BJGH Brazilian Journal of Global Health
Revista Brasileira de Saúde Global

Effectiveness and safety of Venlafaxin for prevention of Vestibular Migraine

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ABSTRACT

OBJECTIVE

To evaluate the efficacy and safety of Venlafaxine for the control of vestibular migraine (VM).

METHODS

This is a systematic review of randomized clinical trials. The following databases were searched: PUBMED (1966-2021), EMBASE (1974-2021) and CENTRAL (Cochrane Library-2021). There was no geographic and period limitation in the survey. Data extraction and study quality assessment were carried out by two independent researchers.

RESULTS

The search strategy identified 47 studies, of which 2 were included in this review, as they met the inclusion and exclusion criteria. Both evaluated the efficacy of venlafaxine in vestibular migraine, comparing the results with other drugs. The first study (2017) compared the effect of venlafaxine with flunarizine and valproic acid, while the second study (2015) compared the efficacy of venlafaxine with propranolol. Both showed improvement of vestibular symptoms in all groups evaluated, but only the groups submitted to treatment with venlafaxine showed a significant change in the emotional DHI (Dizziness Handicap Inventory) score and improvement in depressive symptoms.

CONCLUSIONS

Although venlafaxine appears to have promising results, there is currently a scarcity of studies that allow currently to assess the efficacy and safety of the drug for the treatment of vestibular migraine. The evidence is quite limited, the number of studies and patients evaluated reduced, and it is recommended to conduct new quality randomized clinical trials to elucidate the issue.

DESCRIPTORS

Venlafaxine, Vestibular migraine, Prevention, Evidence-based clinical practice, Systematic review.

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DOI: https://doi.org/10.56242/globalhealth;2021;1;3;57-61

INTRODUCTION

Vestibular migraine (VM) is already considered the second most common cause of dizziness and the first cause of spontaneous episodic vertigo. It affects individuals of different ages, mainly females, and it is difficult to control throughout life[1].

Migraine is a primary episodic headache characterized by unilateral pulsatile cranial pain of moderate to severe intensity with long duration[2]. When the individual diagnosed with migraine presents vestibular symptoms (vertigo or dizziness) of moderate to severe intensity, associated with migraine symptoms (typical headache, phonophobia, photophobia, visual aura) in at least 50% of the crises, we classify the condition as migraine entrance exam (VM)[3].

The main pathophysiological pathway of migraine is related to trigemino-vascular activation of meningeal vessels. Trigeminal activation alters the production and absorption of a series of neurotransmitters, such as serotonin, GABA and norepinephrine, creating a cortical wave that spreads to the cerebellum, leading to balance disorders[4].

There are two main groups of treatment for vestibular migraine: medications for abortion of the crisis and prophylactic treatment, preventing the recurrence of symptoms. In this last group, we found drugs with beta-blocking action, calcium antagonists, anticonvulsants and antidepressants[1].

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor, often used in the treatment of depression. Its use as a prophylactic medication in migraine attacks has been shown to be effective and safe[5-7].

This study aimed to evaluate the efficacy and safety of venlafaxine in preventing vestibular migraine.

METHODS

Study protocol

It is a systematic review following the criteria recommended by the Cochrane Collaboration and described in the *Cochrane Handbook for Systematic Reviews of Intervention*[8].

Search strategy

Research was carried out in the electronic databases: PUBMED (1966-2021), EMBASE (1974-2021) AND CENTRAL - 2021 (Cochrane Library). The date of the last survey was February 4, 2021. There was no date limitation or geographic restriction for the survey.

The official vocabulary identified was extracted from DECS - Health Sciences Descriptor - http://decs.bvs.br/ and MeSH - Medical Subject Headings - http://www.ncbi.nlm.nih.gov/mesh and the corresponding terms for EMTREE. The descriptors and terms used were: Migraine "[Mesh] OR (migrain) OR venlafaxine OR (venlafaxin)". The methodology adopted for the development of the search strategy followed the Cochrane Handbook, as well as the standardization for highly sensitive strategies[8].

Randomized clinical trials (RCTs) were selected, following the parameterization of the evidence level pyramid.

The synthesis method involved the combination of similar studies in a narrative review. The results of individual studies were summarized in a table.

Selection of studies and inclusion criteria

Two independent authors participated in the process of identifying studies in electronic databases. In case of disagreement or uncertainty regarding the relevance of the study based on the title and screening of the abstract, the full article was recovered. Both reviewers read the studies and evaluated each for inclusion or exclusion, following inclusion criteria.

The inclusion criteria were as follows: 1. Randomized clinical trials; 2. Adult patients with a defined MV diagnosis; 3. Use of venlafaxine as a medication to prevent MV crises; 4. Evaluation of efficacy and safety of venlafaxine with other drugs and / or placebo.

Articles unrelated to randomized controlled trials were excluded.

