Article

Annals of Otology, Rhinology & Laryngology
1–7

DOI: 10.1177/0003489419892285
journals.sagepub.com/home/aor
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The Impact of Betahistine versus Dimenhydrinate in the Resolution of Residual Dizziness in Patients with Benign Paroxysmal Positional Vertigo: A Randomized Clinical Trial

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Abstract

Objectives: The aim of this study was to compare the effects of betahistine with dimenhydrinate on the resolution of residual dizziness (RD) of patients with benign paroxysmal positional vertigo (BPPV) after successful Epley maneuver.

Methods: In this double-blind, randomized clinical trial, patients with posterior semicircular canal type of BPPV were included. After execution of the Epley maneuver, patients were assigned randomly to one group for 1 week: betahistine, dimenhydrinate or placebo. The primary outcomes were scores of the Dizziness Handicap Inventory (DHI) and the modified Berg balance scale (mBBS). All patients were asked to describe the characteristics of their subjective residual symptoms. Binary logistic regression analysis was performed to examine the predictors of improved RD. All analyses were conducted using SPSS 19.0.

Results: In total, 117 patients (age range: 20-65 years) participated in this study. After the Epley maneuver, 88 participants had RD. After the intervention, 38 patients exhibited an improved RD. Less than 50% of participants in the three groups showed mild to moderate dizziness handicap. However, there was no significant difference between mBBS scores of groups before or after the intervention. Logistic regression was shown that patients with receiving betahistine were 3.18 times more likely to have no RD than the placebo group. Increasing age was associated with a decreased likelihood of improving RD ($P = .05$).

Conclusion: The analysis of data showed that the use of betahistine had more effect on improving RD symptoms. We recommended future studies using objective indicators of residual dizziness.

Keywords

benign paroxysmal positional vertigo, dizziness, repositioning maneuver, betahistine, dimenhydrinate

Introduction

Benign paroxysmal positional vertigo (BPPV) is the most common peripheral vestibular disorder, accounting for 20% of all vertigo cases.[1-3] The main pathogenesis of BPPV is detachment of otoconia from the utricular macula migrating into the semicircular canals leading to a change in fluid dynamics of endolymph.[1]

Although BPPV could usually be resolved without special treatment, the canalith repositioning procedure (CRP) can promote the recovery of BPPV.[4,5] CRP can help patients to get relief from BPPV by moving the otoconia to utriculus.[6] Successful CRP means that nystagmus (negative Dix–Hallpike test results) and vertigo symptoms disappear after CRP.[7,8] However, some patients with successful CRP for BPPV still report dizziness, which

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may persist for a certain period. This imbalance is often described as a sensation of lightheadedness or dizziness in absence of vertigo or nystagmus, or short-lasting unsteadiness occurring during head movements, standing, or walking.[9] Residual dizziness could cause nervousness, panic, and insomnia and seriously affect the quality of life of patients. Also, residual dizziness might increase the risk of falling, especially in the elderly.[9-11] The overall prevalence of RD is ranged from 31 to 61%.[9] The duration of RD can range from a few days to several weeks.[12]

There is controversy about the causes of residual dizziness: utricular dysfunction, unsuccessful canalith repositioning,[13] an incomplete central adaptation after successful CRP,[14] autonomic dysfunction,[12] underlying systemic conditions, and presence of anxiety/depressive symptoms.[15]

Many treatments have been developed to treat residual dizziness after successful CRP for BPPV. Jung et al[15] reported that the anxiolytics (low-dose etizolam) could effectively reduce the residual dizziness. Deng et al[16] found that Danhong injection, a traditional Chinese medicine, could significantly improve the residual dizziness. Ge et al[17] found that the betahistine could effectively shorten the duration of residual dizziness. Another study reported that compared to the low-dose betahistine (18 mg/day), the high-dose betahistine (36 mg/day) could yield better efficacy in treating residual dizziness.[18] However, the optimal treatment plan is still not determined.

