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Original Article

Histamine Antagonists for Treatment of Peripheral Vertigo: A Meta-Analysis

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OBJECTIVE: Vertigo, the hallucination of movement of oneself or one's surroundings, can have substantial adverse effects on the quality of life of affected patients. It is essential to decrease the frequency, severity, and duration of vertigo attacks using effective medications with minimal debilitating adverse effects. We performed a meta-analysis of available clinical trials to evaluate the efficacy of histamine antagonists in the treatment of vertigo compared to the rate of resolution in untreated control groups.

MATERIALS and METHODS: A systematic search of articles in any language from January 1970 to March 2015 was performed through the following databases: the Cochrane Central Register of Controlled Trials, Medical Literature Analysis and Retrieval System Online, the Excerpta Medica Database, Cumulative Index to Nursing and Allied Health Literature, Latin American and Caribbean Health Sciences Literature, Allied and Complementary Medicine Database, Web of Science, ClinicalTrials.gov, and Google. Randomized controlled trials comparing each kind of antihistamine to untreated control participants in the treatment of vertigo (blinded/unblinded) were screened for inclusion. Three reviewers separately performed data extraction from the included trials using a standard data abstraction form. Three other researchers read the final list of all articles retained. Discrepancies were settled by mutual consensus between the authors. Random effects models were applied to estimate the pooled odds ratio (OR) and 95% confidence interval (CI) using the Review Manager software. The evaluation of publication bias was performed by Egger's test and Begg's funnel plot.

RESULTS: We identified 13 eligible citations. The pooled OR was 5.370, 95% CI (3.263–8.839), and I2=56.0%, with no obvious evidence of publication bias.

CONCLUSION: Our results provide clarification of the effectiveness of several categories of histamine antagonists compared with placebos in controlling peripheral vertigo.

KEYWORDS: Drug therapy, histamine antagonists, meta-analysis, randomized trial, vertigo

INTRODUCTION

Vertigo is generally described as the sensation of disorientation in space accompanied by or with the hallucination of motion related to oneself (subjective vertigo) or to one's surroundings (objective vertigo) [1-3]. There are a number of etiologies associated with vertigo. Accordingly, the main causes of this condition are correlated to origins in the peripheral or central nervous system [4]. More frequently, peripheral etiologies of vertigo, such as benign paroxysmal positional vertigo (BPPV), generally arise from disorders of the internal ear that involve the labyrinthine structures or the vestibular nerve [1, 3].

Impairments of equilibrium as well as positional vertigo and systematic instability can have adverse effects on the quality of life of affected patients and can actually be disabling. Patients with vertigo are at a risk of frequent falls, with subsequent injuries [5]. Nevertheless, it is essential to decrease the frequency, severity, and duration of vertigo attacks using effective medications with minimal debilitating adverse effects. Therefore, the primary approach to treating a patient with vertigo is symptomatic therapy to provide instant relief. Several pharmacologic agents with antivertiginous activity from different categories have been used for this purpose, including antihistamines, anticholinergics, calcium antagonists, benzodiazepines, neuroleptics, corticosteroids, and hemorheologics [6-8]. Antihistamines comprise an extensive class of pharmacologic agents that are believed to act as vestibular suppressants. Additionally, they appear to have a suppressive influence on the central emetic center to alleviate the nausea and vomiting related to motion sickness after acute attacks, even if taken after the onset of symptoms [9]. However, the exact pharmacologic mechanism of these drugs is undefined; most make important contributions to the alteration of the level of neurotransmitters involved in the transmission of impulses from primary to secondary vestibular neurons and to the preservation of tone in the vestibular nuclei [10]. Histamine, dopamine, acetylcholine, and serotonin are transmitters thought to affect the specific cerebral areas that induce vom-

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iting. Most antihistamines have antiemetic properties in addition to their effects on vertigo that are directed against the sites in the brain that control vomiting [5]. To date, attention has largely been focused on the non-pharmacologic treatment of vertigo, such as several positioning maneuvers; however, some experimental work has also been performed using antihistamine drugs.

