Propranolol and Venlafaxine for Vestibular Migraine Prophylaxis: A Randomized Controlled Trial

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Objectives/Hypothesis: We compared the effectiveness of venlafaxine and propranolol for the prophylaxis of vestibular migraine (VM).

Study Design: Prospective, randomized, controlled clinical trial.

Methods: Sixty-four subjects with definite VM were enrolled. The subjects were randomly assigned to receive propranolol (group P, n = 33) or venlafaxine (group V, n = 31) for VM prophylaxis. Dizziness Handicap Inventory (DHI) scores, the Vertigo Severity Score (VSS), and the number of vertiginous attacks were recorded before and 4 months after treatment. The Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) scores were also recorded to monitor the resolution of psychiatric symptoms.

Results: At 4 months after treatment, the DHI total score decreased from 55.8 ± 2.7 to 31.3 ± 3.7 and from 50.9 ± 2.5 to 19.9 ± 2.9 ($P < .001$), the mean number of total vertiginous attacks decreased from 12.6 ± 1.8 to 1.9 ± 0.7 and from 12.2 ± 1.8 to 2.6 ± 1.1 ($P < .001$), and VSS decreased from 7.3 ± 0.3 to 2.1 ± 0.4 and from 7.9 ± 0.3 to 1.8 ± 0.5 ($P < .001$) in groups P and V, respectively. However, the treatment effects were similar in both groups ($P > .05$). BAI scores significantly decreased in both groups, whereas BDI scores decreased only in group V.

Conclusions: This study provided evidence that venlafaxine and propranolol show equal effectiveness as prophylactic drugs for ameliorating vertiginous symptoms in VM patients. However, venlafaxine may be superior to propranolol in ameliorating depressive symptoms.

Key Words: Anxiety, depression, dizziness handicap inventory, migraine, prophylaxis, vertigo.

Level of Evidence: 1b.

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INTRODUCTION

Vestibular migraine (VM) is a form of episodic vertigo associated with migrainous symptoms and was described by Neuhauser et al. in 2001.[1] VM is the one of the most common causes for admission to dizziness clinics with complaints of dizziness and vertigo, although it remains underdiagnosed because of a wide variety of symptoms. VM patients suffer from dizziness and episodic vertigo that can occur spontaneously or because of positional changes, head movements, or visual stimuli. These attacks can be provoked by stress, sleep deprivation, dehydration, menstruation, or certain foods. VM also shows a strong coexistence with psychiatric disorders, anxiety, and depressive disorders.[2,3]

Some patients benefit from behavior and diet modifications. Antimigrainous medication is prescribed as prophylactic treatment to patients who do not benefit from lifestyle modifications.[4,5] However, evidence for the optimal treatment is lacking. Data regarding VM treatment are derived from case series and retrospective studies, rather than randomized controlled trials (RCTs).[6] Also, RCTs providing information regarding the first choice of medical treatment for VM are few. VM prophylaxis is primarily based on guidelines designed for migraine headache therapy.

Propranolol is a nonselective β-blocker that is primarily used to treat hypertension. According to the Cochrane Review, there is high-quality evidence that propranolol is also an effective prophylactic drug for migraine headaches.[7] However, there is insufficient evidence about the effectiveness of propranolol in VM prophylaxis. Venlafaxine, a serotonin–norepinephrine reuptake inhibitor, is an antidepressant drug, with low-quality evidence available for its effectiveness in migraine headache therapy. It is recommended for patients with severe anxiety or depressive symptoms.[8] Compared with placebo, a daily dose of 150 mg was associated with a greater decrease in headache frequency in patients with migraine.[9] However, no study has evaluated the effectiveness of venlafaxine therapy in VM prophylaxis, and only one study has recommended this drug as a first-line therapy on the basis of the authors' experience.[10]

In this study, we compared the effectiveness of propranolol and venlafaxine for VM prophylaxis and investigated the possible relationship between psychiatric symptoms and vertiginous symptoms.