Materials and Methods

This double-blind, randomized clinical trial has been carried out in the Amiralmomenin and the Poursina Hospitals of Guilan University of Medical Sciences, Rasht, Iran between June 2016 and November 2017. BPPV was confirmed by the supine head-turning test or Dix–Hallpike test. Only the canalithiasis type of BPPV patients involved with posterior semicircular canal was included in this study. Inclusion criteria included patients who were 18 to 65 years and had positive symptoms of residual dizziness after successful CRP (confirmed with a resolution of positional nystagmus and symptoms on the initial visit day). Residual dizziness was defined as a sensation of lightheadedness, dizziness or intermittent unsteadiness in absence of vertigo or nystagmus. Exclusion criteria were a positive history of Meniere's disease or vestibular neuritis; a history of psychiatric or neurologic disorder (eg, migraine, multisensory imbalance), cerebrovascular or cardiac diseases; patients who had used any anti-vertigo drug, antihistamine, thiazide diuretic, calcium channel blocker, and benzodiazepine within last month. So as to obtain the most homogeneous sample possible, secondary and post-traumatic forms of BPPV were excluded.

The trial was registered at the Iranian Registry of Clinical Trials (IRCT201506231138N20). The study protocol was approved by the ethical committee of GUMS, Iran (94031803) and complied with the rules delineated in the Helsinki Declaration. Written informed consent was obtained from each subject before the start of the study.

Interventions

All patients underwent repositioning maneuvers according to the technique described by Epley[19] in the same diagnostic session. After execution of the maneuver, the patient was reassessed with the Dix–Hallpike test and, where nystagmus was still present, the Epley maneuver was repeated up to a maximum of four times in the same session. If nystagmus was no longer present, the patient was included. Randomization and blinding were carried out by an independent pharmacist who did not involve in patient care. Block randomization (size of four) was done by a computer-generated random allocation sequence. This was administered by using sealed coded envelopes at the Otorhinolaryngology Research Center of GUMS. The betahistine (Actoserc, Actover Co., Tehran, Iran; 16 mg, three times/day; for group A), dimenhydrinate (Abidi Pharm Co., Tehran, Iran; 50 mg, three times/day; for group B) and placebo (for group C) were placed into a similar gelatinous capsule by the pharmacist. At the end of 1-week intervention, the Dix–Hallpike test was first repeated with the aim of first confirming the resolution of BPPV. Patients who presented paroxysmal nystagmus at the Dix–Hallpike test 7 days later were excluded from the study. Because we aimed to evaluate residual symptoms only in the absence of positional nystagmus.

Measurement Index

The primary outcomes were scores of the 25-item Dizziness Handicap Inventory (DHI) and the modified Berg balance scale (mBBS). All patients answered the questionnaires before CRP and 1 week after CRP. The DHI score was used to help patients to rate the dizziness-related physical impairments, activity limitations, and restrictions in participation.[20] The DHI divided into three subdomains of impact on daily life (functional, emotional and physical), with a total score ranging from 0 (no disability) to 100 (severe disability) on the basis of symptoms frequency. The mBBS is a valid tool to estimate balance condition. The mBBS comprises 12 balance-related tasks. Each task is given a score of zero (unable) to four (independent).[21]

The secondary outcomes were the residual dizziness symptoms characterized by lightheadedness, dizziness, and intermittent unsteadiness. Adverse events were recorded at the second visit. However, patients were also asked to contact the investigator for adverse events during the study.