Thus, we justify this meta-analysis because of the need to combine scientific evidence that demonstrates the efficacy of several common histamine antagonists proposed to treat vertigo. Meta-analysis is a systemic statistical procedure that integrates and contrasts a large amount of data from a series of certain studies on a specific subject. It is ideally an appropriate method to demonstrate the reliability of results as well as disagreements or relationships between findings [11]. The aim of the present review was to analyze the clinical value of antihistamines in the treatment of vertigo.

MATERIALS and METHODS

Search Strategy

A comprehensive literature search from January 1970 to the end of March 2015 was undertaken for clinical trials published in English and other languages from an analysis of the following electronic databases: the Excerpta Medica Database (EMBASE), Medical Literature Analysis and Retrieval System Online (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latin American and Caribbean Health Sciences Literature (LILACS), Allied and Complementary Medicine Database (AMED), Web of Science, ClinicalTrials.gov, and Google. A manual search was also conducted of the references from the retrieved articles for possible inclusion, and the authors of the trials were contacted where required. Furthermore, we searched the National Health Service (NHS) Evidence database, the Turning Research into Practice (TRIP) database, PubMed (Public/Publisher MEDLINE), and Google to retrieve accessible systematic reviews related to this study, with the intention of scanning their reference lists for further trials.

We identified relevant trials using the following expressions: "vertigo*," "dizz*," "benign paroxysmal positional vertigo," "BPPV," "peripheral vertigo," "idiopathic vestibulopathy," "acute vestibular attack," "histamine h 1 antagonist," "histamine h 3 antagonist," "histamine antagonist*,""antihistamine,""histamine analogue,""antivertigo drug," "meta-analysis," "clinical trial," "randomized controlled trial," and "randomized clinical trial." This review was approved by the Institutional Review Board and Ethics Committee of the Shahid Beheshti University of Medical Sciences.

Selection Criteria

Two researchers (S.A. and K.H.) scanned all the titles and abstracts and identified studies which appeared to mostly address the theme of the review and which met the inclusion criteria. We included randomized, controlled clinical prospective studies comparing a single antihistamine versus a placebo or untreated controls. The final trial outcomes were generally measured according to the frequency and severity of vertigo and the proportion of patients who described improvements with the intervention. We also excluded those trials in which the major cause of vertigo was related to head trauma, chronic otitis media, migraine headaches, multiple sclerosis, and tumors. Therefore, the meta-analysis was performed on 13 double-blinded, controlled randomized clinical trials versus placebos (Table 1). Any disagreements between reviewers were discussed and resolved by the third author, and consensus was obtained when necessary.

Data Collection and Analysis

Three reviewers (A.A., H.H., and H.D.) independently screened citations (title, abstract, and keywords) for eligibility and extracted data from the included trials using a standard data abstraction form. The abstracts were assessed for relevance, and the full text of potentially appropriate articles was retrieved. Three other authors (A.S., H.K., and M.T.) read the ultimate subset of retained articles. Discrepancies were settled by mutual consensus between the authors.

Statistical Analysis

The individual and pooled statistical analyses as odds ratios (OR) with 95% confidence intervals (CI) were described. The outcome measures of the main studies were dichotomous. Study heterogeneity was examined using the I^2 statistic and *P* values from the χ^2 test, in which numbers greater than 75% indicate considerable heterogeneity [12], and larger values represent rising heterogeneity [13]. In cases of insignificant heterogeneity, the OR of the pooled results was calculated by means of the Mantel–Haenszel fixed-effects model [14]. Otherwise, pooled-effect estimations were performed using a model with random effects according to the DerSimonian and Laird method, which tends to provide broader 95% CIs because the findings of the constituent studies vary among themselves [12].

Potential publication bias was assessed by Begg's funnel plot, in which the standard error (SE) of the logarithm (log) of every included study was plotted in contrast to its log (OR) [15]; asymmetry suggests a publication bias. The asymmetry of the funnel plot was assessed via the linear regression method of Egger's test [16]. All tests were two-sided, and $p<0.05$ was considered statistically significant.

