Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 44–50

OPEN ACCESS

Original Article

Comparative Effectiveness of Betahistine vs Dimenhydrinate in Reducing Dizziness Handicap Scores in Patients with Peripheral Vestibular Disorders

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1213

Accepted: October 07th, 2024
Approved: March 18th, 2025

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Abstract

Background : Peripheral vestibular disorder is a disorder of the peripheral vestibular system. Its symptoms affect the quality of life from moderate to severe. An objective assessment is quite difficult therefore a questionnaire method has been developed such as Dizziness Handicap Inventory (DHI). Aim of the treatment is to achieved optimal quality of life by using symptomatic treatment like dimenhydrinate and betahistine. This study was aimed to prove the effectiveness of betahistine and dimenhydrinate and to compare the effectiveness in reducing DHI score

Methods : This was an intervention study with pretest and posttest control group designs, randomized control trial, double blind study at ENT-HNS Clinic, CDC Dr. Kariadi Hospital and Dr.Soetrasno Hospital Rembang. Data was collected from September 2015 to June 2016. Subject filled out the DHI pre-test questionnaire, stratified randomly divided into 2 group. One group received betahistine 12 mg / 8 hours and the other received dimenhydrinate 50 mg / 8 hours in a double-blind selection process. After 2 weeks of drug administration, subject filled out a post test questionnaire of DHI.

Results : Subjects were 44 people; dimenhydrinate, 20 people (45.5%) and betahistine, 24 people (54.4%). Result showed that DHI score of post test is lower than pre test in both group with significance value of $p < 0.05$. There is no significant difference in DHI score of dimenhydrinate compared with betahistine group ($p = 0.137$).

Conclusion : Betahistine and dimenhydrinate are shown to be effective in lowering the DHI score.and betahistine not proven to be more effective.

Keywords : Peripheral vestibular disorders, Dimenhydrinate, Betahistine, Dizziness Handicap Inventory

INTRODUCTION

Peripheral Vestibular Disorders (PVD) are disorders of the peripheral vestibular system caused by changes in the sensitivity of vestibular receptors to linear and angular acceleration, asymmetric abnormalities in central vestibular activity or changes in reaching *Lobby Eye System*.[1] PVD appears more suddenly after a change in position or movement of the head, with a feeling of intense spinning or what is often called vertigo, accompanied by nausea, vomiting, sweating, can be accompanied by ringing in the ears, lack of hearing and is not accompanied by focal neurological symptoms.[2,3]

The prevalence of PVD is 5% in the adult population in one year.[4] The incidence increases every year, occurs more often in women (2.7: 1) and the incidence increases with increasing age.[5] Data from outpatient visits at Dr. Kariadi General Hospital, Semarang in 2013, recorded 255 sufferers with complaints of vertigo, 134 sufferers underwent vestibulometry examinations at *Clinic Diagnostic Centre* – Ear Nose Throat (CDC – ENT) and 63 sufferers with a diagnosis Benigna Paroxysmal Positional Vertigo (BPPV).

PVD symptoms affect the sufferer's quality of life from moderate to severe (80%). These disorders include the physical, functional and emotional nature of the sufferer.[6] Objective assessment of the severity of PVD symptoms is quite difficult, so a questionnaire method was developed to assess the quality of these complaints. One method of assessment is *Dizziness Handycap Inventory* (DHI).[7]

The DHI is a questionnaire that is useful for assessing physical abilities related to complaints of dizziness and disturbances in emotional and functional aspects. DHI has been adapted into several languages, including Swedish, Dutch, Japanese and Chinese.[8,9]

DHI contains 25 types of assessment questions with a score of 0–100, which includes 7 physical assessments, 9 functional assessments and 9 emotional assessments. DHI has been validated in several studies and proven to be related to the severity of vertigo symptoms and can measure changes or improvements in symptoms.[9]

PVD therapy seeks to achieve optimal quality of life according to the course of the disease, namely by reducing or eliminating the sensation of vertigo with minimal side effects. Therapeutic options include causative, symptomatic, rehabilitative therapy, avoiding trigger factors and lifestyle changes.[3] Symptomatic therapy is usually with vestibular suppressant drugs *(vestibulo – suppress)* given in the acute phase with the aim of alleviating vegetative symptoms without disrupting the compensation process.[10]

