; the patient had to answer with yes, no, sometimes according to the difficulties that faced him/her due to dizziness complaints. Questions answered with yes were given 4 points, questions answered with sometimes were given 2 points, and questions answered with no were given zero point.

Computerized dynamic postougraphy (CDP) (Neurocom) the sensory organization test (SOT)

It was done to all patients in the quiescent interictal stage. It included 6 conditions, the first 3 conditions were done on a fixed platform (C1) with eyes open, (C2) eyes closed, (C3) in a sway-referenced visual enclosure. The other three conditions were done on a sway-referenced platform (C4) with eyes open, (C5) with eyes closed, (C6) in a sway-referenced visual enclosure. Each condition

contains three trials, each lasting for 20 s. During each trial, patients were instructed to ignore any surface or visual surround motion and remain as stable as possible.

Video-Nystagmography Test (VNG) using computerized video-nystagmography 2 channels (micromedical technologies, mobile eyes, spectrum 8.10)

VNG was done to all patients in their quiescent interictal stage, it includes (Spontaneous Nystagmus, tests for gaze stabilization, tests for oculo-motor function (random saccade test, smooth pursuit test, and optokinetic test), positional tests, and positioning test.

Statistical plan

The collected data was revised, coded, tabulated, and introduced to a PC using Statistical Package for Social Science (SPSS 15.0 for Windows; SPSS Inc, Chicago, IL, 2001). Data was presented and suitable analytical statistics was done according to the type of data obtained for each parameter.

Results

The patients were divided into 3 groups, 15 patients in each group.

Their age ranged between 18 and 50 years with a mean age of 37.7 years old in the CIN group, 38.3 years old in the Inderal group, and 39 years old in Topiramate group and there were no statistically significant age differences between groups. Male to female ratio was 1: 3.5.

This table showed no statistically significant differences between the 3 groups regarding course duration of headache and vertigo.

VNG test revealed normal oculomotor subtests, no spontaneous nystagmus, and only 1 patient had BPPV upon Dix-Halpike test. Caloric test showed unilateral weakness in only 1 patient. Finally positional test showed that 29/45 (64%) had positional nystagmus as follows; horizontal nystagmus in 20/29 (69%) which was fixed in direction and abolished with fixation and vertical upbeating nystagmus in 9/29 (31%). The nystagmus had been absent in the follow-up in 5 patients (3 patients from the Cinnarizine group and 2 patients from the Inderal group).

Discussion

It was suggested that prophylaxis for VM is necessary when three or more episodes per month occur, lasting over an hour at least and affecting daily activities. The objectives of preventive treatment include reduction of the attack frequency, duration, and severity and consequently decreasing the negative impact of VM on the patient´s quality of life [9].

Prophylactic treatment options include beta-blockers (propranolol, metoprolol), calcium channel blockers (cinnarizine, flunarizine), antiepileptic drugs (Topiramate, sodium valproate), antidepressants (amitriptyline, nortriptyline, venlafaxine), antiserotonergic drugs (pizotifen), antihypertensives (candesartan, lisinopril), and monoclonal antibodies against CGRP (erenumab, fremanezumab, galcanezumab) [10]. Besides lifestyle modification and also vestibular rehabilitation, all of which were studied previously through either using different outcome measures.

In the present study, comparison was done between the calcium channel blocker Cinnarizine (Cinnarizine), the beta-blocker propranolol (Inderal) and the antiepileptic drug Topiramate (Topamax) as regards the symptomatic characteristics of the attacks of headache and vertigo, DHI and objectively by CDP. The three groups showed none statistically significant differences between the three groups regarding course duration of headache and vertigo (Table 1).

Beginning with the symptomatic characteristics of the attacks of headache and vertigo, Table 2 showed that there was improvement regarding the duration, frequency, and severity of headache attacks and also the frequency and duration of vertiginous attacks among the three groups. It was noted that Topiramate was

Table 1 Comparison between groups regards course duration of headache and vertigo attacks (in months)

Course duration of headache[a]	Mean ± SD	Median	Range (min.–max.)	*F*	*P* value	Sig
Cinnarzine group	138.4 ± (132.1)	72.0	12.0–480.0	0.47	0.626	**NS**
Propranolol group	103.2 ± (83.5)	72.0	18.0–240.0			
Topiramate group	118.0 ± (72.6)	120.0	6.0–240.0			
Course duration of vertigo[b]				**K**		
Cinnarzine group	25.6 ± (21.2)	24.0	3.0–72.0	1.38	0.501	**NS**
Propranolol group	58.7 ± (77.0)	36.0	1.0–240.0			
Topiramate group	38.5 ± (32.2)	36.0	3.0–108.0			

[a] One-way ANOVA

[b] Kruskal-Wallis test

Table 2 Comparison between the three drugs as regards changes in attack duration (hours), frequency (number/month), severity of headache (VAS), duration of vertiginous attack (hours), and its frequency (number/ month) before and after medical treatment (Kruskal–Wallis and one-way ANOVA tests)

