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Flunarizine as a preventive measure against vestibular migraine: a literature review

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ABSTRACT

OBJECTIVE

Vestibular migraine is the leading cause of episodic vertigo and the second most common cause of dizziness in adults, due to its high prevalence, negative impacts on individual health, and increased public health expenditures, preventive treatment should be implemented early. This paper aimed to evaluate the efficacy of Flunarizine as a preventive for vestibular migraine crises in comparison to other drugs.

METHODS

Vestibular migraine is the leading cause of episodic vertigo and the second most common cause of dizziness in adults, due to its high prevalence, negative impacts on individual health, and increased public health expenditures, preventive treatment should be implemented early. This paper aimed to evaluate the efficacy of Flunarizine as a preventive for vestibular migraine crises in comparison to other drugs.

RESULTS

Qualitatively, the analysis showed that Flunariniza was positive for decreasing the frequency of vertigo in cases of vestibular migraine, with moderate degree of evidence, relative risk of 0.34 and confidence interval 0.15 to 0.76. The meta-analysis showed a positive result of Flunarizine as a preventive drug for the study population. No serious side effects were reported from the use of the medication, which makes it safe for use by patients.

CONCLUSIONS

Flunarizine is a good drug for prevention of vestibular migraine.

DESCRIPTORS

Flunarizine, Vestibular Migraine, Prevention.

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INTRODUCTION

Vestibular migraine is the main cause of episodic vertigo and the second most common cause of dizziness in adults[1]. It is defined by the presence of vestibular symptoms in association with migraine symptoms (headache, phonophobia, photophobia, phosphenes), which occurs in up to 3.2% of the population[2]. It may last from minutes to days and has a major negative impact on public health and quality of life[3].

Although its pathophysiological mechanism is not fully known, it is believed that there is a combination of dysregulation of central mechanisms and peripheral labyrinthine alterations involved in the genesis of symptoms[4,5].

Treatment in vestibular migraine encompasses crisis prevention and acute symptom management. Several classes of drugs may be used as preventatives, among them betas blockers, anticonvulsants, antidepressants, and calcium channel antagonists[6].

Flunarizine, a calcium channel antagonist with antihistamine properties, acts by preventing labyrinthine vessel contraction and blood flow alteration, thus preventing symptoms. It is a good option for crisis prevention since it can initially be administered only once a day and is well tolerated by patients in general.

Its main side effects are drowsiness, parkinsonism, and suicidal ideation in predisposed patients and those taking it for a long time[7].

Due to the high prevalence of the disease, its negative impacts on individual health, and increased public health costs, pharmacological and non-pharmacological preventive treatment should be implemented early[8].

The purpose of this study was to assess the efficacy of Flunarizine as a preventive for vestibular migraine crises in comparison to other drugs commonly used in preventive therapy.

METHODS

Study protocol

This is a systematic review of scientific literature following the criteria recommended by the Cochrane Collaboration and described in the Cochrane Handbook for Systematic Reviews of Intervention.

Search strategy

A search was performed in the electronic databases: PUBMED (1984-2021) and CENTRAL - 2021 (Cochrane Library). The last search date was June 22, 2021.

The official vocabulary identified was extracted from DECS - Health Sciences Descriptor - http://decs.bvs.br/ and in MeSH - Medical Subject Headings - http://www.ncbi.nlm.nih.gov/ mesh and the corresponding terms for EMTREE. The following descriptors and terms were used: (vestibular migraine OR migrainous vertigo) AND (Flunarizine) AND (prophylaxis).

The methodology adopted for the development of the search strategy followed the Cochrane Handbook, as well as the standardization for high sensitivity strategies.

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

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

Study selection and inclusion criteria

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

The inclusion criteria were as follows: i) Randomized clinical trials; ii) Adult patients diagnosed with vestibular migraine (VM); iii) Use of flunarizine as a medication to prevent VM seizures and iv) Evaluation of efficacy and safety of flunarizine with other drugs (such as amitriptyline, valproic acid, venlafaxine, propranolol, desvenlafaxine) and/or placebo.

Articles not related to randomized clinical trials were excluded.