The class of vestibular suppressant drugs that is widely known and included in the 2013 National Formulary is class anticholinergics, antihistamines and benzodiazepines. One type of drug is dimenhydrinate, which is a first generation antihistamine with a usual dose of 50 mg per administration with a half-life of 4–6 hours, because of its strong sedation effect given 3 times a day.[10,11] Dimenhydrinate quickly causes sedation and sleep modulating effects, that needs to be taking care during their administration.[12] The highest retail price of dimenhydrinate is IDR. 30/tablets.[13] The Association of Indonesian Neurologists recommends betahistine as a choice of vestibular suppressant medication because the way it works is different and can speed up compensation.[3] Betahistine is a histamine with a usual dose of 6–24 mg per administration, half-life of 3–4 hours, given 2–3 times per day.[11] The highest retail price for betahistine is IDR. 1250/tablet.[13]

Two similar research reported that the combination of cinnarizine and dimenhydrinate reduce vertigo symptoms more quickly than betahistine.[14,15] Another research reported something different, namely that there was no significant difference between administering a combination of cinnarizine and dimenhydrinate compared to betahistine to reduce the symptoms of vertigo in Meniere's syndrome.[16] The effectiveness of betahistine compared to dimenhydrinate using the DHI score has not been studied previously.

The aim of the research is to prove the effectiveness of betahistine and dimenhydrinate and to prove that betahistine is more effective than dimenhydrinate in reducing the DHI score in patients with peripheral vestibular disorders.

METHODS

Intervention research by design *pretest and posttest control group design*. Determination of groups by double-blind random method. The output was DHI score. The research was conducted at the ENT-HNS Clinic, CDC RSUP Dr. Kariadi, ENT Clinic at Dr. Soetrasno Rembang Regional General Hospital (RSUD) for the period, at September 2015 to June 2016. Research subjects were PVD sufferers, aged between 18–60 years, cooperative and willing to take part in the research. Exclusion criteria were PVD sufferers who were receiving vestibular suppressant drug therapy, had allergic reactions to the drugs dimenhydrinate and betahistine, were taking anticholinergic drugs, antidepressants, first generation antihistamines, had contraindications to administering betahistine and dimenhydrinate, and were suffering from DM and hypertension. PVD sufferers who met the inclusion criteria were asked to sign a consent form and then their age, gender, history taking, routine physical examination, standard ear examination and vestibulometry were recorded. Every PVD sufferer is given causative therapy, rehabilitative therapy and avoidance of trigger factors and lifestyle changes. Patients filled out the DHI questionnaire before

administering the drug (pre test). Patients who were included as research subjects were then randomized by means stratified randomization and each patient was given one type of medication (dimenhydrinate 50 mg or betahistine 12 mg), taken 3 times a day for 1 week (21 items). The packaging for the medicine given was the same. Medicines are given directly by medicine officers. At the end of the second week the patient would be interviewed again to fill out the DHI questionnaire after administering the drug (post test).

Descriptive analysis was carried out for patient demographic data. Test the normality of the data using the test Saphiro-Wilk. Comparative test analysis uses paired t-test (parametric test) or Wilcoxon test (non-parametric test) and unpaired t-test (parametric test) or Mann Whitney (non-parametric test). Statistical calculations employed the SPSS computer program. The research protocol has been approved by the Medical Research Ethics Committee of FK Undip/RSUP Dr. Kariadi Semarang.

RESULTS

This research was conducted from September 2015 to June 2016 at the ENT-HNS clinic, CDC RSUP Dr. Kariadi Semarang and the ENT Clinic of Dr. Soetrasno Rembang Regional Hospital with a total of 44 research subjects. There was no research subjects drop out and all data was complete. The characteristics of the research subjects, namely the distribution of gender, age, type of PVD, as well as the percentage between the dimenhydrinate group and the betahistine group before treatment can be seen in Table 1.

The distribution of research subjects based on treatment groups was quite evenly distributed. Table 1 shows that 20 subjects received dimenhydrinate (45.5%) and 24 subjects received betahistine (54.4%). The mean pre-test DHI score in the dimenhydrinate group was 44.9 ± 15.6 and in the betahistine group 41.2 ± 4.9. There was no significant difference between the pre-test DHI scores between the two treatment groups (p<0,05). Post-test DHI scores in both groups decreased. The average DHI score for the pre-test dimenhydrinate group was 44.9 while the post-test was 6.3.

For the betahistine group, the average pre-test DHI score was 41.2 and post-test 8.3. (p<0,05). Post-test DHI scores in both groups decreased. The average DHI score for the pre-test dimenhydrinate group was 44.9 while the post-test was 6.3. For the betahistine group, the average pre-test DHI score was 41.2 and post-test 8.3. The DHI score in each group includes the total DHI score and the three sub-scores shown in Table 2.