MATERIALS AND METHODS

Study Design

This outpatient, open-label, prospective, randomized controlled trial with parallel group assignment was conducted at Haseki Training and Research Hospital, a tertiary referral health center. Patients were enrolled between January 1, 2014 and September 15, 2014, and patient activities ended on December 15, 2014. Local ethics committee approval (Protocol No. 53) and written informed consent from all participants were obtained before study initiation. This study is registered at clinicaltrials.gov (NCT02350985).

Subjects

All patients with suspected VM were referred to both an otolaryngologist (M.S.) and a neurologist (H.A.) to ensure that they fulfilled the VM criteria and to rule out other vestibular disorders. Detailed neurological and neurotological examinations, audiometric investigations, videonystagmography, and bithermal caloric testing were performed to exclude additional vestibular or neurological disorders. All patients were required to be 18 years or older, with a history of definite VM (at least 2 months) as defined by the Bárány Society and Migraine Classification Subcommittee of the International Headache Society.[11] Patients were excluded before randomization if they had a known history of allergic reactions to venlafaxine or propranolol, if they were under the care of a psychiatrist, if they were pregnant or planning for pregnancy, if they had a significant illness or medical condition such as cancer or liver or kidney failure, or if they had certain medical conditions that could interfere with propranolol or venlafaxine therapy, such as atrioventricular block, bradyarrhythmia, asthma, chronic obstructive pulmonary disease, and diabetes mellitus.

Interventions

The study was conducted using two parallel treatment arms with balanced allocation (1:1), propranolol (group P) and venlafaxine (group V). Following the verification of eligibility, the patients were randomly assigned to either treatment arm. To achieve balanced randomization, a random permutated block with a block size of six was used. Randomization was performed using the sealed envelope method (A.K.). Patients in group P received propranolol at a flexible dose of 40 mg to 160 mg, with an escalating dosage starting at 40 mg orally in the morning for a week, followed by 40 mg in the morning and 40 mg in the evening. Thus, the total dose was up to 160 mg daily. Patients in group V received venlafaxine 37.5 mg at bedtime for 2 weeks, followed by 75 mg at bedtime, with an escalating dosage for 2-week periods. Thus, the total dose was up to 150 mg daily. All participants were asked to self-titrate their medication and inform the researchers (T.Y., H.A.).

Assessment

Primary outcome. The primary outcome was the effectiveness of venlafaxine in comparison with that of propranolol for the amelioration of vestibular symptoms in VM patients. To assess the effects of treatment on vestibular symptoms, the following parameters were assessed at baseline and 4 months after treatment: Dizziness Handicap Inventory (DHI) scores, the number of vertiginous attacks in the last month, and the Vertigo Severity Score (VSS). Vestibular symptoms such as spontaneous, positional, visually induced, and head-motion–induced vertigo are defined to qualify a diagnosis of VM by the Bárány Society. However, it is very hard to quantify the frequency of vertiginous attacks by using visually induced or head-motion–induced vertigo. Therefore, we used spontaneous vertigo (internal or external) of moderate to severe intensity lasting more than 5 minutes or/and positional vertigo for recording vertiginous attacks. The decrease in the number of attacks was assessed as complete resolution, substantial control (>50% decrease), moderate control (25%–50% decrease), and minimal control (<25% decrease) with unchanged or worsened frequency.

Secondary outcomes. The secondary outcome was the association between the amelioration of vertiginous symptoms and that of psychiatric symptoms. To assess this outcome, the difference between baseline and 3-month post-treatment Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) scores was analyzed in both groups.

Follow-up

For the first month after randomization, the patients were instructed to visit the clinic biweekly for the evaluation of adverse effects and to ensure patient compliance with the drug dosage. All patients were asked to maintain a diary with a record of any vertigo attacks experienced during treatment. Patients were asked to note each spontaneous vertigo attack and each day having positional vertigo as one event to determine the frequency of vertiginous attacks. The effective duration of treatment was considered as 12 weeks. In addition, adverse effects, reasons for exclusion, reasons for refusal to participate, and other reasons for noncompliance with the study protocol were recorded during patient visits or phone interviews.