Analysis outcomes

The primary endpoint of analysis involved:

a) Efficacy of venlafaxine, the number of dizziness attacks being assessed.

As secondary outcomes, the following were evaluated:

b) Changes in quality of life.

c) Change in anxiety and depression rates.

d) Adverse effects.

Data extraction

Data extraction was performed by two independent researchers. Were characterized: authorship of the article, publication date, study design, sample size, number of participants per intervention, age of participants, gender, and classification of vestibular migraine (probable or defined).

Evaluation of the quality of articles

The studies were evaluated using the GRADE approach to assess the overall quality of the evidence. The quality of the evidence reflects the extent to which there is reliability in relation to the estimated effect for the applicability of the results found. There are four possible classifications regarding the quality of the study: high, moderate, low, and very low. A high-quality classification of evidence implies confidence in the estimation of the effect, and it is very unlikely that other research will change the confidence in the estimation of the effect. A very low-quality rating implies that any estimate of effect obtained is very uncertain.

The GRADE approach classifies evidence from randomized controlled trials that have no serious limitations as high quality. However, several factors can lead to the downgrading of evidence to moderate, low, or very low. The degree of classification is determined by the seriousness of the following factors: limitations of the study (risk of bias); inconsistency, indirect nature of the evidence, imprecision, and publication bias[9].

This process was also carried out by two independent authors.

Statistical analysis

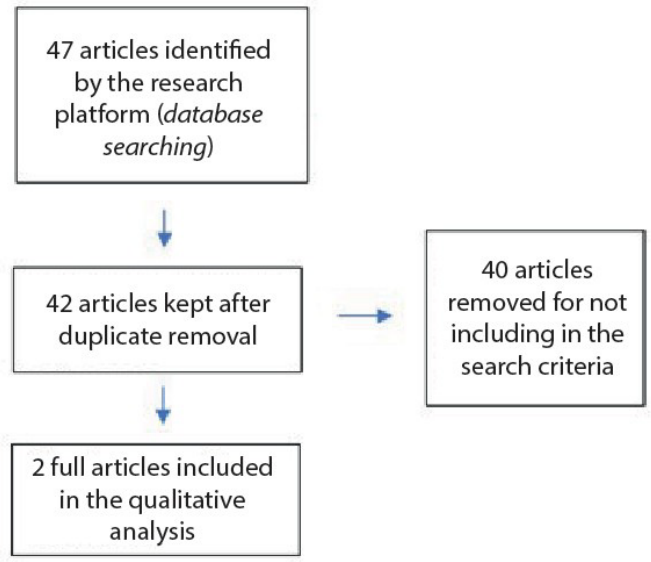
As these are dichotomous variables, the risk ratio - relative risk (RR) was calculated and the 95% confidence interval (95% CI) was described.

RESULTS

Study Selection

The search strategy retrieved 47 articles from the electronic databases searched. After removing 5 duplicate articles, the titles and abstracts of the remaining 40 articles were evaluated, 2 of which were eligible for the study.

Flowchart 1 presents the findings from the signed search strategy.



Flowchart 1. Research strategy in electronic databases: PUBMED (1966-2021), EMBASE (1974-2021) AND CENTRAL - 2021 (Cochrane Library).

Characteristics of the studies

Two articles were included in this review[10,11], both of which were randomized clinical trials with parallel groups, one with simple blinding[10] and the other open.

The study by Liu et al[10] included 75 participants divided into 3 groups, 23 used venlafaxine 75mg, 22 used flunarizine and 20 used valproic acid. There was a loss of 10 patients over the course of the study, developed over a period of 3 months, distributed among the groups, for similar causes. The study by Mehti et al[11] included 64 participants, of which 33 were medicated with propranolol and 31 with venlafaxine 37.5mg. Over the course of the study, which lasted for 4 months, 12 participants left the study, but the reasons for this loss are not described.

The primary outcomes assessed by both articles were the same: number of vertigo attacks, changes in the Dizziness Handicap Inventory (DHI) score and the Vertigo Severity Score (VSS) scale. DHI is a questionnaire developed in 1990 with the aim of assessing self-perception of the disabling effects caused by dizziness. It is divided into three parts that assess the individual's physical, functional, and emotional condition[12]. VSS is a scale of 36 questions that relate signs of severity of dizziness and their relationship with anxiety[13].

The secondary outcomes analyzed were changes in anxiety and depression rates and adverse effects of medications.

Assessment of the quality of evidence

The articles were evaluated following the GRADE approach, considering the main outcome, the improvement of vertiginous symptoms. The evaluation of inconsistency, indirect evidence or imprecision proved to be of low risk for both articles. The study by Liu et al[10], presented a high risk of bias, since randomization, allocation and blinding were inadequate. The article by Mehti et al[11] presented a moderate risk of bias, since randomization was adequate, but there was no blinding of the team and, possibly, of the patients.

