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OTOLOGY

Does betahistine treatment have additional benefits to vestibular rehabilitation?

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Abstract The aim of this study was to investigate the effect of high-dose betahistine treatment added to vestibular rehabilitation (VR) on the disability, balance and postural stability in patients with unilateral vestibular disorder. The VR group (group 1, $n = 24$) and the VR + betahistine group (group 2, $n = 23$) were analyzed retrospectively. All patients were evaluated before and after an 8-week customized VR in terms of disability (Dizziness Handicap Inventory, DHI), dynamic balance [Dynamic Gait Index (DGI)] and postural stability (static posturography). In group 1 and group 2, differences between DHI, DGI and falling index score on static posturography before and after the exercise program were significant ($p < 0.05$). In addition, a significant difference was detected only in group 2 in the variables evaluated in static posturography-Fourier 4 analysis ($p < 0.05$). Both VR and betahistine + VR have a positive effect on disability and balance in patients with unilateral vestibular disorder. Betahistine treatment added to VR was effective in increasing postural stability.

Keywords Vestibular rehabilitation · Betahistine · Vestibular dysfunction · Balance

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Introduction

Vertigo, dizziness and imbalance are the main symptoms in vestibular disorders. These can lead to physical (decrease in postural control, falling) and psychological (anxiety/depression, panic, agoraphobia) defects. As a result of these defects occurring in vestibular patients, disruption in general health status and quality of life may be observed [1, 2]. In this respect, the objective of treatment in vestibular disorder is to control the symptoms, prevent disability and increase the quality of life. To achieve this, vestibular rehabilitation and medical treatment are recommended in the treatment of vestibular patients [1].

Vestibular rehabilitation has become one of the main treatment modalities for patients suffering from vestibular dysfunctions [3]. Vestibular rehabilitation is an exercise program comprising eye, head and body movements to stimulate the vestibular system and restore central compensation. Graded exercises are utilized to train the brain to compensate for defective or abnormal vestibular inputs, improve the role of alternative visual or proprioceptive inputs, develop new strategies for gaze and postural control, increase the threshold to vertigo and promote postural stability [1].

In patients with vestibular disorder, the most investigated medical treatment is betahistine treatment in terms of reducing vestibular symptoms and increasing the quality of life [1]. Betahistine, a structural analog of histamine, is a weak histamine H1 receptor agonistic and a more potent H3 receptor antagonist. It has been suggested that the improvement in vestibular compensation is related to changes in histamine turnover [1, 4, 5]. The mechanism of the action of betahistine is not known with certainty, but it acts to improve cochlear and vestibular blood flow and facilitates histamine synthesis and release in the brain and as well as

in peripheral labyrinthine receptors [1, 4, 5]. Although it was shown in a few studies that betahistine has significant efficacy in improving the patient's physical, functional and emotional status [6, 7], delaying the need for vestibular neurectomy and facilitating postoperative vestibular compensation [8], it has not been investigated yet whether vestibular rehabilitation is an adjuvant treatment. In this respect, the objective of this study was to investigate the effect of high-dose betahistine treatment added to vestibular rehabilitation on disability, balance and postural stability in patients with unilateral decompensated vestibular disorder.

Materials and methods

The data collected from 47 patients with unilateral vestibular disorder, who were receiving rehabilitation in the vestibular rehabilitation unit between 2007 and 2009 [vestibular rehabilitation (group 1, $n = 24$), vestibular rehabilitation + betahistine (group 2, $n = 23$)] were examined retrospectively.

All patients were reviewed by the board of consultant physicians from the ear, nose and throat, neurology and physical medicine and rehabilitation departments (The Dizziness Council), which assembled once a week to evaluate every patient with vertigo, dizziness and balance problems and recruit eligible patients into the study and also those appropriate for vestibular rehabilitation. Among these were patients diagnosed to have unilateral chronic peripheral vestibular dysfunction by neurological and otological examinations and vestibular function tests (electronystagmography, bithermal caloric test, ocular motor testing and positional testing) performed by a neuro-otologist or neurologist. Caloric tests were performed to demonstrate a peripheral vestibular deficit by using a Nicolet device (Nicolet Instrument Inc., Madison, USA). Canal paresis in caloric test was defined as a side difference of >25% for the maximal slow phase velocity (SPV_{max}) of nystagmus between the two ears [9].