The data analysis for this review was performed using Review Manager software (RevMan, version 5.0.18 for Macintosh, 2008; The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Literature Search Results

A total of 89 references were retrieved at the end of the searches performed in March 2015. We found no trials awaiting progress or assessment. According to Figure 1, 13 potential studies were considered eligible for inclusion in this review [17-29]. Among the included studies, which were all published from 1977 to 2006, seven articles were published in the English language, and the other studies were published in Polish, French, Dutch, Italian, and German (Table 1). No disagreement was found between the authors regarding the inclusion/exclusion of the trials.

All the studies addressed the treatment of peripheral vertigo in adults. These included studies focused on the efficacy of different interventions. They comprised a total of 888 participants. Overall, eight studies assessed the effects of betahistine on the improvement of vertiginous symptoms.

Table 1. Characteristics of the included studies

Study	Treatment	Sample size	Dose (daily)	Outcome measure	Duration of treatment
Kantor 2006 [17]	Betahistine	62	16 mg×3	symptoms videonystagmography	1 month
Mira 2003 [18]	Betahistine	63	16 mg×2	symptoms	3 months
Hausler 1989 [19]	Cinnarazine	40	75 mg×2	symptoms electronystagmograms	1 week
Oosterveld 1989 [20]	Betahistine	48	16 mg×3	symptoms	5 months
Legent 1988 [21]	Betahistine	81	16 mg×3	symptoms	12 weeks
Jackson 1987 [22]	Astemizole	76	5, 10, and 20 mg	symptoms electronystagmograms	13 weeks
Fischer 1985 [23]	Betahistine	73	16 mg×3	symptoms	16 weeks
Oosterveld 1984 [24]	Betahistine	164	12 mg×3	symptoms	6 weeks
Oosterveld 1982 [25]	Flunarizine	82	10 mg	symptoms	1 month
Canty 1981 [26]	Betahistine	59	16 mg×2	symptoms	20 weeks
Singarelli 1979 [27]	Betahistine	76	8 mg×4	symptoms	20 days
Schwerdtfeger 1978 [28]	Flunarizine	14	10 mg	symptoms electronystagmograms	1 month
Selim 1977 [29]	Flunarizine	50	10 mg	symptoms	3 months

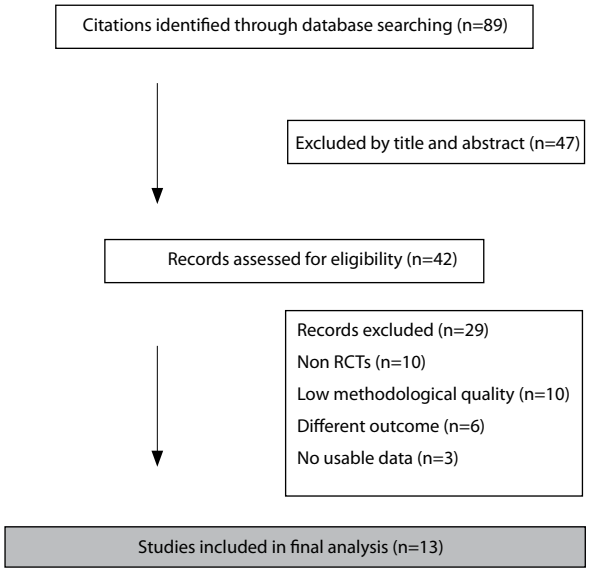

Figure 1. Flow chart of article screening in the meta-analysis. RCT: randomized controlled trial

A similar outcome measure, the resolution of symptoms, was collected in all trials. Three studies [19, 22, 28] considered electronystagmography results, and one [17] considered videonystagmography results as the measure of the effects of treatment. The clinical diagnosis of peripheral vertigo was achieved by initial clinical history and examination.