Effects of the intervention

In observing the primary outcome, Liu et al[10] identified that venlafaxine improved the DHI response in all domains (physical, functional, and emotional), improved the VSS response and decreased the number of vertigo attacks, being all data found with statistical significance. Flunarizine partially improved DHI and improved VSS response but did not reduce the number of vertigo attacks. Valproic acid partially improved DHI and reduced the number of vertigo attacks, but had no impact on VSS. None of the drugs had reported adverse effects.

In the article by Mehti et al[11], there was a significant improvement in the values of DHI, VSS and the number of vertigo attacks in the groups treated with propranolol and venlafaxine, with no statistically significant difference between them. However, when observing the symptoms of anxiety and depression, patients who used venlafaxine showed a significant decrease in the assessed scores. Adverse effects were observed in both groups, at similar rates, 12% in the propranolol group (hypotension and bronchospasm) and 13% in the venlafaxine group (drowsiness and sexual dysfunction), requiring discontinuation of the drug.

The main effects of the interventions reported here are summarized in Table 1.

Table 1. Summary of the main effects of the interventions evaluated by the studies.

Study	Outcome Analysis Criteria	Statistical analysis	Outcomes	Result
Liu F et Al, 2017	Dizziness Handicap Inventory (DHI) and Vertigo Severity Score (VSS)	ANOVA; t-tests; chi square	DHI score physicist	Significant decrease with the 3 medications (p <0.05).
			DHI functional score	Significant decrease with the 3 medications (p <0.05).
			DHI emotional score	Significant decrease with the use of venlafaxine (p = 0), with no difference with flunarizine (p = 0.12) and AV (p = 0.11).
			VSS	Decrease in vestibular symptoms with the use of venlafaxine (p = 0) and flunarizine (p = 0.03).
Mehti S et Al, 2015	Dizziness Handicap Inventory (DHI); Vertigo Severity Score (VSS); BAI; number of dizzying attacks	t-tests; Wilcoxon; linear logistic regression analysis	DHI total	Significant decrease with the 2 medications (p<0.001).
			number of dizzying attacks	Significant decrease with 2 medications (p <0.001), with complete control in 38% of patients with propranolol and 50% with venlafaxine.

Statistical evaluation

The heterogeneity of the articles did not allow the performance of meta-analysis, since the controls used medications with extremely different actions. The relative risk of using venlafaxine when compared to other drugs was as follows: flunarizine: 0.7122; valproic acid: 1.1434; propranolol: 0.8125.

DISCUSSION AND CONCLUSIONS

The association between migraine and vertigo has long been recognized, but the nature of this relationship is uncertain. Several studies have already proven that the prevalence of dizziness in migraine patients exceeds the eventual occurrence. An example of this is the prevalence of migraine in Germany, which affects about 14% of the population, while about 7% have vertigo. The risk that the association of these two symptoms is occasional would be statistically 1%, however, the current incidence is 3.2%[1].

The apparent association of these two symptoms helps to understand the pathophysiology of MV, which follows the basis of migraine itself. The dysfunction of the brainstem generates an error in the sensory stimulus. Stimulation of the trigeminal pathway and meningeal vessels leads to severe pain and triggers a series of synapses to the cerebral cortex and cerebellum[14].

To avoid this cascade of pain and, consequently, dizziness, prophylactic treatment has a fundamental role. Several guidelines suggest that the first choice of prophylactic medication is beta-blocker. It is not clear how it reduces the number of headache attacks, but they can affect the catecholaminergic center and act on serotonin receptors. Propranolol is the most widely used beta-blocker[15].

Another medication used in the studies evaluated was valproic acid, a medication classified as an anticonvulsant. The use of this class of medication in migraine is due to its potential in modulating the pain system, specifically in the system that involves migraine, since it improves the action of GABA and blocks the sodium and calcium channels (directly related to the processes vascular)[16].

Flunarizine is a drug that also has a calcium channel blocking action. Its action in controlling vertigo attacks is well known, as it inhibits the contraction of labyrinthine hair cells. In MV, there is an improvement in the number of vertigo and headache attacks, as already demonstrated in some articles[17].

Anxiety is a common comorbidity in migraine and is often associated with vestibular disorders, especially MV. The drugs mentioned above have low performance on neurotransmitters related to emotional control, such as serotonin and norepinephrine. Venlafaxine appears as a potential drug to fulfill this role[18].

Acting in inhibiting the reuptake of serotonin and norepinephrine, the drug acts on the pathophysiological system of migraine and improves anxiety and depression. The articles evaluated here show just that. In addition to improving dizziness, there was a marked improvement in depressive symptoms.

Although venlafaxine appears to have promising results, there is currently a scarcity of studies that allow currently to assess the efficacy and safety of the drug for the treatment of vestibular migraine. The evidence is quite limited, the number of studies and patients evaluated reduced, and it is recommended to conduct new quality randomized clinical trials to elucidate the issue.

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