Patients having any problems that could interfere with rehabilitation [ambulatory problems, restricted cervical movement (flexion, extension, lateral flexion and rotation <30°), disorder affecting visual and somatosensorial systems, cognitive, orthopedic or neurological disorders], and those having fluctuating and intermittent vertigo, benign paroxysmal positional vertigo or symptoms for <2 months were excluded. None of the patients included in the study was receiving vestibular-suppressing medications. Demographic (age, gender, education, use of eyeglasses) and clinical data (additional disease, migraine history, hearing problems, fall history in the previous 6 months and in the disease period) of all patients were recorded.

Approval of this study was obtained from our university. All subjects gave written informed consent.

All patients were assessed by the following tests before and after rehabilitation:

Disability

Dizziness Handicap inventory

This is a multidimensional self-assessment scale that quantifies the level of disability and handicap in three subscales: physical, emotional and functional. It is possible to use both the total score and the scores of the three subscales separately. The scores range from 0 to 100, where 100 means a high level of disability and handicap from symptoms of dizziness [10].

Dynamic balance

Dynamic Gait Index

The Dynamic Gait Index (DGI) was used to describe each patient's dynamic gait performance. Patients completed the eight walking items of the DGI, including walking on level surfaces, with a quick pivot turn, at different speeds, with head movements (pitch and yaw), over and around objects and up and down steps. Each item was scored on an ordinal scale (range 0–3) based on established descriptors, with a maximum total score of 24 [11]. Scores of <20 were related to falls in people with vestibular disorders [12].

Postural stability

Static posturography

Postural control was measured using the Tetrax Interactive Balance System (Tetrax, Ramat Gan, and Sunlight Medical, Tel Aviv, Israel). This method of posturography is based on the assessment of the vertical pressure fluctuations on four independent force plates, each placed beneath the two heels and toe parts of the subject while standing in an upright position. The software of the system elaborates four basic parameters, obtained by standing in eight positions. The intensity of sway is measured by Fourier transformation. Fourier (F) transformation is derived from four independent wave signals, presented in the form of a spectrum and broken down into the following eight frequency bands: $F1$ 0.01–0.1 hertz (Hz); $F2$ 0.1–0.25 Hz; $F3$ 0.25–0.35 Hz; $F4$ 0.35–0.50 Hz; $F5$ 0.5–0.75 Hz; $F6$ 0.75–1.00 Hz; $F7$ 1.00–3.00 Hz; $F8$ 3.00 Hz and above. Low frequencies (0.01–0.1 Hz) are linked with visual control. The medium–low frequencies (0.1–0.5 Hz) are sensitive to vestibular stress and disturbances. The medium–high frequencies

(0.5–1.00 Hz) reflect somatosensory activity and postural reflexes mediated by lower extremities. Bursts of high frequencies (over 1 Hz) are often induced by dysfunctions in the central nervous system. The standard examination protocol includes standing for 32 s in each of the eight positions as follows: (1) head straight, eyes open, support solid; (2) head straight, eyes closed, support solid; (3) head straight, eyes open, support soft (foam rubber); (4) head straight, eyes closed, support soft; (5) head turned to the right, eyes closed, support solid; (6) head turned to the left, eyes closed, support solid; (7) head up, eyes closed, support solid; and (8) head down, eyes closed, support solid. Tetrax evaluates eight positions and calculates a value called falling index. Falling index is expressed as a numeric value between 0 and 100, determined by the stability of patient, Fourier conversion and synchronization results. A value of 0 denotes no risk of fall, while 100 denotes high risk of fall. Patients are classified into three groups: low (0–35), moderate (36–57) and high risk (58–100). In our study, falling index and F4 frequency band were used for the evaluation [13, 14].