Outcomes of analysis

The primary outcome of analysis involved:

a. Efficacy of flunarizine, with the number and frequency of dizziness crises being assessed.

As secondary endpoints, the following were assessed:

b. Changes in quality of life.
c. Changes in anxiety and depression indices.
d. Adverse effects.

Data extraction

Data extraction was performed by two independent researchers. The following were characterized: date of publication, study design, sample size, number of participants per intervention, age of participants, gender, and diagnosis of vestibular migraine in the participants of the papers.

Quality assessment of articles

The studies were evaluated using the ROB TABLE to analyse the possible risks present in the included articles. The following areas were analysed:

- Selection bias by means of random sequence generation, selective description, and allocation secrecy.
- Performance bias through blinding of participants and researchers.
- Bias bias through incomplete outcome data.
- Other risks: applied methodology, sponsorship, and conflict of interest.

The domains were classified as high, moderate, or low. This classification was performed for each of the articles included in the study. This process was also performed by two independent authors.

Search strategy for the articles

To obtain the articles included in the analysis, the Pubmed and Cochrane databases were searched.

In the Pubmed database the search terms (vestibular migraine) OR (migrainous vertigo) AND (Flunarizine) AND (prophylaxis) were used. A total of 18 articles were located from 1984 to 2021, and 3 randomized clinical trials were selected for inclusion.

In the Cochrane database, the search terms (vestibular migraine) OR (migrainous vertigo) AND (Flunarizine) AND (prophylaxis) were used. A total of 40 articles were located from 1997-2020, and 3 randomized clinical trials were selected for inclusion.

Study Selection

The search strategy retrieved 55 articles in the searched electronic databases. After removing 15 duplicate articles, the titles, and abstracts of the remaining 40 articles were evaluated, and 3 articles were eligible for the study because they

were randomized clinical trials.

Characteristics of the studies

Three articles were included in this review, all randomized clinical trials with parallel groups, one of them with simple blinding and the rest with uncertain blinding.

The study by Lepcha et al[9] included 52 participants, and in the intervention group, 25 were medicated with Flunarizine 10mg/day in addition to symptomatic treatment with Betais- tin if dizziness attacks and paracetamol if headache attacks. In the control group, 23 patients received only symptomatic treat- ment for dizziness and/or headache crises. Four patients (7.7%) were lost during the study due to inability to contact patients.

For pre-intervention evaluation, a questionnaire was used to characterize the type, duration, and intensity of headache, as well as the presence of aura and vestibular symptoms.

For the post-intervention re-evaluation, the questionnaire was used again, as well as an additional questionnaire to characterize the degree of symptom improvement.

The study by Liu et al[10] included 75 participants divided into 3 groups, 23 used Venlafaxine 75mg, 22 used Flunarizine 10mg and 20 used Valproic Acid 2mg. There were 10 patients lost throughout the study, developed over a period of 3 months, distributed among the groups for similar causes.

For pre-intervention evaluation a complete otoneurolaryngological clinical evaluation was performed, in addition to specific complementary and imaging exams if necessary. For post-intervention re-evaluation the DHI (Dizziness Handicap Inventory) and VSS (Vertigo Severity Score) questionnaires were used, besides the number of vertigo crises presented by the patient in the previous month.

The study by Yuan et al[11] included 32 participants, and in the intervention group 12 patients received Flunarizine 10mg/day for 3 months, besides Betaistin 36mg/day for 48 hours and symptomatic if there were vertigo crises. In the control group 11 patients received only betaistine 36mg/day for 48h and symptomatic during vertigo crises. There were 4 patients (14%) lost during the study for unspecified reasons.

For pre-intervention evaluation the number of vertigo episodes in the last 3 months was defined, in addition to the VAS (Visual Analog Scale) to characterize the intensity of these episodes.

For the post-intervention re-evaluation, the total number of vertigo crises during the treatment as well as their intensity were evaluated again.

The primary outcomes assessed by the articles were the same: Flunarizine efficacy by analysing the number of vertigo attacks, changes in the Dizziness Handicap Inventory (DHI), in the Vertigo Severity Score (VSS) and in the Visual Analogue Scale (VAS). The DHI is a questionnaire that was developed in 1990 in order to assess self-perception of the disabling effects of dizziness. It is divided into three parts that assess the individual's physical, functional and emotional condition. The VSS is a scale of 36 questions that relate signs of dizziness severity and its relationship to anxiety.