	Mean ± SD	Range (min.–max.)		*P* value	Sig
Attack duration of headache			*K*		
Cinnarzine group	−0.30(±0.53)	−0.98–1.00	1.38	0.502	NS
Propranolol group	−0.04(±0.39)	−0.96–0			
Topiramate group	0.91(±4.11)	−0.98–11.00			
Frequency of headache			F		
Cinnarzine group [a,b]	−0.17 (±0.30)	−0.75–0	9.47	0.009	HS*
Propranolol group [b,a]	−0.43 (±0.36)	−0.95–0			
Topiramate group [c,b]	−0.55 (±0.16)	−0.88–(−0.25)			
Severity of headache			F		
Cinnarzine group [a,b]	−24 (±.21)	−.57–.13	3.59	0.036	S*
Propranolol group [b,a]	−34 (±.17)	−.56–.00			
Topiramate group [c,b]	−40 (±.13)	−.60–(−.13)			
Duration of vertiginous attacks			K		
Cinnarzine group	2.80 (±12.27)	−1.00–47.0	3.78	0.151	NS
Propranolol group	−0.57 (±0.39)	−0.97–0			
Topiramate group	0.76 (±0.34)	−1.00–0			
Frequency of vertiginous attacks			F		
Cinnarzine group	−0.43 (±0.39)	−0.97–0.33	0.48	0.621	NS
Propranolol group	−0.53 (±0.31)	−0.88–0			
Topiramate group	−0.55 (±0.34)	−0.94–0			

Table 2 showed that Topiramate was superior to CIN in reducing the frequency and severity of headache attacks with significant differences between both drugs

N.B: (a,b,c group have the same letters, there were no significant differences between them but have different letters there were significant differences between them. (Negative signal in mean is due to after treatment was lower than before treatment)

superior to Cinnarzine and propranolol in the improvement of duration, frequency, and severity of headache attacks but a statistically significant difference was present in frequency, and severity of headache attacks only. Cinnarizine was more efficient in the reduction of duration of vertiginous attacks than the others, but statistically insignificant.

Previous study indicated no significant difference between the drugs used for the prophylaxis of VM (propranolol, topiramate, calcium channel blockers (CCBs) in terms of the improvement in vestibular symptoms, intensity, and frequency of headache attacks, but Topiramate and propranolol were superior to CCBs in the improvement of frequency of headache [11].

While another study could not find any statistical differences in duration and frequency of headache and dizziness severity among the different medications (CCBs or Beta Blockers (BBs) and antiepileptic drugs) or combination of drugs (CCBs + BBs). So, concluded that the choice of regimen was more related to each physician's preference/experience or co-morbid conditions (e.g., depression, overweight, and hypertension) rather than the severity of presenting symptoms [12].

As regards the effect of pharmacological therapy on the improvement of total score of DHI questionnaire and degree of handicapping, there was no statistically significant difference between these drugs as shown in Table 3. Nearly the same results were reported by another study where they found that the DHI score of 83 patients with VM had decreased significantly after taking prophylactic medication with no significant difference between these drugs [12].

Table 3 Comparison between three drugs regards changes in total score of DHI before and after medical treatment (one-way ANOVA test)

DHI Total score	Mean (± SD)	Range (min.–max.)	*F*	*P* value	Sig
Cinnarzine group	−0.3 (±0.2)	−0.7–0.05	1.78	0.180	**NS**
Propranolol group	−0.4 (±0.2)	−0.7–(−0.1)			
Topiramate group	−0.5 (±0.2)	−0.8–(−0.1)			

Table 3 showed that the total scores of DHI were improved in Topiramate group more than the other 2 drugs but with no statistically significant difference between three drugs

Posturography is not a diagnostic test but is useful in assessing overall functional abilities or fall risk and for evaluating the efficacy of vestibular management. Table 4 showed that a minority of VM patients had abnormal SOT results. This indicated the presence of balance problems in VM patients even in an attack-free period. VM patients mostly use somatosensory input to maintain their balance. The 4, 5, 6 abnormal pattern suggests not only that patients with VM are unable to rely on vestibular information, but also that they have difficulty using visual information [13].

Table 4 Results of sensory organization test (SOT) among the 3 drugs before and after treatment (conditions 1, 2, and 3 were normal in the 3 study groups): ($n=31$, the rest of patients did not

