Efficacy of Cinnarizine/ Dimenhydrinate Compared to Betahistine in the Management of Adults with Peripheral Vestibular Disorder: A Meta-Analysis

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ABSTRACT

Title Efficacy of cinnarizine/dimenhydrinate compared to betahistine in the management of adults with peripheral vestibular disorder: a systematic review of randomized controlled trials (RCTs).

Objective To compare the effectiveness of cinnarizine/dimenhydrinate with betahistine in the management of adult patients with peripheral vestibular disorder.

Data Sources A systematic review of English articles by searching electronic databases at the University of Santo Tomas (Cochrane, Medline, CINAHL, PubMed, ScienceDirect, DOAJ, Biomed Central), Libraries in Metro Manila, and hard copies of journals and professional societies were identified. The search was done from May 2012 to July 2012 using the following search terms: Betahistine*; Cinnarizine*; and vertigo* or dizziness*.

Study Selection Only double-blind RCTs studying the administration of cinnarizine/dimenhydrinate or betahistine in patients with peripheral vestibular disorder were included. The quality of data was assessed using CASP: an RCT appraisal tool.

Data Extraction One review author extracted data from included studies using predefined data fields and the other author checked the extracted data.

Data Synthesis All pooled analysis was based on fixed effect models. Two RCTs (n=127) met our inclusion criteria. Heterogeneity was observed in both studies after one week of treatment, which was reduced when compared after four weeks of treatment. A fixed combination of cinnarizine 20 mg/dimenhydrinate 40 mg 3x a day significantly reduced the weighted mean difference (WMD) (p-value 0.00001, 95% confidence interval) of the mean vertigo score and the WMD (p-value 0.002, 95% confidence interval) of the concomitant symptom score after four weeks of treatment. No statistically significant difference was seen in the vestibulospinal and vestibulo-ocular tests.

Conclusions This systematic review of RCTs confirms that the fixed combination of cinnarizine/dimenhydrinate could decrease the intensity of vertigo and improve the concomitant symptoms better than betahistine after four weeks of treatment (Grade C Recommendation, NHMRC guidelines 2009).

Keywords: cinnarizine, dimenhydrinate, betahistine, vertigo, vestibular disorder.

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INTRODUCTION

Rationale

Vertigo is a frequent symptom self-reported in the general population with a 12-month prevalence of 22.9% and an incidence of 1.8% seeking medical consultation (1). Its prevalence rises with age and is about two to three times higher in women than in men (2,3). Vertigo results when there is asymmetric dysfunction of the vestibular system in the inner ear (4). Pathogenesis may involve the peripheral vestibular system comprising the semicircular canals, otoliths, hair cells, and vestibular nerve up to the root entry zone in the brainstem. The central vestibular system is composed of the vestibular nuclei, oculomotor nuclei, vestibulo-ocular reflex tracts, cerebellum, brainstem reticular formation, area postrema, and other components (5).

The ability to maintain balance is vital for the activities of daily living and vertigo imposes great limitations on the patients' ability to meet their daily responsibilities. Most patients with vertigo are prone to falls. Eventually, this incapacity may lead to immobilization. The clinical impact of vertigo and its consequences sustains the need to develop an effective therapy to resolve the symptoms (6).

Betahistine has been widely accepted as the standard treatment for peripheral vestibular disorders by increasing capillary blood flow of the labyrinthine vascular system (6). Cinnarizine, a calcium channel antagonist has a fixed combination with dimenhydrinate, an H1 receptor antagonist. Their mechanism of action is beneficial because of a dual mode; cinnarizine, regulating calcium influx into the vestibular cells in the long term improves cerebral circulation, and dimenhydrinate, which exerts regulatory effects on the vestibular nuclei (6,7). Several studies have implicated both as beneficial in the management of vertigo (6-8). However, a further analysis was required to assess which drug was more effective in the management of patients with peripheral vestibular disorder. It was the aim of this study to compare the effectiveness of cinnarizine/dimenhydrinate with betahistine in the management of adult patients with peripheral vestibular disorder.