The betahistine group shows a lower post-test DHI score than the pre-test, with a mean difference of 32.9 ± 14.3 and p value < 0.05. The sub-score E, sub-score F and sub-score P post-test are also lower than the pre-test with a mean difference of 9.7 and 12.6 and 9.3 respectively. The significance values for the three sub-scores are p<0.05. The results of this analysis are shown in Table 3.

The post-test DHI score in the dimenhydrinate group was lower than the pre-test, with a mean difference of 38.6 ± 14.8 and a significance value p<0.05. The value of each sub-score, namely the emotional sub-score, functional sub-score and physical sub-score, is lower in the post-test compared to the pre-test with the mean difference respectively being 10.4 and 14.1 and 14.0 with the significance value being p<0.05. The results of this analysis are shown in Table 4.

The post-test total DHI score of the dimenhydrinate group compared with the betahistine group provides value p = 0.137 with a mean difference of -2.0 ± 1.3. The emotional sub-score, function sub-score and post-test physical sub-score of the dimenhydrinate group compared to the betahistine group provide value p of 0.160 and 0.197 and 0.601 respectively. The results of this analysis are shown in Table 5.

The side effect most complained about was drowsiness from 10 people (7 people; dimenhydrinate group, 3 people; betahistine group) while 34 people did not have any complaints. There was no significant difference in side effects that appeared in the two treatment groups (p<0,05). The results of the analysis regarding side effects in the two treatment groups are shown in Table 6.

DISCUSSION

The distribution of research subjects based on treatment groups was fairly evenly distributed, with 20 subjects receiving dimenhydrinate (45.5%) and 24 people receiving betahistine (54.4%). The characteristics of research subjects such as gender, age, type of PVD, duration of complaints, symptoms and DHI scores in the two groups before treatment were not significantly different, which means that the characters before treatment were balanced so that the two groups were considered homogeneous, which means the two groups could be compared.

The gender frequency in this study was 25% male and 75% female. This gender proportion is almost the same as one research that aim to compare the efficacy of flunarizine and betahistine dyhidrochloride using DHI. That research found a male gender proportion of 48% and female 52%.[17] Another research also found a gender proportion of 41.6% males and 58.4% females,[18] and also provides a male to female gender ratio of 1:1.96 and is dominant in all age groups.[19] Most epidemiological research data on vertigo shows that the prevalence of vertigo is greater in women.

Many epidemiological studies show that the prevalence of vertigo is closely related to age. This study found that the largest number of research subjects was in

TABLE 1
Characteristics of research subjects

Variable	Dimenhydrinate n = 20 (45.5%)	Betahistine n=24 (54.4%)	Total	Mark *p**
Gender				
Man	6 (13.6%)	5 (11.4%)	11 (25%)	0.484**
Woman	14 (31.8%)	19 (43.2%)	33 (75%)	
Age				
21 – 30 years old	2 (10.0%)	4 (16.7%)	6 (13.6%)	0.903***
31 – 40 years old	7 (35%)	4 (16.7%)	11 (25%)	
41 – 50 years old	5 (25%)	9 (37.5%)	14 (31.8%)	
51 – 60 years old	6 (30%)	7 (29.2%)	13 (29.6%)	
Types of PVD				
BPPV	6 (30.0%)	12 (50%)	18 (40.9%)	0.091***
Syndrome Meniere	10 (50%)	11 (45.8%)	21 (47.7%)	
Labyrinthitis	4 (20%)	1 (4.2%)	5 (11.4%)	
Neuronitis vestibular	0 (0%)	0 (0%)	0 (0%)	
Complaint Duration (in weeks)				
Median	4	12	8	0.051***
Min–max	1–104	1–104	1–104	
Accompanying symptoms				
Dizzy influenced	6 (30.0%)	12 (50%)	18 (40.9%)	0.091***
Position	10 (50%)	11 (45.8%)	21 (47.7%)	
Tinnitus otorhea	4 (20%)	1 (4.2%)	5 (11.4%)	
Score DHI pre test mean±SB				
DHI total	44.9 ± 15.6	41.2 ± 14.9	42.9 ± 15.1	0.433#
Subskor E	11.1 ± 6.5	11.2 ± 6.7	11.2 ± 6.5	0.961
Sub shoes F	16.6 ± 6.5	15.8 ± 8.0	16.2 ± 7.3	0.749
Subskor P	17.1 ± 6.7	12.9 ± 5.9	14.8 ± 6.6	0.055

*p< 0.05 (significant), ** Chi-Square test, *** Mann-Whitney U test, # unpaired t-test