Statistical Analysis

In total, 67 patients were enrolled to provide a power of 80% for the detection of a five-point change from baseline DHI in 3 months, assuming a type I error rate of 0.05, a 10% loss to follow-up, and a standard deviation of seven points for the change in DHI. Data were analyzed using the Number Cruncher Statistical System 2007 and the Power Analysis and Sample Size 2008 statistical software (both from NCSS Statistical Software, Kaysville, UT). Data with a normal distribution are descriptively presented as means ± standard errors, whereas those without a normal distribution are presented as medians and interquartile ranges. Treatment effectiveness was defined as changes in the outcome measures at 12 weeks after treatment. Paired t tests were used for normally distributed variables (e.g., DHI, BAI, and BDI scores), whereas the Wilcoxon signed rank test was used for non-normally distributed variables (VSS and number of vertiginous attacks). To determine the influence of a decrease in psychiatric symptoms on the primary endpoint (DHI, VSS, and number of vertiginous attacks), linear logistic regression analysis was used. Primary endpoint analysis was conducted using the intention-to-treat method. Missing data were handled by the multiple imputation method. Differences were considered statistically significant at $P < .05$ and $P < .01$.

RESULTS

In total, 73 patients were enrolled; the clinical characteristics of VM in these patients are summarized in Table I. From the 73 patients, six did not meet the inclusion criteria and three refused to participate. Eventually, 64 patients were randomized (33 in group P and 31 in group V), and 52 completed the study (26 in both

| TABLE I. | | |
Clinical Characteristics of Subjects With a Definitive Diagnosis of Vestibular Migraine.		
Vestibular symptoms, n (%)*	Spontaneous vertigo	59 (81%)
	Positional vertigo	28 (38%)
Additional symptoms, n (%)	Dizziness[†]	65 (89%)
	Oscillopsia	11 (15%)
	Intolerance to head motion	66 (90%)
	Nausea	60 (82%)
	Vomiting	30 (41%)
Migrainous symptoms accompanying at least 50% of the vertiginous attacks, n (%)	Headache	25 (34%)
	Photophobia	48 (66%)
	Phonophobia	43 (59%)
	Visual aura	15 (21%)
Cochlear symptoms, n (%)	Tinnitus	24 (33%)
	Aural fullness	19 (26%)
	Hearing loss	8 (11%)
	Perceptual hearing loss	16 (22%)
Total no. of spontaneous vertiginous attacks (lifetime), n (%)	5–20	19 (26%)
	21–50	13 (18%)
	>50	41 (56%)
Precipitating factors, n (%)	Menstruation	19 (26%)[‡]
	Stress	59 (81%)
	Sleep irregularities	46 (63%)
	Dehydration	20 (27%)
	Bright/flickering light	48 (66%)
	Diet	16 (22%)
	Others	10 (14%)

*Symptoms used for determining frequency of vertiginous attack.
[†]Dizziness: sensation of disturbed spatial orientation.
[‡]Percentage of women with vestibular migraine.

groups). The baseline data at randomization for the two treatment groups are summarized in Table II. In group P, two patients discontinued treatment because of the lack of improvement, four were excluded because of adverse effects, and one left the study without providing any reason. In group V, four patients were excluded because of adverse effects and one left without providing any reason. No patient in group V left because of a lack in improvement. The study design and patient inclusion procedure are summarized in a flow diagram according to the CONSORT (Consolidated Standards of Reporting Trials) statement (Fig. 1).

DHI

A decrease in DHI scores after treatment indicates an improvement. The DHI total score decreased from 55.8 ± 2.7 to 31.3 ± 3.7 and from 50.9 ± 2.5 to 19.9 ± 2.9 in groups P and V, respectively; the treatment effect was -24.5 ± 3.7 and -31.0 ± 3.6, respectively ($P = .190$). The treatment effects according to the physical, functional, and emotional domains of DHI were -6.0 ± 1.1, -11.7 ± 1.9, and -6.7 ± 1.8, respectively, in group P, and -8.8 ± 1.0, -14.0 ± 2.0, and -8.3 ± 1.4, respectively, in

group V. In both groups, the mean DHI total scores and the mean scores for the individual domains showed a significant decrease after treatment ($P < .001$). Furthermore, the treatment effects were comparable between the two groups ($P > .05$). Changes in the different outcome measures in both groups are shown in Table III.