METHODOLOGY

Eligibility for the study requires a population of adults aged 18 years old and above with peripheral vestibular disorder who were given cinnarizine 20 mg/dimenhydrinate 40 mg per tab or betahistine 12 mg per tab to control their symptoms. Randomized controlled trials (RCTs) comparing the efficacy of administering cinnarizine/dimenhydrinate versus betahistine on patients with peripheral vestibular disorder and their effect on decreasing the intensity of vertigo were included. The side effects of the medications were also monitored. The primary outcome measure was decrease in mean vertigo score (Visual Analog Scale 0-4) comparable to decreasing intensity of vertigo whereas secondary outcome measures were mean concomitant symptom score (Visual Analog Scale 0-4), angular and lateral deviation values (Unterberger stepping test), and frequency of caloric-induced nystagmus. Publications were limited to English language only. No publication date nor publication status were imposed.

Studies were identified by searching electronic databases at the University of Santo Tomas (Cochrane, Medline, CINAHL, PubMed, ScienceDirect, DOAJ, Biomed Central), libraries in Metro Manila, hard copies of journals, and professional societies. This search was applied to Medline, Cochrane, CINAHL, PubMed, ScienceDirect, DOAJ, and Biomed Central. The search was done from May 2012 to July 2012. The following search terms were used to search all trial registers and databases: betahistine*; cinnarizine*; and vertigo* or dizziness*.

Eligibility assessment was performed independently in an unblinded standardized manner using CASP: a randomized controlled trial appraisal tool by two (2) reviewers. In case of disagreement, a third reviewer would be asked. Eligibility criteria for the study inclusion were adult participants 18 years and older who were diagnosed with peripheral vestibular disorder. Intervention given was cinnarizine 20 mg/dimenhydrinate 40 mg per tab and compared with betahistine 12 mg per tab. Outcome measures should be decreased intensity of vertigo and concomitant symptom scores. A data extraction sheet was developed, pilot tested on five randomly selected included studies, and refined accordingly. One review author extracted the following data from included studies and the other author checked the extracted data. Disagreements were resolved by discussion between the two authors; if no agreement could be reached, it was planned that a third author would decide. Information was extracted from each included trial on: (1) characteristics of trial partici-

pants (including age, body mass index, method of diagnosis) and trials, inclusion, and exclusion criteria, (2) type of intervention (including dose, duration, and frequency), (3) type of outcome measure (mean vertigo score for vertigo and concomitant symptoms). To ascertain the validity of eligible randomized trials, pairs of reviewers working independently and with adequate reliability determined the adequacy of randomization and concealment of allocation, blinding of patients, healthcare providers, data collectors, and outcome assessors; and extent of loss to follow up.

Improvement of symptoms by a reduction in intensity of vertigo was the primary measure of treatment effect. The meta-analyses were performed by computing the weighted mean difference (WMD) in a fixed effect model using the Generic Inverse Variance Method in RevMan 5. Quantitative analyses were performed on an intent-to-treat basis and were confined to data derived from the period of follow-up. The primary outcome measure was the relief of vertigo by a decrease in mean vertigo score via Visual Analog Scale (0-4). These include unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, and blackout. Secondary outcome measures include mean concomitant symptom score on Visual Analog Scale (0-4), which includes nausea, vomiting, sweating, tachycardia, tinnitus, and impaired hearing. Angular and lateral deviation values (Unterberger stepping test) and frequency of caloric-induced nystagmus were also measured. The questionnaire was developed by the authors and verified by the health authorities. Statistical pooling using Review Manager 5 Java 6 edition will be done. If not possible, the narrative synthesis will be done and grades of recommendation identified using the NHMRC grades of recommendation. For each trial, we plotted the effect by the inverse of its standard error. The symmetry of such "funnel plots" was assessed visually. We assessed the possibility of publication bias by evaluating a funnel plot of the trial mean differences for asymmetry, which can result from the nonpublication of small trials with negative results. We acknowledge that other factors such as differences in trial quality or true study heterogeneity could produce asymmetry in funnel plots.