TABLE 2
Description of DHI scores in both pre-test and post-test groups

Mean ± SB	Dimenhydrinate		Betahistine	
	Pre test	Post test	Pre test	Post test
Score DHI	44.9 ± 15.6	6.3 ± 4.1	41.2 ± 14.9	8.3 ± 4.5
Emotion Sub Score (E)	11.1 ± 6.5	0.7 ± 1.1	11.2 ± 6.7	1.5 ± 2.0
Functional Sub Score (F)	116.6 ± 6.5	2.5 ± 2.4	15.8 ± 8.0	3.2 ± 2.2
Physical Sub Score (P)	17.1 ± 6.7	3.1 ± 2.7	12.9 ± 5.9	3.5 ± 2.7

TABLE 3
Analysis of betahistine on decreasing DHI scores in PVD sufferers

Variable	Mean ± SB	Mark *p**	Mean Difference ± SB (I 95%)
DHI total pre test – DHI total post test	41.2 ±14.9 8.3 ± 4.5	0.000	32.9 ± 14.3 (26.9 – 38.9)
Sub skor E pre test – Sub skor E pasca test	11.2 ± 6.7 1.5 ± 2.0	0.000	9.7 ± 5.9 (7.2 – 12.2)
Pre test F sub score – Post test F sub score	15.8 ± 8.0 3.2 ± 2.2	0.000	12.6 ± 8.7 (8.9 – 16.3)
Pre test P sub score – Post test P sub score	12.9 ± 5.9 3.5 ± 2.7	0.000	9.3 ± 5.6 (6.9 – 11.7)

*$p < 0.05$ (significant), Wilcoxon test

TABLE 4
Analysis of dimenhydrinate on decreasing DHI scores in PVD sufferers

Variable	Mean ± SB	Mark *p**	Mean Difference ± SB (I 95%)
DHI total pre test – DHI total post test	44.9 ± 15.6 6.3 ± 4.1	0.000	38.6 ± 14.8 (31.7 – 45.5)
Sub skor E pre test – Sub skor E pasca test	11.1 ± 6.5 0.7 ± 1.1	0.000	10.4 ± 6.3 (7.4 – 13.4)
Pre test F sub score – Post test F sub score	16.6 ± 6.5 2.5 ± 2.4	0.000	14.1 ± 6.6 (11.0 – 17.1)
Pre test P sub score – Post test P sub score	17.1 ± 6.7 3.1 ± 2.7	0.000	14.0 ± 7.1 (10.6 – 17.3)

*$p < 0.05$ (significant) Wilcoxon test

the 41–50 year age group (31.8%), more than the 51–60 year age group. Different results compared research that conducted in Romania, which showed that the demographic picture of vertigo was mostly in the 50–59 year age group (66 out of 245 samples).[20] There was no significant difference in the age of the research subjects between the two treatment groups.

The most common peripheral vestibular disorder is Meniere's syndrome (47.7%). Similar to previous study which obtained the number of Meniere's syndrome, 56% of the population with peripheral vestibular vertigo.[18] In this study, there were 3 types of PVD, namely BPPV, Meniere's syndrome and labyrinthitis, but between these three types there were no significant differences. All subjects in this study complained of dizziness with the most common accompanying symptom being tinnitus (47.7%), in accordance with the most common type of peripheral vestibular disorder in this study.

The duration of the subject's complaints in this study gave a median value of 8 weeks, with a minimum complaint of 1 week and a maximum complaint of 104 weeks. In contrast to the research that compares the efficacy and safety of betahistine dihydrochloride as treatment of recurrent vertigo, the average duration of complaints in their research was 31.6 and 32.5 months.[18] In this study, there was no difference between the two treatment groups regarding the length of complaints from research subjects thus it was not analyzed further.

Betahistine is effective in reducing the DHI score of PVD sufferers, which is shown in the decrease in the total DHI score between the pre-test and post-test and is also shown in each sub-score, namely the emotional sub-score, functional sub-score and physical sub-score ($p<0.05$). These results indicate that betahistine can be used as sole therapy to reduce vertigo complaints.