Number of Vertiginous Attacks

With regard to the number of vertiginous attacks, in group P, complete control was achieved in 10 patients (38%), substantial control in 13 (50%), moderate control in two (8%), and minimal control with unchanged frequency in one (4%). In group V, complete control was achieved in 13 patients (50%), substantial control in nine (35%), moderate control in two (8%), and minimal control with unchanged frequency in two (8%). The mean number of vertiginous attacks decreased from 12.6 ± 1.8 to 1.9 ± 0.7 in group P and from 12.2 ± 1.8 to 2.6 ± 1.1 in group V; the treatment effect was -10.7 ± 1.8 and -9.59 ± 1.8, respectively ($P = .657$). In both groups, the mean number of vertiginous attacks showed a significant decrease after treatment ($P < .001$).

VSS

VSS defines the severity of vertiginous attacks that impair the patient's quality of life. It is presented on a 10-point Likert scale, and a decrease in VSS indicates an improvement. VSS decreased from 7.3 ± 0.3 to 2.1 ± 0.4 in group P and from 7.9 ± 0.3 to 1.8 ± 0.5 in group V; the treatment effect was -5.3 ± 0.4 and -6.2 ± 0.5 in groups P and V, respectively ($P = .124$). In both groups, the mean VSS scores were significantly decreased after treatment ($P < .001$).

| TABLE II. | | | |
Baseline Data at Randomization.			
	VMTT		
Demographics	Propranolol, n = 33	Venlafaxine, n = 31	P Value
Enrollment age, yr, mean (minimum, maximum)	38 (18, 60)	42 (21,60)	.089
% Female	93.9	90.3	.607
DHI scores, mean (SE)			
Physical	14.3 (0.7)	14.7 (0.7)	.626
Functional	25.7 (1.4)	22.4 (1.3)	.074
Emotional	15.8 (1.1)	13.8 (1.1)	.214
Total	55.8 (2.7)	50.9 (2.5)	.178
Average vertiginous attack per month, median (IQR)	10 (4.5–22.5)	8 (4–20)	.870
VSS, median (IQR)	8 (6–8)	8 (7–10)	.130
BAI, mean (SE)	25.9 (2.3)	25.2 (2.5)	.847
BDI, mean (SE)	16.9 (1.7)	18.5 (1.8)	.517

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; DHI = Dizziness Handicap Inventory; IQR = interquartile range; SE = standard error; VMTT = Vestibular Migraine Treatment Trial; VSS = Vertigo Severity Score.
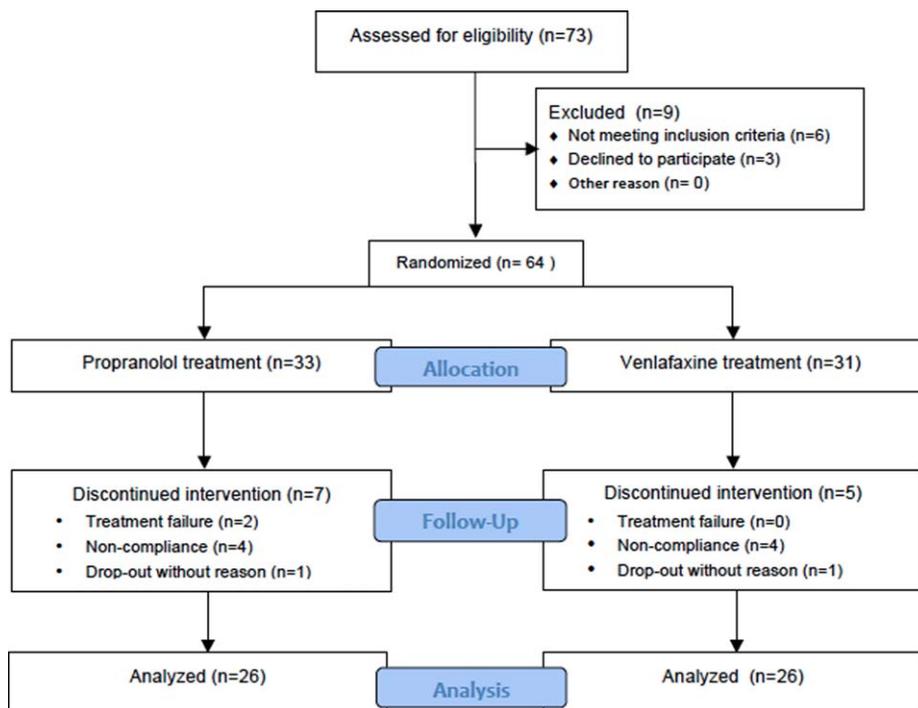
Fig. 1. Flow diagram of the study design and patient inclusion process. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