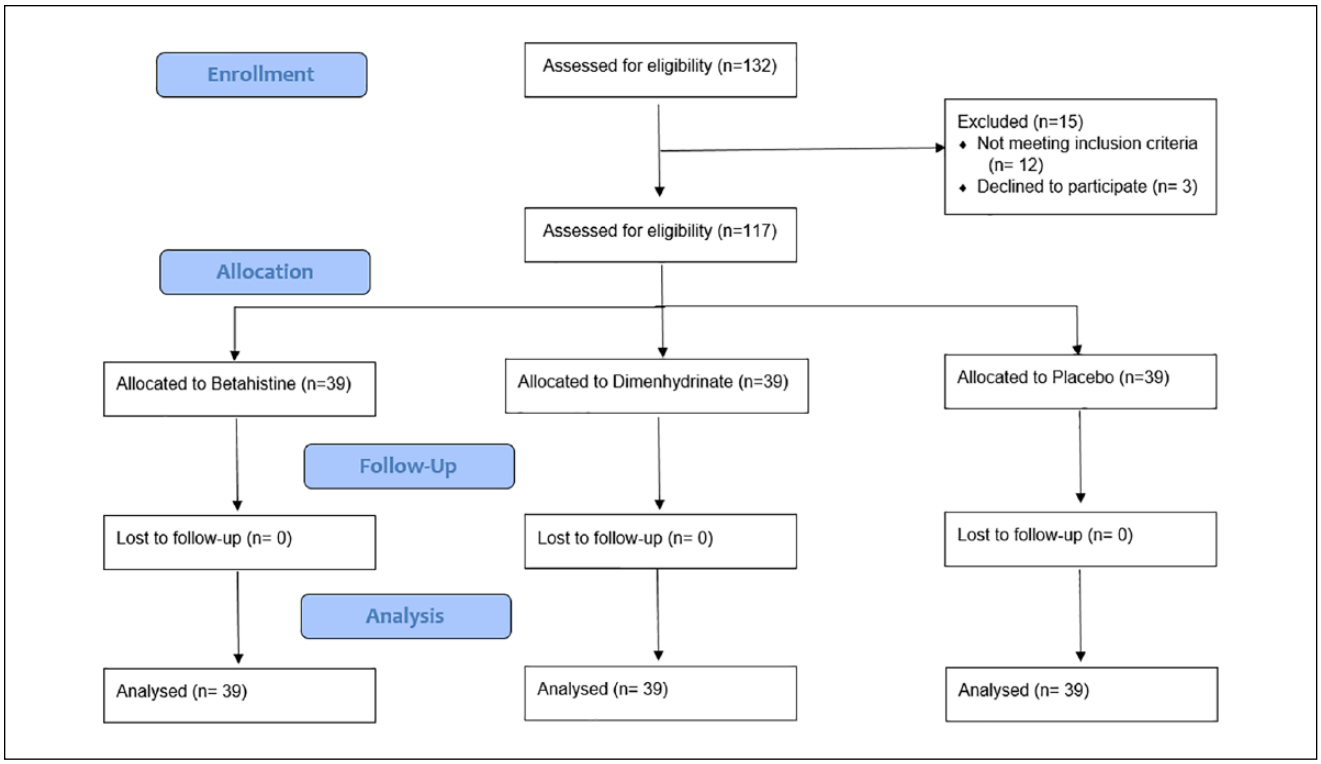

Figure 1. Flow diagram of the study.

Statistical Analyses

The study was conducted in accordance with the CONSORT 2010 statement for reporting randomized trials.[22] The power analysis was performed using G*Power (V.3.1.9.2; Universitat Düsseldorf, Germany). Considering an α-error 5% (two-tailed test) and a power of 90%, with the average effect size value 0.6 (based on the study of Guneri et al), the estimated sample size was estimated in 39 patients per group. An intention-to-treat analysis was performed to avoid overestimation of clinical effectiveness. All randomized patients were included in the statistical analysis, regardless of the treatment implemented and regardless of the withdrawal status of the patient. Missing patient responses in the allocated treatment arms were imputed as baseline observation carried forward (no improvement). The Kolmogorov–Smirnov test was used to assess the normal distribution of variables. Chi-squared test was used for comparison of RD symptoms between before and after intervention in each group. Binary logistic regression analysis included factors in univariate analysis with $P < .1$ and it was performed to examine the predictors of improved RD. The criterion for statistical significance was set at $P < .05$, and all analyses were conducted using SPSS 19.0 (IBM Corporation, Armonk, NY, USA).