Exercise program

An exercise program developed by a physical medicine and rehabilitation specialist, considering the history, physical examination and diagnostic tests, was prescribed for the patients. This program consisted of education and exercise components. Functions of the balance system, causes of dizziness, and rationale and contraindications for performing of exercise were explained during the education component. Patients were actively involved in adapting the exercise program to their symptoms, capabilities and lifestyle. The exercises were personalized by the physical medicine and rehabilitation specialist according to the symptoms and functional disability of the patient. The treatments included one or more of the following elements: balance and gait training; activities to promote the use of varied sensory inputs for maintaining balance, especially somatosensation; and activities to improve vestibular adaptation for those with remaining vestibular function. Patients with little to no vestibular function were taught to substitute vision and somatosensation for their lost vestibular function. During the training period in the hospital, compliance was monitored by a physician. The exercise program consisted of one session per week for a period of 8 weeks, and each session lasted for approximately 30–45 min in the rehabilitation unit. Illustrations of the exercises were also given to the patients to enable them to carry out these exercises at home twice a day. Patients in group 2 used 96 mg of betahistine per day (vasoserc 24 mg tablet 2 × 2) for 8 weeks in addition to vestibular rehabilitation. Any adverse events were evaluated by the investigator.

Statistical analysis

The data were analyzed using the SPSS version 15 statistical package. Demographic variables were compared by Chi-square test or Fisher's exact test. The Kolmogorov–Smirnov test was used to test for normal distribution of the baseline values of the patients. Analysis of variance for repeated measures was applied for normally distributed variables to compare means of groups, analyze the difference before and after the treatment and test whether these differences between the two groups were comparable (interaction). The following tests were used when interactions between the parameters were statistically significant:

1. independent samples *t* test (to test the difference between two groups before treatment);
2. paired *t* test (to test the difference between the results before and after treatment within each group);
3. analysis of covariance (to compare end-of-treatment results of groups by correcting for baseline values).

Mann–Whitney *U* test and McNemar–Bowker test were used for variables that were not normally distributed. A p value of <0.05 was regarded as statistically significant.

Results

Demographical and clinical data of the patients are presented in Table 1. There were no significant differences between the two groups in terms of demographic and clinical data ($p > 0.05$). Dizziness Handicap Inventory (DHI), DGI and static posturograpy scores (falling index—Fourier

Table 1 Demographical and clinical features of patients in group 1 (vestibular rehabilitation) and group 2 (vestibular rehabilitation + betahistine)

	Group 1 ($n = 24$)	Group 2 ($n = 23$)
Age (mean ± SD)	46.96 ± 14.86	45.43 ± 11.78
Gender (male/female) (n, %)	8 (33.3)/ 16 (66.7)	6 (26.1)/ 17 (73.9)
Education (primary school, %)	62.5	60.8
Concomitant disease (%)		
Hypertension	54.5	45.5
History of migraine (present, %)	20.8	17.4
Hearing problem (present, %)	87.5	78.3
Use of spectacles (present, %)	67.5	56.5
History of fall within the last 6 months (present, %)	37.5	39.1
Duration of disease (month, mean ± SD)	32.56 ± 32.69	40.04 ± 42.52

* $p < 0.05$

Table 2 Comparison of group 1 (vestibular rehabilitation) and group 2 (vestibular rehabilitation + betahistine) before and after the exercise program with regard to symptom (VAS), disability (DHI) and balance

	Group 1 (mean ± SD)		Group 2 (mean ± SD)	
	PreReh	PostReh	PreReh	PostReh
DHI total	56.46 ± 23.80	38.08 ± 25.13*	54.78 ± 21.33	30.78 ± 22.68*
DGI	18.67 ± 5.20	22.54 ± 2.25*	17.22 ± 4.38	21.61 ± 2.35*
Static posturograph-falling index score	60.08 ± 37.34	38.48 ± 33.15*	67.91 ± 32.52	31.39 ± 23.29*