Results of Literature Search

The initial search strategy yielded 96 related articles (Figure 1). After duplicates were removed,

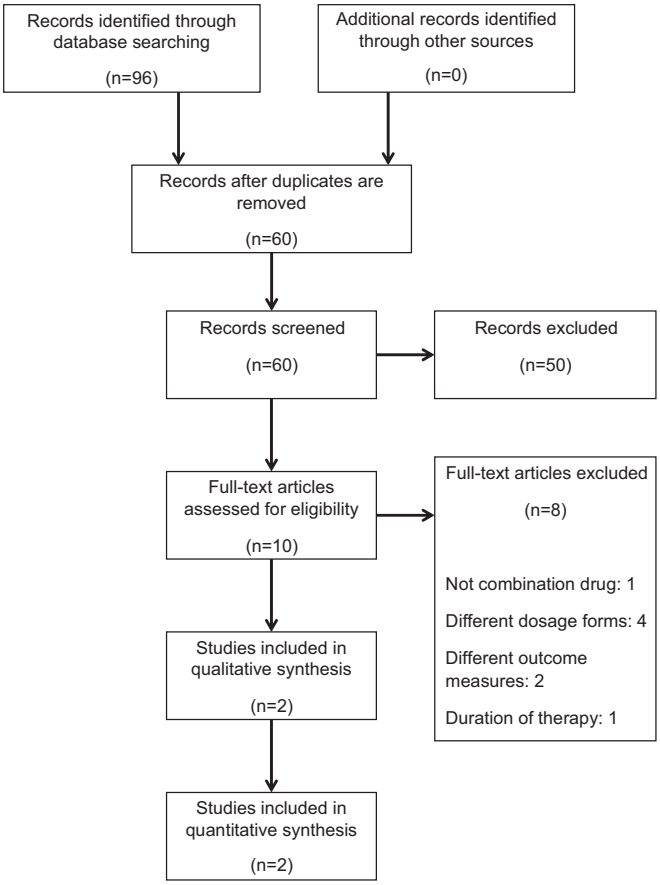

Figure 1. Flow Diagram.

60 articles were screened on the basis of title and abstract. A total of 10 full-text articles were further examined. Eight (8) of these studies were excluded for the following reasons: did not use combination drug (1), used different dosage form (4), different duration of treatment (1), and different outcome measures (2). Based on demographic data (Table 1), patients were similar in both groups belonging to adults with an age range of 30-84 years old with a body mass index of 23 to 29. Both studies compared the efficacy and tolerability of cinnarizine/dimenhydrinate against betahistine in patients with peripheral vestibular disorder.

Critical Appraisal of Articles Included

All articles included in the review met most of the criteria of the Critical Appraisal Skills Programme (CASP) by the International Center for Allied Health Evidence of the University of South Australia. The authors used the recommendations of the National Health and Medical Research Council of Australia (December 2009) to determine the level of evidence and grade of recommendation.

Table 1. Mean Age and Body Mass Index of Study Population.

Parameter	Trials (n=127)	cinnarizine/dimenhydrinate (n=63)	betahistine (n=64)
Mean Age	Hahn et al, 2008	54.3 ± 12.1	53.1 ± 11.0
	Cirek et al, 2005	49.60 ± 12.31	48.58 ± 11.76
Mean Body Mass Index	Hahn et al, 2008	26.1 ± 3.3	26.0 ± 3.7
	Cirek et al, 2005	26.99 ± 4.16	26.06 ± 3.34