Effects of Interventions

In all trials, changes in vertigo were identified according to the frequency and/or severity of symptoms. Clinical symptoms were described as either "resolved" or "persistent" and "improved" or "not improved." Generally, 307 patients demonstrated an "improved" outcome in the group treated with several antihistamines, and 136 patients experienced this outcome in the control study. All studies except for three trials demonstrated statistically substantial improvement in the treated patients over the controls. Pooled analysis of the trial data yielded an OR of 5.370 (3.263–8.839) in favor of treatment. Figure 2 demonstrates the results of the pooled estimates for the 13 trials.

Among all the articles, eight studies reported the efficacy of treatment with betahistine compared with a placebo substance. The meta-analysis performed on these studies calculated an OR in favor of treatment with betahistine corresponding to 3.337 with a 95% CI between 2.346 and 4.747 (Figure 3).

Publication Bias

Publication bias among the eligible investigations was examined via the Begg's funnel plot and Egger's regression test. The bias was only present through Egger's test (P=0.02) prior to the removal of one trial [25]. After deletion of this study, heterogeneity decreased by 29.6% (I^2=40.36, P=0.07). We then reappraised the publication bias and found that no bias existed (P=0.073). The Begg's funnel plot has a relatively symmetric distribution as well (Figure 4).

DISCUSSION

The management of patients with vertigo is controversial to some extent because the pathophysiology of vertigo is often unclear. Many pharmacological agents have been found to have an antivertiginous activity. Medications possessing vestibular suppressive and antiemetic activities are known as the key methods for the management of vertigo. Traditional vestibular suppressants include three main classes: histamine antagonists, *anticholinergic* agents, and *benzodiazepine* analogs [30]. These medications reduce nystagmus caused by vestibular imbalance and also prevent mo-

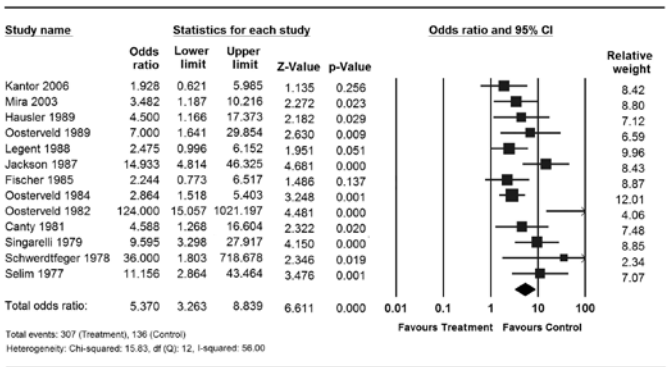

Figure 2. Comparison of antihistamines versus placebos/controls. CI: confidence interval

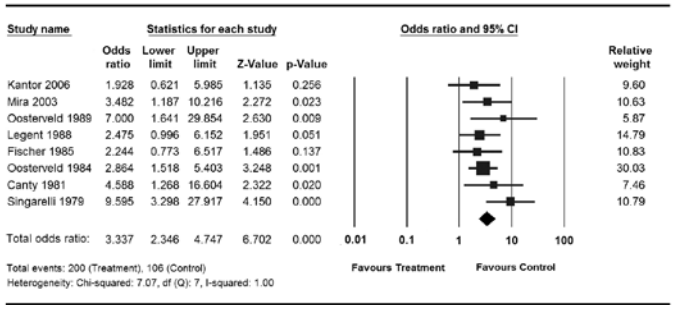

Figure 3. Comparison of betahistine versus placebos/controls. CI: confidence interval