PreReh before rehabilitation, *PostReh* after rehabilitation, *DHI* Dizziness Handicap Inventory, *DGI* Dynamic Gait Index

* $p < 0.05$ within groups

Table 3 Comparison of group 1 (vestibular rehabilitation) and group 2 (vestibular rehabilitation + betahistine) before and after the exercise program with regard to postural stability

F4	Group 1 (mean ± SD)		Group 2 (mean ± SD)	
	PreReh	PostReh	PreReh	PostReh
FIRM EO	6.41 ± 3.97	5.97 ± 3.85	8.32 ± 7.11	4.76 ± 2.69*
FIRM EC	9.67 ± 5.69	8.63 ± 6.49	13.38 ± 8.79	7.29 ± 3.06*
FOAM EO	7.16 ± 2.74	6.88 ± 3.90	9.98 ± 4.84	6.70 ± 3.88*
FOAM EC	11.88 ± 7.96	10.01 ± 6.03	19.05 ± 11.55	11.33 ± 8.38*

F4 Fourier transformation 0.35–0.50 Hz, *PreReh* before rehabilitation, *PostReh* after rehabilitation, *EO* eyes open, *EC* eyes closed

* Within groups

4) before the rehabilitation did not also differ between the two groups ($p > 0.05$; Tables 2, 3).

In group 1 and group 2, differences between DHI, DGI and static posturography (falling index score before and after the exercise program) were significant (Table 2, $p < 0.05$). In addition, a significant difference was detected in the variables evaluated in static posturography-Fourier 4 analysis in group 2 ($p < 0.05$, Table 3). In group 1, no significant difference was found in terms of the variables evaluated in static posturography-Fourier 4 analysis ($p > 0.05$, Table 3). Drug-related gastrointestinal side effects (epigastric disturbance) were observed in three patients in group 2, and none of the patients with this complaint discontinued the treatment.

Discussion

At the end of our study, it was found that both vestibular rehabilitation and betahistine + rehabilitation treatment had positive effects on disability (DHI) and dynamic balance measurements (DGI) in patients with unilateral vestibular disorder. In addition, it was concluded that betahistine treatment added to vestibular rehabilitation was effective in increasing postural stability.

Symptoms and loss of balance related to vestibular disorder cause significant disability by causing emotional, physical and functional incapacity. Significant improvement in DHI was observed in betahistine treatment (32–48 mg for 2–3 months) with both placebo [7] and flunarizine [15]. Numerous studies found positive effects of vestibular rehabilitation on disability due to dizziness, as measured by DHI [16–19]. In our study, significant improvement was observed in DHI in both groups. There are no available studies showing the effect of betahistine added to vestibular rehabilitation on disability, and we believe that long-term randomized and controlled studies to be carried out in the future will elucidate this issue.

Gait and balance disturbance is an important problem in peripheral vestibular disorders [20, 21]. It was reported that the risk of falling increases in peripheral vestibular disorders [20, 21]. Although vestibular rehabilitation was shown to decrease falling and restore gait disturbance [22, 23], our literature survey has not revealed any study carried out with betahisine on this issue. In our study, improvement was observed in dynamic measurements in both groups, but no efficacy additional to vestibular rehabilitation was shown in the betahistine group.

Improvement in postural stability in peripheral vestibular disorder by vestibular rehabilitation has been demonstrated in studies [19, 24, 25]. Our study determined only the positive effect of betahistine + vestibular rehabilitation treatment on postural stability. Since postural stability is an objective evaluation method, its results are important and it may be considered that betahistine provides additional efficacy in compensation. Our literature review did not

reveal any study showing the effect of betahistine treatment on postural stability, and our study demonstrated that betahistine treatment may be useful in patients who apply for vestibular rehabilitation.