SOT		Before treatment		After treatment	
		N	%	*N*	%
Cinnarzine group ($n=9$)					
Condition 4	Normal	7	77.8%	9	100.0%
	Abnormal	2	22.2%	Zero	0.0%
Condition 5	Normal	6	66.7%	9	100.0%
	Abnormal	3	33.3%	Zero	0.0%
Condition 6	Normal	6	66.7%	7	77.8%
	Abnormal	3	33.3%	2	22.2%
Composite Score	Normal	7	77.8%	9	100.0%
	Abnormal	2	22.2%	Zero	0.0%
Propranolol group ($n=11$)					
Condition 4	Normal	9	81.8%	10	90.9%
	Abnormal	2	18.2%	1	9.1%
Condition 5	Normal	10	91.0%	11	100.0%
	Abnormal	1	9.0%	Zero	0.0%
Condition 6	Normal	6	54.6%	10	90.9%
	Abnormal	5	45.4%	1	9.1%
Composite Score	Normal	9	81.8%	11	100.0%
	Abnormal	2	18.2%	Zero	0.0%
Topiramate group ($n=11$)					
Condition 3	Normal	10	90.9%	10	90.9%
	Abnormal	1	9.1%	1	9.1%
Condition 4	Normal	10	90.9%	10	90.9%
	Abnormal	1	9.1%	1	9.1%
Condition 5	Normal	9	81.8%	9	81.8%
	Abnormal	2	18.2%	2	18.2%
Condition 6	Normal	5	45.4%	9	81.8%
	Abnormal	6	54.6%	2	18.2%
Composite score	Normal	9	81.8%	10	90.9%
	Abnormal	2	18.2%	1	9.1%

Table 4 showed abnormalities in conditions 4, 5, and 6 in the 3 groups. After treatment, most of the patients showed improvement, especially in the propranolol group

Previous study reported that 45% of VM patients had abnormal values in condition 5 and 6 [13]. Another study found an increase in sway in patients with VM in conditions (4, 5, and 6) [14].

After medical treatment, Cinnarizine, Propranolol (Inderal), and Topiramate (Topamax) groups showed improvement in these abnormal conditions and composite score as shown in Table 4. These findings reflect the functional improvement of balance after medical treatment.

Table 5 showed the highest improvement in composite score was noted among Topiramate group but with no significant difference; this indicated the effectiveness of Topiramate in treatment of balance affection in VM patients.

A Cochrane review in 2015 was set out to identify effective pharmacological agents for the prevention of vestibular migraine, but they were unable to identify any completed study that met the strict inclusion criteria required for Cochrane reviews [15].

The meta-analysis done in 2021 could not also establish the preferred treatment modality due to significant heterogeneity and lack of standardized reporting on outcomes in the studies [16].

Side effects of the drugs (safety)

No serious side effects were observed in patients who completed the study period. In the CIN group, two patients suffered from GIT upset symptoms. In Propranolol group one patient reported hypotension twice. In Topiramate group, two patients reported numbness (paraesthesia) in their arms in the first week of treatment only, and one patient reported weight loss. Previous study reported adverse events with CIN in 9 (22.5%) of patients, which all were mild to moderate such as GIT upset, blurred vision, and weight gain, and no serious side effects such as extrapyramidal reactions or depression were reported during the medication administration [4].

Another study reported that Propranolol's side effects like hypotension, bronchospasm, and bradycardia were

Table 5 Comparison between three drugs regards changes in before and after composite score of CDP (one-way ANOVA test)

Composite score	No. of patients	Mean (± SD)	Range (min.-max.)	*F*	*P* value	Sig
Cinnarzine group	9	.07 (±.09)	−.01–.28	1.94	0.163	NS
Propranolol group	11	.02 (±.05)	−.06–.10			
Topiramate group	11	.07 (±.04)	.03–.16			

Table 5 showed that CIN, propranolol, and Topiramate were effective in improving the composite score of CDP, but with no statistically significant difference between them

observed in 15% of patients, side effects were tolerated and withdrawal of treatment was not required in any cases due to drug side effects [17]. It was also reported that 44% and 28% of patients in Topiramate 200 mg, 100 mg groups respectively had side effects in the form of paraesthesia, difficulty with concentration, weight loss, and fatigue [18].

Finally, in the answer to the question, what is the most effective drug in treatment of VM, we found that Topiramate is superior to Cinnarzine in improvement of frequency and severity of headache attacks with a statistically significant difference; however, the best one is the one that best fits the patient's clinical profile and it may be necessary to change the prescribed medication if the patient's symptoms persist or side effects occurred.

Conclusion

There was improvement regarding the duration, frequency, and severity of headache attacks and also the frequency and duration of vertigo attacks among the 3 groups, besides the improvement in the degree of dizziness handicap and the functional improvement in balance. However, it was noted that Topiramate is superior to CIN in improvement of frequency and severity of headache attacks with statistically significant difference.

The side-effect profiles of various pharmacologic agents as well as patient comorbidities likely influence the selection of the pharmacological prophylactic treatment for VM. The effectiveness of the treatment should be evaluated after adequate duration of intervention.

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Authors' contributions
N A formulated the research question, design of the work, data analysis, and revised the manuscript. ET conducted the design of the work and revised the manuscript. AS conducted the acquisition and analysis of the data for the work. GE conducted the acquisition, analysis, and interpretation of data for the work, and edited the manuscript. All authors contributed to the writing of the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the research ethical committee (REC), Ain Shams University.
Written consent was obtained from all patients before testing after explaining the aim of the study and the procedure to be done.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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