Results

In total, 117 patients (age range 20-65 years) participated in this study and were randomly assigned to one of three intervention arms (Figure 1). All patients returned after 1 week of intervention. None of them had nystagmus during the Dix–Hallpike test and therefore were not excluded from the study. The three groups were comparable with respect to relevant baseline characteristics (Table 1). Twenty-two patients (18.8%) had previously experienced similar episodic vertigo (probably BPPV). Eighty-eight participants (75.2%) had RD after Epley maneuver at day 0. The most common complaint in the participants was lightheadedness (47.0%), followed by dizziness (45.3%), and unsteadiness (38.5%). No patients dropped out of the study after the allocation. In addition, we did not observe a positive Dix–Hallpike test in the participants at day 7. After the intervention, 38 patients exhibited an improved RD (Table 2). The most common complaint in the participants at the second visit was lightheadedness (31.6%), followed by dizziness (16.2%), and unsteadiness (14.5%). The analysis of data showed that lightheadedness improved in neither groups. While unsteadiness was significantly improved in three groups (Chi-squared tests, P values for groups A, B and C: .008, .002 and .02, respectively). Moreover, dizziness was decreased significantly in group A ($P = .02$). The

Table 1. Demographic and Clinical Characteristics of Participants.

Characteristic	Betahistine	Dimenhydrinate	Placebo	Total
Sex (no [%])				
Female	20 (51.3)	24 (61.5)	24 (61.5)	68 (58.1)
Male	19 (48.7)	15 (38.5)	15 (38.5)	49 (41.9)
Age (year [mean±SD])	41.9±9.5	41.3±10.4	41.0±10.3	41.4±10.0
Canal involved (no [%])				
Right side	17 (43.6)	19 (48.7)	22 (56.4)	58 (49.6)
Left side	22 (56.4)	20 (51.3)	17 (43.6)	59 (50.4)
Duration of illness (day [mean±SD])	3.8±1.8	3.6±1.6	4.0±2.0	3.8±1.8
No. of CRPs performed (no [%])				
1	10 (25.6)	8 (20.5)	10 (25.6)	28 (23.9)
2	12 (30.8)	15 (38.5)	9 (23.1)	36 (30.8)
3	12 (30.8)	12 (30.8)	15 (38.5)	39 (33.3)
4	5 (12.8)	4 (10.3)	5 (12.8)	14 (12.0)
Residual Dizziness (no [%])	29 (74.4)	29 (74.4)	30 (76.9)	88 (75.2)
mBBS (mean±SD)	45.7±5.5	46.4±3.2	46.8±3.6	46.3±4.2
DHI scores (mean±SD)				
Total	29.6±16.8	28.8±16.8	36.8±21.4	31.7±18.4
Functional	9.6±6.3	9.5±6.4	12.4±8.8	10.5±7.3
Emotional	6.0±6.4	6.0±7.2	8.9±8.7	7.0±7.6
Physical	17.9±4.6	17.2±4.6	19.0±4.8	18.0±4.8

SD, standard deviation; CRP, canalith repositioning procedure; mBBS, modified Berg balance scale; DHI, Dizziness handicap inventory.

Table 2. Changes in the Measured Outcomes after 1 week Follow-Up.

Characteristic	Betahistine	Dimenhydrinate	Placebo	Total
Improved RD (no [%])	17 (58.6)	13 (44.8)	8 (26.7)	38 (43.2)
mBBS (mean±SD)	1.2±5.1	−.1±1.5	−.1±1.0	.4±3.2
DHI scores (mean±SD)				
Total	−13.0±6.7	−10.2±5.4	−12.2±7.8	−11.8±6.8
Functional	−3.9±3.0	−2.8±1.8	−2.8±3.1	−3.2±2.7
Emotional	−1.2±2.4	−1.0±2.7	−1.7±2.8	−1.3±2.8
Physical	−10.7±3.3	−9.1±3.7	−10.0±4.4	−9.9±3.9

RD, residual dizziness; SD, standard deviation; mBBS, modified Berg balance scale; DHI, Dizziness handicap inventory.

patients did not state any side effects including hypotension, drowsiness or any other reactions.