BAI

A decrease in BAI scores indicates the amelioration of anxiety symptoms. The BAI score decreased from 25.9 ± 2.3 to 18.4 ± 2.0 in group P and from 25.2 ± 2.5 to 14.0 ± 2.2 in group V; the treatment effect was -7.5 ± 2.1 and -11.2 ± 2.8, respectively ($P = .270$). In both groups, the mean BAI scores showed a significant decrease after treatment ($P = .001$ and $P < .001$ in groups P and V, respectively).

BDI

A decrease in BDI scores indicates the amelioration of depressive symptoms. The BDI score decreased from 16.9 ± 1.7 to 14.9 ± 1.9 in group P and from 18.5 ± 1.8 to 10.0 ± 1.5 in group V; the treatment effect was -2.0 ± 1.3 and -8.6 ± 1.8 in groups P and V. In group P,

the BDI score showed no significant change after treatment ($P = .131$), whereas it showed a significant decrease in group V ($P = .001$). The treatment effect was significantly greater in group V than in group P ($P = .002$).

Amelioration of Psychiatric Symptoms: Effects of BAI and BDI Scores on DHI Score, VSS, and Number of Vertiginous Attacks

We investigated the association between psychiatric symptoms and vertiginous symptoms using linear regression analysis. The improvement in BAI and BDI scores was not associated with the DHI total score ($F_{(3,22)} = 3.91$, $P = .055$) in group P. In addition, the BAI and BDI scores did not influence VSS and the number of vertiginous attacks ($F_{(3,22)} = 1.40$, $P = .265$ and $F_{(3,22)} = 0.215$, $P = .885$) in this group. On the other

TABLE III.
Treatment Effect Data for the Assessment of Outcome Measures.

Outcome Measures	Propranolol		Venlafaxine		
	Mean	SE	Mean	SE	P (95% CI)
DHI physical score	−6.0	1.1	−8.8	1.0	0.091 (−0.5 to 5.9)
DHI functional score	−11.7	1.9	−14.0	2.0	0.464 (−3.9 to 8.4)
DHI emotional score	−6.7	1.3	−8.3	1.4	0.398 (−2.1 to 5.2)
DHI total score	−24.5	3.3	−31.0	3.8	0.190 (−3.3 to 16.3)
No. of vertiginous attacks	−10.7	1.8	−9.6	1.7	0.595 (−6.0 to 3.8)
VSS	−5.3	0.4	−6.2	0.5	0.152 (−0.3 to 2.1)
BAI	−7.5	2.2	−11.2	2.8	0.270 (−2.9 to 10.4)
BDI	−2.0	1.3	−8.6	1.8	0.002 (−2.4 to 10.7)

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CI = confidence interval; DHI = Dizziness Handicap Inventory; SE = standard error; VSS = Vertigo Severity Score.

hand, the improvement in BAI and BDI scores was associated with the improvement in the DHI total score ($F_{(3,22)} = 6.565$, $P = .002$) in group V, although it did not affect VSS and the number of vertiginous attacks ($F_{(3,22)} = 1.397$, $P = .270$ and $F_{(3,22)} = 1.61$, $P = .386$, respectively).

Treatment Intolerance Rates

Eight patients (12% in group P and 13% in group V) reported serious adverse effects necessitating treatment discontinuation. In group V, two patients reported fatigue, one reported somnolence, and one reported sexual dysfunction (male). In group P, three patients reported hypotension or syncope, and one reported bronchospasm.