Study Characteristics

The studies selected for review were RCTs published in English. The duration of the intervention was four weeks for both studies of Hahn and Cirek. The included studies involved 127 participants with the trial by Hahn being multicentric, while Cirek et al. involved only one center. The main inclusion criteria entail adults (>30 y/o) with at least one vertigo symptom of medium intensity in a 5-point visual analog scale confirmed by craniocorpography and electronystagmography with calorics. Patients with confirmed Meniere's disease, BPPV, areflexia, psychogenic vertigo, with known contraindications to medications, and pregnant and breastfeeding women were excluded from the studies. The intervention received was a fixed combination of cinnarizine 20 mg/dimenhydrinate 40 mg per tab and the comparator was betahistine 12 mg per tab. Both medications were given three times a day. The primary outcome measure was a decrease in mean vertigo score and secondary outcome measures include a decrease in concomitant symptom score, angular and lateral deviation values (Unterberger stepping test), and frequency of caloric-induced nystagmus.

Assessment of risk of bias within studies

Both studies exhibited blinding of patients, healthcare providers, and data collectors. Randomization was not concealed. We are uncertain whether outcome assessors were blinded. All patients included in the study were accounted for because they used the intent-to-treat principle. Both studies were funded by the pharmaceutical company which may be a source of bias.

Results of Individual Studies

The outcome measures were categorized as favors C or favors B when there was evidence of positive discrimination to either cinnarizine/dimenhydrinate or betahistine, respectively.

Primary Outcome

The mean vertigo score had improved to a significant degree with the intervention after 1 week of treatment in the trial by Cirek as evidenced by a p-value of 0.002 (Table 2). The trial by Hahn produced no significant difference between the two treatments as evidenced by a p-value of 0.85. The evidence was not sufficiently robust to determine comparative effectiveness between the two treatments after 1 week. The mean vertigo score had improved to a significant degree with the intervention after four weeks of treatment in both studies. This was evidenced by the p-value of 0.001 and 0.013 for the studies of Cirek and Hahn, respectively (Table 2). Based on the NHMRC guidelines, this systematic review presents level II evidence that the fixed combination of cinnarizine and dimenhydrinate significantly causes improvement in mean vertigo score when compared with betahistine. Figure 2 shows the forest plot for the decrease in mean vertigo score comparing cinnarizine/dimenhydrinate

Table 2. Decrease in Mean Vertigo Score.

Trials	cinnarizine/dimenhydrinate		betahistine		p-value		Interpretation	Level of evidence
	1 week treatment	4 weeks treatment	1 week treatment	4 weeks treatment	1 week treatment	4 weeks treatment		
Cirek 2005	0.65 ± 0.42	1.07 ± 0.58	0.31 ± 0.38	0.51 ± 0.56	0.002	0.001	Favors C	Level II
Hahn 2008	1.30 ± 0.65	0.97 ± 0.62	1.27 ± 0.54	0.64 ± 0.38	0.83	0.013	Equivocal after 1 week; favors C after 4 weeks	