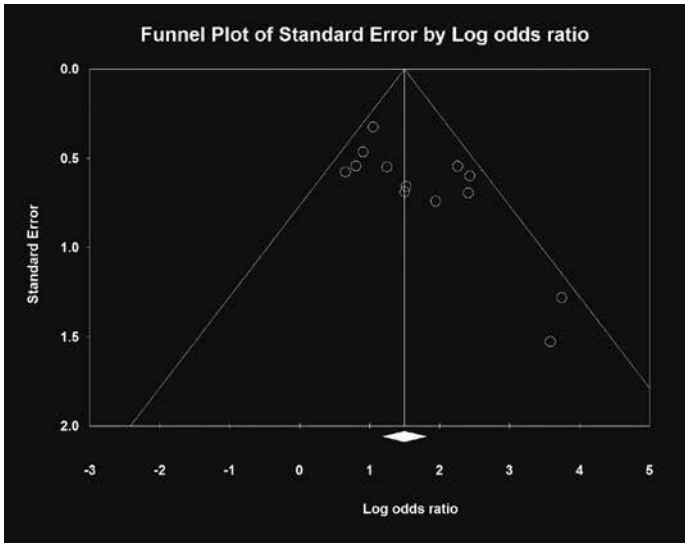

Figure 4. Begg's funnel plot for publication bias of the included studies

tion sickness and decrease the severity of its symptoms. Accordingly, pharmaceutical management of vestibular disorders is also useful in the treatment of associated symptoms such as nausea, vomiting, and anxiety [31, 32].

Antagonists of the *histamine* H1-receptor are widely practical therapeutic options available for the prevention and treatment of the central symptoms of vertigo. This pharmacological classification includes several medications such as cinnarizine, diphenhydramine, dimenhydrinate, meclizine, astemizole, and promethazine. These agents inhibit signaling pathway transduction through histaminergic neurotransmission from the vestibular nuclei to the medullary vomiting center [33]. Furthermore, based on this pharmacological profile, flunarizine, an H1-histamine antagonist, was recognized as an effective agent in treating the central or peripheral forms of vertigo. Apart from the extensive use of antihistaminergic drugs acting on central H1-histamine receptors, betahistine, which has a moderate H3 antagonistic action, has been recommended in some analyses. It has been proposed that betahistine affects histamine release by inhibiting the negative feedback loop. Thus, this mechanism facilitates brain histaminergic neurotransmission. In addition, betahistine increases internal ear blood circulation, and its vasodilatory action improves vestibular function [30].

Several strengths and limitations of this review require consideration. Firstly, we formulated a clinical question and performed inclusive searches of multiple online databases and referenced parts of relevant studies. No language restrictions were applied, and we used broad search terms to avoid making the question too specific to be sufficiently sensitive. Secondly, we included only randomized, controlled trials to reduce selection bias. The total I^2 estimate calculated in this meta-analysis is considered to be moderate. This may be due to the relative heterogeneity between some studies [13]. Furthermore, the total study size was small, and the data of the included trials seemed relatively different and inadequate for performing a comprehensive subgroup analysis.

In our meta-analysis, we demonstrated that there is a proof of concept for supporting the efficiency of several categories of histamine antagonists compared with placebos. However, there is no strong evidence that several histamine antagonists provide a long-term improvement of symptoms. Also, there is insufficient evidence regarding the comparison of these agents with other pharmaceutical therapies or surgical methods for peripheral vertigo.

Despite the influential nature of the pooled analyses, we must acknowledge some possible confounders. The pooling of results from heterogeneous populations (i.e., those with various etiologies of vertigo) is a potential confounder. Moreover, the scarcity of a definite method to confirm the improvement of vertiginous symptoms in several trials could interfere with the comparisons.

In summary, the pharmacological treatment of vertigo is complicated and rarely unsatisfactory. Accordingly, although we can use a variety of medical methods for symptomatic therapy, the side effects must be considered. Patient satisfaction, persistent recovery, adverse effects, and the interaction of these therapeutic modalities with other interventions must be taken into consideration.

Further trials are required to compare the effectiveness of a single medication with other groups to show the superiority of one over another. Principally, attention should be given to investigating the balance between the increased risk of adverse events and clinical benefits.

Ethics Committee Approval: This study was approved by the Institutional Review Board and Ethics Committee of the Shahid Beheshti University of Medical Sciences.

Peer-review: Externally peer-reviewed.

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