Besides vascular action in the inner ear, modulation of the peripheral vestibular sensory cells and excitatory effect on the neuronal activity of cortical and subcortical structures, betahistine interacts strongly with the histaminergic system increasing histamine synthesis and release in the tuberomammillary nuclei of the posterior hypothalamus. The action of histamine on the vestibular cells on the affected side may contribute to a rebalancing of neuronal activity between the two sides (vestibular compensation). Vestibular deficits require a considerable period for compensation to occur and these long-term adaptive mechanisms can be facilitated pharmacologically using histaminergic-like drugs such as betahistine [26]. Although our study demonstrated an improvement in disability and dynamic balance in both groups (vestibular rehabilitation, vestibular rehabilitation + betahistine), it was observed that the group that received vestibular rehabilitation with betahistine also demonstrated a positive effect on postural stability. The reason for this may be the use of betahistine in low doses or for a short period. As a matter of fact, it was shown in pharmacological studies carried out on animal models that the high-dose betahistine treatment ($\geq$10 mg/kg) provided vestibular compensation when applied for 3 weeks to 3 months [5]. Clinical studies also revealed that a high dose (48 mg tid) was more effective in reducing vertigo attacks compared to low dose (16 or 24 mg tid), and the efficacy of treatment in the high-dosage group increased over time [27]. Moreover, Allum et al. [28] reported that the use of betahistine for more than 2 months may provide vestibulo-spinal reflex compensation. However, optimal dose and period for the use of betahistine is still unknown. In our study, although it was used at a higher dose and for 2 months compared with the dose used in clinical practice, betahistine given concomitantly with vestibular rehabilitation showed an additional effect only on postural stability. Therefore, further studies with high dose applied for longer periods ($\geq$2 months) need to be carried out.

Inclusion of a homogenous disease group (unilateral vestibular disease) and the evaluation of patients by objective methods may be considered as the advantages of our study. However, our study had some limitations: it was retrospective; betahistine treatment with different doses and periods was not applied; and the number of patients was insufficient. It will be appropriate to investigate the effect of betahistine added to vestibular rehabilitation (on a greater population and at different doses and periods) on symptom, disability, balance and postural stability in future randomized and controlled studies.

Consequently, it was determined that both vestibular rehabilitation and betahistine + rehabilitation treatments have a positive effect on disability and balance in patients with unilateral vestibular disorder. In addition, it was also concluded that betahistine treatment added to vestibular rehabilitation was effective in increasing postural stability. In the future, it will be appropriate to investigate the effect of different doses and periods of betahistine treatment added to vestibular rehabilitation in peripheral vestibular disorder.

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References

1. Mira E (2008) Improving the quality of life in patients with vestibular disorders: the role of medical treatments and physical rehabilitation. Int J Clin Pract 62:109–114
2. Hillier SL, Hollohan V (2007) Vestibular rehabilitation for unilateral peripheral vestibular dysfunction. Cochrane Database Syst Rev 4:CD005397
3. Tee LH, Chee NW (2005) Vestibular rehabilitation therapy for the dizzy patient. Ann Acad Med Singap 34:289–294
4. Barresi M, Bruschini L, Li Volsi G, Manzoni D (2005) Effects of betahistine on the spatiotemporal response properties of vestibulospinal neurons to labyrinthine volleys. Eur J Pharmacol 515:73–82
5. Tighilet B, Trottier S, Lacour M (2005) Dose- and duration-dependent effects of betahistine dihydrochloride treatment on histamine turnover in the cat. Eur J Pharmacol 523:54–63
6. Claes J, Van de Heyning PH (2000) A review of medical treatment for Ménière's disease. Acta Otolaryngol Suppl 544:34–39
7. Mira E, Guidetti G, Ghilardi L, Fattori B, Malannino N, Maiolino L, Mora R, Ottoboni S, Pagnini P, Leprini M, Pallestrini E, Passali D, Nuti D, Russolo M, Tirelli G, Simoncelli C, Brizi S, Vicini C, Frasconi P (2003) Betahistine dihydrochloride in the treatment of peripheral vestibular vertigo. Eur Arch Otorhinolaryngol 260:73–77
8. Colletti V (2000) Medical treatment in Ménière's disease: avoiding vestibular neurectomy and facilitating postoperative compensation. Acta Otolaryngol Suppl 544:27–33
9. Jongkees LB, Maas JP, Philipszoon AJ (1962) Clinical nystagmography: a detailed study of electro-nystagmography in 341 patients with vertigo. Pract Otorhinolaryngol 24:65–93
10. Jacobson GP, Newman CW (1990) The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg 116:424–427
11. Wrisley DM, Walker ML, Echternach JL, Strasnick B (2003) Reliability of the Dynamic Gait Index in people with vestibular disorders. Arch Phys Med Rehabil 84:1528–1533
12. Whitney SL, Hudak MT, Marchetti GF (2000) The Dynamic Gait Index relates to self-reported fall history in individuals with vestibular dysfunction. J Vestib Res 10:99–105
13. Kohen-Raz R (1991) Application of tetra-ataxiametric posturography in clinical and developmental diagnosis. Percept Mot Skills 73:635–656
14. Turner M (1998) Evaluation of the Tetrax Interactive Balance System and Equitest Using Normal Subjects. Faculty of Engineering