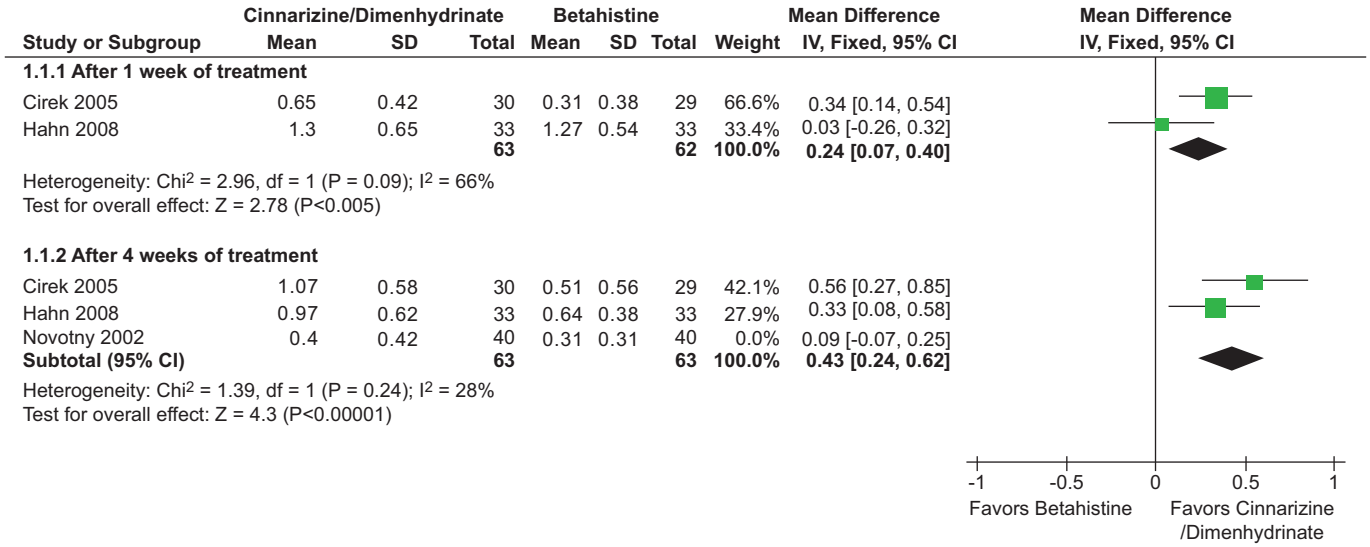

Figure 2. Forest Plot Comparing Cinnarizine/Dimenhydrinate Versus Betahistine in Decreasing Mean Vertigo Score.

with betahistine as well as a summary of the mean and standard deviations of the mean vertigo score from the two studies taken after a week and after four weeks of treatment. The effect measure was the weighted mean difference for a continuous outcome using standard deviation as a measure of variation. The results were analyzed using the generic inverse variance method in Revman. There was moderate heterogeneity between the population in the subgroup after one week of treatment whereas there was little heterogeneity between the population in the subgroup after four weeks of treatment. In Figure 2, the 95% confidence intervals of both studies do not overlap 0, except for the study of Hahn after the first week of treatment. The 95% confidence interval of the overall estimate, both after one week and after four weeks of treatment does not overlap 0. Therefore, there was statistical significance at the study level except for the study by Hahn after one week of treatment. There was also statistical significance at the meta-analysis level. The intervention group was better than the control group as the overall effect estimate and its 95% confidence interval are to the right of the line of no effect. The results favor the intervention. Therefore, the pooled analysis showed that the combination of cinnarizine/dimenhydrinate was better than betahistine in decreasing the symptoms of vertigo in patients with peripheral vestibular disorder.

Secondary Outcome

The mean concomitant symptom score had decreased to a significant degree with the intervention after 1 week of treatment in the trial by Hahn. This was evidenced by the p-value of 0.004. However, the trial of Cirek did not produce statistically significant results when compared with betahistine (Table 3). The evidence was not sufficiently robust to determine comparative effectiveness between the two treatments after one week. The mean concomitant symptom score had decreased to a significant degree with the intervention after four weeks of treatment in both trials. This was evidenced by the p-value of 0.009 and 0.023 by Cirek and Hahn, respectively (Table 3). This systematic review presents level II evidence that the fixed combination of cinnarizine/dimenhydrinate significantly causes a reduction in the

Table 3. Decrease in Concomitant Symptom Score.