The secondary outcomes analysed were the adverse effects of the medications used.

RESULTS

Intervention Effects

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

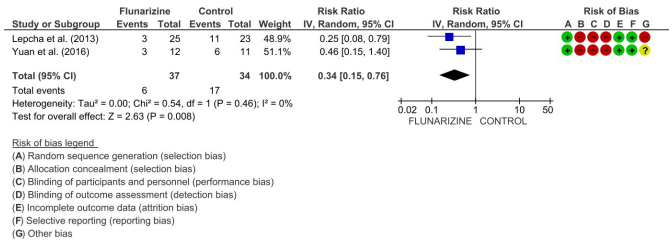
In the work by Lepcha et al[9] a decrease in frequency and intensity of vertigo crises was observed in patients receiving Flunarizine compared to the control group, with statistical significance ($p<0.05$). There were no statistically significant side effects of the medications used in either group.

Statistical analysis

The common outcome of the studies by Lepcha et al[9] and Yuan et al[10] was a reduction in the frequency of vertigo crises, which was assessed in the same parameters in both articles. Therefore, we carried out a meta-analysis including these two studies to assess the outcome of reduction in the frequency of vertigo crises.

During the meta-analysis it was verified that the sample was clinically heterogeneous, and therefore a random effect was used for evaluation, and a confidence interval of 95% was considered in the studies (Figure 1).

Figure 1. Meta-analysis related to the efficacy of Flunarizine as a preventive for vestibular migraine attacks.



In the study by Yuan et al[10], an increased confidence interval was found, with a Forrest Plot graph touching the nullity line, which did not occur in the study by Lepcha et al[9]; however, in the overall analysis, Flunarizine was found to have a favorable result compared to other drugs for decreasing the frequency of vestibular migraine seizures, with a confidence interval of 0.15 to 0.76 and a relative risk of 0.34. There is no statistical heterogeneity in the sample, since I^2 was zero.

DISCUSSION

This literature review had as its primary objective the evaluation of the efficacy of Flunarizine as a preventive drug for vestibular migraine; we assessed the number and frequency of dizziness crises in patients who used Flunarizine (intervention group) and patients who used other drugs for this purpose (control group).

In the literature, there are few intervention studies performed with this drug, and 3 randomized clinical trials were analysed and included.

The article by Lepcha et al[9] evaluated this outcome by means of a specific questionnaire that assessed type, duration and intensity of headache, besides vestibular symptoms, aura, and degree of improvement of symptoms after medication.

The study by Yuan et al[11] evaluated the outcome studied by means of the VAS (Visual Analogue Scale), in addition to the total number of vertigo attacks before and after drug treatment.

The study by Liu et al[10] used the DHI (Dizziness Handicap Inventory) and VSS (Vertigo Severity Score) questionnaires, in addition to the number of vertigo crises presented by the patient in the previous month.

The meta-analysis carried out with the articles by Lepcha et al[9] and Yuan et al[11] showed effectiveness of Flunarizine in relation to the control groups (use of other preventive med-

ications) for the objective studied, which can be seen in the chart. Moreover, in all the studies analysed, there were no reports of serious side effects from the use of the medication, which makes it safe to use.

The data were analysed using the GRADE method, which showed moderate evidence of Flunarizine for the studied objective.

There are few studies available in the scientific literature on the use of Flunarizine in vestibular migraine, many of which are heterogeneous among themselves, especially in the mode of assessment and follow-up of patient improvement, carried out mainly with subjective assessment methods. Moreover, there are flaws in the aspects of randomization and allocation of patients in the available studies, which makes it difficult to reliably assess the action of the drug as prevention for vestibular migraine. These limitations may be considered as confounding factors of the present study, which highlights the need for more good quality clinical trials for better study and elucidation on this topic.

CONCLUSION

Flunarizine is a good medication for preventing vestibular migraine, especially in reducing the number of seizures with a moderate degree of evidence; however, further studies in the scientific literature are needed for better understanding and accuracy on this topic.

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