About two-thirds of patients in three group had DHI score in the range 16 to 52, suggestive of mild to moderate vertigo (group A to C: 79.5%, 61.5% and 69.2%, respectively). We found that at the end of 1-week intervention, there was mild to moderate dizziness handicap in <50% of participants (group A to C: 46.2%, 43.6% and 48.7%, respectively). On analyzing the results from the mBBS, there was no significant difference between groups before or after the intervention (Table 2).

Logistic regression was performed to ascertain the effects of age, duration of illness, DHI and mBBS scores as well as intervention groups on the likelihood that participants have no RD. The logistic regression model was statistically significant, $\chi^2(6)=13.34$, $P<.04$. The model explained 14.5% (Nagelkerke *R2*) of the variance in the improvement of RD and correctly classified 67.5% of cases. Patients with receiving betahistine were 3.18 times more likely to have no RD than the placebo group. Increasing age was associated with a decreased likelihood of improving RD ($P=.05$), but DHI and mBBS scores were not associated with an increased likelihood of improvement of RD (Table 3).

Discussion

Residual Dizziness symptoms could cause nervousness, panic, and insomnia and seriously affect the quality of life of patients. Many treatments have been suggested to treat RD symptoms after successful CRP for BPPV. Jung et al[23] reported that the anxiolytics (low-dose etizolam) could

Table 3. Binary Logistic Regression Analysis of Predicting Factor for Improving Residual Dizziness.

Factors	B	SE	Wald	P	OR	95% CI
Age	−.05	.02	4.01	.05	.96	.91-1.00
Duration of illness	−.20	.11	3.15	.08	.82	.66-1.02
mBBS	−.01	.06	.02	.90	.99	.88-1.12
DHI scores	.01	.01	.18	.67	1.01	.98-1.03
Intervention group						
Placebo (ref)						
Betahistine	1.16	.51	5.19	.02	3.18	1.18-8.59
Dimenhydrinate	.64	.49	.18	.67	1.01	.98-1.03

B, coefficient value; SE, standard error; OR, odds ratio; CI, confidence interval; mBBS, modified Berg balance scale; DHI, Dizziness handicap inventory; ref, reference.

effectively reduce RD symptoms. Ge et al[24] found that the betahistine could effectively reduce the duration of RD. In a meta-analysis, Nauta[25] demonstrated a significant benefit of betahistine in various types of vertiginous syndromes. A meta-analysis was done by Della Pepa et al[26] to evaluate the efficacy of betahistine in the treatment of vertiginous syndromes not related to Meniere's disease, such as BPPV. The results of the meta-analysis confirmed the therapeutic benefit of betahistine compared to placebo. However, the optimal treatment of RD has not been determined yet. The rationale for using an antihistamine (dimenhydrinate) and a histamine analogs (betahistine) in the present study for symptomatic relief of RD is derived from their mechanisms of action.

In our study, three-fourths of the participants had RD which 59% and 45% of them in group A and B showed improvement of RD, respectively. However, only 27% of patients who underwent successful CRP and received placebo reported the recovery of RD. In support of our finding, Guneri and Kustutan[27] found that 48 mg of betahistine daily, in addition to Epley maneuver, gave more effective results than Epley maneuver alone or combined with placebo in improving symptoms in four different scales of vertigo symptoms evaluation. Kim et al[28] investigated the role of vestibular suppressant, analyzing the effect of dimenhydrinate in relieving RD after successful maneuvers. In a randomized controlled trial, they compared the presence of lightheadedness or mild headache (the most common symptoms after CRPs) in three groups treated with no medication, placebo or 50 mg dimenhydrinate per day, respectively. Even if the DHI scores (total and for each subscale) did not show a substantial difference, they found that the residual symptoms were significantly lower in the medication group, suggesting that this type of medication could be helpful in preventing RD. Although betahistine and dimenhydrinate are drugs commonly used in the treatment of vertigo, literature is sparse about the comparison of improving RD between them. Cirek et al[29] showed that the effects of betahistine on reducing vertigo and concomitant symptoms were relatively slow in onset. Compared with betahistine, the effects of cinnarizine/dimenhydrinate combination were not only significantly greater but also more rapid in onset. Thus, betahistine appears to be an appropriate treatment for long-term interval therapy rather than for the control of acute vertigo attacks. It seems that betahistine promotes and facilitates central vestibular compensation after successful CRPs. This effect is probably caused by the up-regulation of histamine turnover and release mediated through the H3 receptor antagonism. Betahistine modifies neuronal discharge in the vestibular nuclei by inhibiting effect on spike generation of neurons in lateral and medial vestibular nuclei.[30]