Trials	cinnarizine/dimenhydrinate		betahistine		p-value		Interpretation	Level of evidence
	1 week treatment	4 weeks treatment	1 week treatment	4 weeks treatment	1 week treatment	4 weeks treatment		
Cirek 2005	-1.50 ± 0.48	0.72 ± 0.49	-0.32 ± 0.39	-0.44 ± 0.50	0.111	0.009	Equivocal after 1 week and favors C after 4 weeks treatment	Level II
Hahn 2008	-1.02 ± 0.80	-1.15 ± 0.83	-0.56 ± 0.60	-0.73 ± 0.63	0.004	0.023	Favors C	

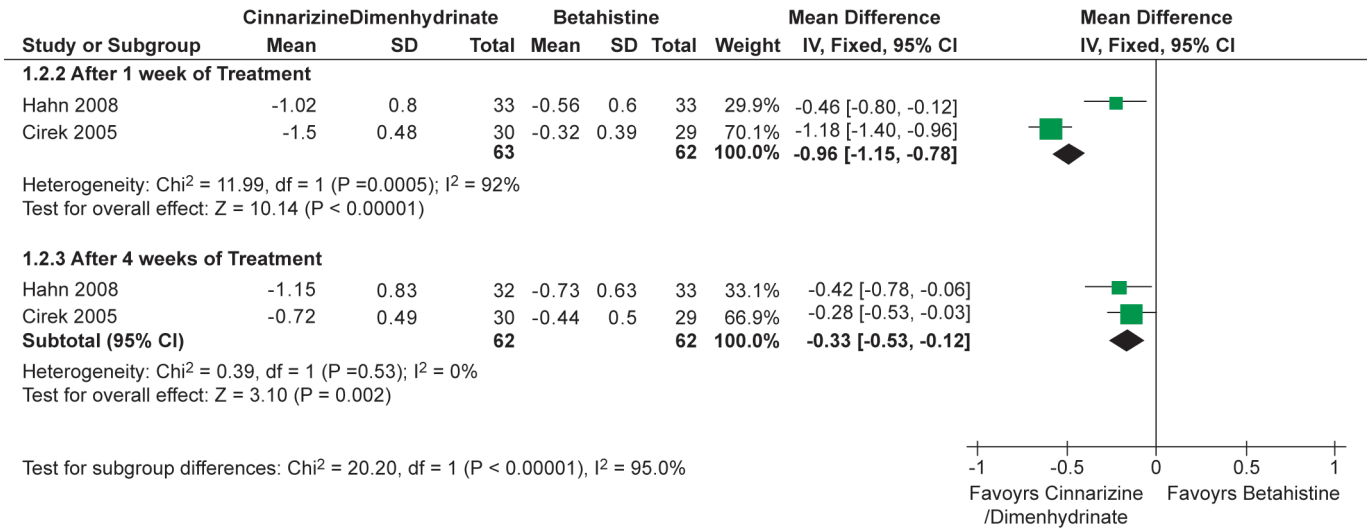

Figure 3. Forest Plot Comparing Cinnarizine/Dimenhydrinate Versus Betahistine in Decreasing Concomitant Symptom Score.

mean concomitant symptom score when compared with betahistine based on NHMRC guidelines. Figure 3 shows the forest plot for the mean concomitant symptom score comparing cinnarizine/dimenhydrinate with betahistine as well as a summary of the data for the mean and standard deviation from the two studies taken after a week and after four weeks of treatment. The results were analyzed using the Generic Inverse Variance Method in Revman. There was a large heterogeneity between the studies reflected after one week of treatment and no heterogeneity between the two studies after four weeks of treatment. The heterogeneity may be due to the difference in population, treatment, or by chance. In this figure, the 95% confidence interval of both studies does not overlap 0. The 95% confidence interval of the overall effect estimate also does not overlap 0 in both subgroups. Therefore, there was statistical significance at both the study level and meta-analysis level. The intervention group was better than the control group as the overall effect estimate and its 95% confidence interval are to the left of the line of no effect. The results favor cinnarizine/dimenhydrinate. Therefore, the pooled analysis showed that the combination of cinnarizine/dimenhydrinate was better than betahistine in decreasing the concomitant symptoms of vertigo in patients with peripheral vestibular disorder.

The results of both studies were confirmed with vestibulospinal tests and vestibulo-ocular tests. In both studies, the mean values of angular deviation, lateral sway, and longitudinal deviation decreased during the course of the study, with no significant differences between the two treatments. Moreover, both therapies caused a decrease in frequency of induced nystagmus in the caloric test, but no statistically significant differences could be detected between the treatment groups. However, data was not shown.