The mean difference between pre-test and post-test total DHI was 32.9 ± 14.3. The mean value of this difference is higher than the mean DHI value previous study, namely 24.3 ± 20.1. The difference in mean values is because the researchers assessed DHI after 4 weeks of betahistine therapy with a betahistine dose of 16 mg, 3 times a day.[17] This difference shows that at 2 weeks

TABLE 5
Betahistine compared to dimenhydrinate on reducing the patient's DHI score Peripheral vestibular disorders

Variable	Mean ± SB	Mark *p**	Mean Difference ± SB (I 95%)
DHI total post-test kel. dimenhydrinate – DHI total post-test kel. betahistine	6.3 ± 4.1 8.3 ± 4.5	0.137	-2.0 ± 1.3 (-4.6 – 0.6)
Sub score E post test kel. dimenhydrinate – Sub score E post test kel. betahistine	0.7 ± 1.1 1.5 ± 2.0	0.160	-0.8 ± 0.5 (-1.8 – 0.2)
Sub score F post test kel.dimenhydrinate – Sub score F post test kel.betahistine	2.5 ± 2.4 3.2 ± 2.2	0.197	-0.750 ± 0.7 (-2.1 – 0.6)
P sub score post test kel.dimenhydrinate – Sub score P post test kel.betahistine	3.1 ± 2.7 3.5 ± 2.7	0.601	-0.4 ± 0.8 (-2.1 – 1.1)

*p <0.05 (significant) Mann Whitney test

TABLE 6
Side effects of administration of dimenhydrinate and betahistine

Variable	Dimenhydrinate n = 20 (45.5%)	Betahistine n=24 (54.4%)	Total	Mark *p**
Side effects				0.08
There isn't any complaint	13 (65%)	21 (87.5%)	34 (77.3%)	
Sleepy	7 (35%)	3 (12.5 %)	10 (22.7%)	
Hypersensitivity	0	0	0	
Eyes / lips dry	0	0	0	
Nausea, vomiting	0	0	0	

*p < 0.05 (significant) Mann Whitney test

betahistine therapy can reduce vertigo symptoms as indicated by a decrease in the DHI score, and increasing the time of administration of betahistine therapy will further reduce vertigo symptoms.

Dimenhydrinate is effective in reducing the DHI score of PVD sufferers, which is shown in the decrease in the total DHI score between the pre-test and post-test and is also shown in each sub-score, namely the emotional sub-score, functional sub-score and physical sub-score (p<0.05). The results of this study prove that dimenhydrinate can be used as a sole therapy for vertigo therapy.

The mean difference in total DHI pre test compared to post test was 38.6 ± 14.8. A study in Palermo designed research by administering combined dimenhydrinate therapy with cinnarizine, on the 18th day a DHI assessment was carried out and the DHI difference value was 8.5 and on the 65th day the difference was 19.3.[21] The decrease in the DHI score was smaller than in this study, this could be caused by the study using a combination of drugs while in this study monotherapy was chosen. However, this research can show a significant difference in the administration of dimenhydrinate. This proves that dimenhydrinate remains an effective therapeutic option for PVD.

The post-test total DHI score of the dimenhydrinate group compared with the betahistine group showed that there was no significant difference in the decrease in the DHI score of PVD sufferers between research subjects who received betahistine and those who received dimenhydrinate, both in total DHI scores and in sub-scores (p=0.137, 0.160, 0.197 and 0.601 respectively). This study shows that betahistine and dimenhydrinate are equally effective in reducing PVD symptoms as indicated by a decrease in DHI scores. The results of this study are similar to research that conducted in Cukurova University Medical Faculty, which reported that dimenhydrinate and betahistine were equally effective in reducing the symptoms of nystagmus in vertigo patients in different ways, so dimenhydrinate and betahistine

cannot be combined.[22] This study can recommend administering betahistine to replace dimenhydrinate in PVD therapy when PVD sufferers cannot tolerate the side effects of dimenhydrinate.

The most common side effect was drowsiness (22.7%) but it did not cause *drop out*, while 77.3% of research subjects did not complain of any side effects. In recurrent vertigo patient study, when administering betahistine for 8 weeks, 4 out of 29 subjects complained of side effects but did not cause drop out.[17] There was no statistical difference in the side effects between the two groups (p=0.08)

The limitation of this study is that it only assesses improvements in vertigo symptoms using the DHI score, which is subjective in nature. Researchers did not analyze other factors that influence vertigo complaints, such as the duration of the complaint, body metabolic factors and blood pressure.

CONCLUSION

The conclusions of this research are Betahistine and Dimenhydrinate have been proven to be effective in reducing the DHI score in patients with peripheral vestibular disorders. Betahistine was not proven to be more effective than dimenhydrinate in reducing the DHI score in patients with peripheral vestibular disorders.

SUGGESTION

The suggestion from this research is that further research is needed using samples from the same type of vestibular disorders, using different and objective measurement instruments and analyzing influencing factors.

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