Whereas our study showed RD symptoms were alleviated significantly more frequent with betahistine or dimenhydrinate than placebo, we failed to significant differences in DHI or mBBS score among the three groups. The most important RD symptoms in our patients were lightheadedness and dizziness, which could not be assessed with the DHI questionnaire. In line with our finding, previous studies showed no significant impact of betahistine or dimenhydrinate on DHI.[28,31] In a randomized controlled clinical trial, Acar et al[26] evaluated alleviation of RD after successful maneuvers. They found no significant differences in the DHI scores of patients with RD among betahistine, and placebo. Also, Kim et al[28] observed no significant reduction in DHI score in the dimenhydrinate group compared with the control group, suggesting that the residual symptoms could not be evaluated by DHI score alone.

In contrast with previous studies, we used logistic regression analysis to mitigate the effect of covariates and to examine the predictors of improved RD. RD improvement seems to be unaffected by duration of vertigo before the Epley maneuvers. This finding is in contrast with previous studies[9,32] reporting a correlation between RD after the particle repositioning maneuver and a longer duration of BPPV. Stambolieva and Angov[33] proposed that the short presence of otoconia didn't damage sensory receptor, and restoring the normal function of motion-sensitive hairs cells and stabilizing the posture could be observed by the Epley maneuver. The average duration of BPPV in our patients was 3.8 days (range 1-7) which was shorter than previous studies. Therefore, early recognition and treatment patients with BPPV may diminish this correlation in our population.

The adjusted OR estimated was 3.2 for the use of betahistine. The confidence interval for adjusted OR does not contain the value 1. Therefore, we can conclude that—after correction for covariates—the use of betahistine has more effect on improving RD symptoms compared to dimenhydrinate and the use of placebo. Dimenhydrinate is an H_1 receptor antagonist with marked anticholinergic properties, which acts predominantly on the central vestibular system

and vomiting center.[29,34] However, betahistine works both peripherally and centrally. Primarily, it is a full agonist on the H_1 receptors located on blood vessels in the inner ear. This gives rise to local vasodilation and increased permeability, which helps to reverse the underlying problem of endolymphatic hydrops. More importantly, betahistine has powerful antagonistic effects at H_3 receptors. This stimulation explains the potent vasodilatory effects of betahistine in the inner ear, which are well documented. Centrally betahistine enhances histamine synthesis in tubero-mammilary nuclei and its release within the vestibular nuclei. In addition, it regulates alertness via cerebral H_1 receptors.[35] These actions can facilitate the recovery ameliorating the quality of life of patients suffering from BPPV.[16]

Several limitations of our study should be mentioned. First, the sample size in each group was relatively small, limiting the available power and ability to find more subtle changes of DHI and mBBS. Second, the treatment was only continued for 1 week. The long-term effects of betahistine were not assessed here. Third, only the canalithiasis type of BPPV patients with posterior semicircular canal involvement was included. Finally, we used symptoms to evaluate the efficacy of betahistine and dimenhydrinate, but they were subjective data. Future studies should use some objective indicators, such as slow phase velocity of positional nystagmus, to further evaluate the efficacy of these two treatments on residual dizziness after successful CRP for BPPV.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by a grant from Guilan University of Medical Sciences, Iran (94031803).

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