Risk of Bias Across Studies

For the outcome on decrease in mean vertigo score, evidence of heterogeneity (I^2 = 66%) after one week and (I^2 = 28%) after four weeks of treatment were seen. A funnel plot showing symmetry indicates a low risk of publication bias. Similarly, evidence of heterogeneity was seen in the outcome for decrease in mean concomitant symptom score after one week (I^2 = 92). No evidence of heterogeneity was seen (I^2 = 0) after four weeks of treatment. The heterogeneity in the subgroup may be influenced by the population involved, how the data were gathered or if there were too few included studies to determine the risk of bias. Also, both studies have a high risk of reporting bias as only data with statistically significant differences were presented. No data were shown for the objective tests which are confirmatory outcome measures in the study.

DISCUSSION

Overall, there was evidence that shows improvement in the mean vertigo score and a decrease in mean concomitant symptom score in the treatment using cinnarizine/dimenhydrinate, which was better than with betahistine after four weeks of treatment. These were shown in both trials with results in favor of cinnarizine/dimenhydrinate in decreasing the mean vertigo score and mean concomitant symptom score after four weeks of treatment. However, there were

equivocal results in the vestibulospinal tests and vestibulo-ocular tests. These objective tests showed improvement of symptoms using both medications. The remarkable difference that the study showed was better symptom relief of patients given cinnarizine/dimenhydrinate in terms of the Visual Analog Scale. However, the evidence was not sufficiently robust to determine the comparative effectiveness of cinnarizine/dimenhydrinate and betahistine after one week of treatment. Only two RCTs with 1-month duration of treatment compared the two medications. It was possible that the trials did not evaluate enough patients to allow definitive conclusions. Moreover, the studies did not explain the inconsistencies regarding the results. There were significant differences in the decrease in mean vertigo score and mean concomitant symptom score but no significant differences between the two treatment groups in the vestibulospinal and vestibulo-ocular tests.

The systematic review showed level II evidence with a moderate risk of bias, with some inconsistency reflecting genuine uncertainty around the clinical question and substantial clinical impact. Populations studied in the evidence are similar to the target population in the guideline and applicable to our healthcare context. The authors give this level of evidence a Grade C recommendation. The body of evidence provides some support for the recommendation but care should be taken in its application. Therefore, the systematic review shows that the fixed combination of cinnarizine/dimenhydrinate could be used to decrease vertigo and cause improvement of symptoms in patients with peripheral vestibular disorder.

LIMITATIONS

The meta-analysis reported here combines data across studies in order to estimate treatment effects with more precision than in a single study. Nonetheless, the study possesses inherent weaknesses. The main limitation of this study was the number of studies available for review. The inability to retrieve unpublished studies was also a drawback of this study. We were not able to retrieve some published articles because of the absence of such a searching mechanism. Publication bias might account for some of the effects we observed. Heterogeneity, as shown in the asymmetrical funnel plot, suggests that selective reporting may have led to an overestimation of an effect. In addition, incomplete reporting of the results, particularly the objective tests may hamper the interpretation and synthesis of the included studies.

CONCLUSIONS

In summary, this systematic review of RCTs until July 2012 suggests that the fixed combination of cinnarizine/dimenhydrinate could decrease the intensity of vertigo and improve concomitant symptoms better than betahistine after four weeks of treatment. However, little data was evident to draw a conclusion with the objective tests. A logical next step for future trials would be a comparison of this protocol against a fixed combination of cinnarizine/dimenhydrinate with different dosages, longer duration of treatment, and bigger population. Several studies have already been identified during the search for literature. To date, we are unaware of additional studies that compare betahistine with cinnarizine/dimenhydrinate on vertigo outcome.

Disclosures

The authors have nothing to disclose.

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