DISCUSSION

To the best of our knowledge, we conducted the first RCT assessing the effectiveness of prophylactic treatment for VM by comparing propranolol and venlafaxine. We found that both drugs significantly decreased the DHI total score, VSS, and the number of vertiginous attacks. However, neither treatment group showed superiority over the other one with regard to an improvement in vertiginous symptoms. Unlike the other results, depressive symptoms ameliorated only after venlafaxine therapy, with an association between the improvement in BAI and BDI scores and the improvement in the DHI total score.

A few retrospective studies have provided limited data about the effectiveness of propranolol or β-blockers in VM prophylaxis.[3,12–15] The overall response rates for propranolol were reported to range between 72% and 100%.[3,13,14] However, few of those studies used criteria for definite VM and/or included an adequate patient sample.[14,15] The exclusion of psychiatric disorders, Meniere's disease, and vestibular paroxysmia, which show symptoms similar to those of VM, is important. Van Ombergen et al.[15] used the Bárány nomenclature, which highlights the co-occurrence of migrainous symptoms and vertiginous symptoms, to arrive at a definitive diagnosis of VM. However, in their study, only 26% (n = 17) of patients were definitively diagnosed with VM, and 74% of patients showed symptom amelioration with propranolol 80 mg daily. In a retrospective study including 74 patients, Baier et al.[14] compared the efficacy of various drugs. They only included patients with a definitive diagnosis of VM according to the Neuhauser criteria. In their study, 67% patients received β-blocker therapy (15 propranolol and 34 metoprolol) with a wide dose range, and they showed a significant decrease in vertiginous symptoms with regard to intensity, duration, and frequency. However, the authors reported the overall success rate for the various drugs without specifying the efficacy of β-blocker therapy for VM prophylaxis. The only prospective study on VM prophylaxis evaluated 36 patients who received propranolol, metoprolol, flunarizine, clonazepam, or amitriptyline[16] and reported the satisfactory control of symptoms in 69% patients. However, the authors did not specify whether patients with probable VM were included. In addition, the power of that study was limited, with 12 patients receiving propranolol therapy.

To our knowledge, only one study has discussed VM prophylaxis, and it concluded that venlafaxine 37.5 mg daily was an effective first-line treatment.[10] Venlafaxine can be a first-line therapy for VM, particularly because VM is strongly associated with psychiatric comorbidities.[2,3] However, no study has evaluated the effectiveness of this drug in VM prophylaxis. Our study showed that venlafaxine is an effective prophylactic drug for VM, although it is not superior to propranolol in decreasing vertiginous and anxiety symptoms. Therefore, both propranolol and venlafaxine can be used as first-line drugs in VM prophylaxis. Nevertheless, we recommend the prescription of venlafaxine as a first-line therapy only for VM patients with severe depressive symptoms. Of note, other conditions should also be considered for venlafaxine therapy, with treatment selection based on individual factors such as gender, age, body mass index, psychiatric comorbidities, and coexisting medical illnesses.

This study has some strength and limitations. With regard to the strengths, this is the first RCT that includes patients with definite VM that was refractory to lifestyle modifications, which eliminate any possible effects of triggers. Furthermore, treatment effectiveness was analyzed using well-accepted outcome measures (DHI, VSS, and frequency of vertiginous attacks), and the resolution of psychiatric symptoms was monitored using BAI and BDI, which provided additional information for determining the appropriate treatment for VM patients with severe depressive or/and anxiety symptoms.

With regard to the limitations, we did not compare propranolol and venlafaxine with placebo. Nevertheless, both propranolol and venlafaxine showed a significant improvement that was greater than the placebo effect determined in a meta-analysis, which showed that the placebo effect cannot be higher than 21%.[17] Furthermore, this study was not blinded, although we believe this did not lead to any bias. Finally, we did not evaluate changes in migrainous symptoms such as headache, photophobia, or phonophobia; this could have provided additional information on the association between the amelioration of vestibular symptoms and the decrease in headache frequency, particularly in group V.

CONCLUSION

The results of this study, designed to investigate the effectiveness of propranolol and venlafaxine in VM prophylaxis, suggest that both drugs provide clinically relevant benefits for VM patients and that venlafaxine is preferred over propranolol for VM patients with severe depressive symptoms.

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