and Applied Science Institute of Sound and Vibration Research, University of Southampton, Southhampton
15. Albera R, Ciuffolotti R, Di Cicco M, De Benedittis G, Grazioli I, Melzi G, Mira E, Pallestrini E, Passali D, Serra A, Vicini C (2003) Double-blind, randomized, multicenter study comparing the effect of betahistine and flunarizine on the dizziness handicap in patients with recurrent vestibular vertigo. Acta Otolaryngol 123:588–593
16. Topuz O, Topuz B, Ardiç FN, Sarhuş M, Ogmen G, Ardiç F (2004) Efficacy of vestibular rehabilitation on chronic unilateral vestibular dysfunction. Clin Rehabil 18:76–83
17. Cohen HS, Kimball KT (2003) Increased independence and decreased vertigo after vestibular rehabilitation. Otolaryngol Head Neck Surg 128:60–70
18. Meli A, Zimatore G, Badaracco C, De Angelis E, Tufarelli D (2006) Vestibular rehabilitation and 6-month follow-up using objective and subjective measures. Acta Otolaryngol 126:259–266
19. Yardley L, Donovan-Hall M, Smith HE, Walsh BM, Mullee M, Bronstein AM (2004) Effectiveness of primary care-based vestibular rehabilitation for chronic dizziness. Ann Intern Med 141:598–605
20. Whitney SL, Marchetti GF, Schade A, Wrisley DM (2004) The sensitivity and specificity of the Timed "Up & Go" and the Dynamic Gait Index for self-reported falls in persons with vestibular disorders. J Vestib Res 14:397–409
21. Kammerlind AS, Ledin TE, Odkvist LM, Skargren EI (2005) Effects of home training and additional physical therapy on recovery after acute unilateral vestibular loss—a randomized study. Clin Rehabil 19:54–62
22. Cohen HS, Kimball KT (2004) Decreased ataxia and improved balance after vestibular rehabilitation. Otolaryngol Head Neck Surg 130:418–425
23. Kammerlind AS, Ledin TE, Odkvist LM, Skargren EI (2006) Influence of asymmetry of vestibular caloric response and age on balance and perceived symptoms after acute unilateral vestibular loss. Clin Rehabil 20:142–148
24. Horak FB, Jones-Rycewicz C, Black FO, Shumway-Cook A (1992) Effects of vestibular rehabilitation on dizziness and imbalance. Otolaryngol Head Neck Surg 106:175–180
25. Strupp M, Arbusow V, Maag KP, Gall C, Brandt T (1998) Vestibular exercises improve central vestibulospinal compensation after vestibular neuritis. Neurology 51:838–844
26. Lacour M, van de Heyning PH, Novotny M, Tighilet B (2007) Betahistine in the treatment of Ménière's disease. Neuropsychiatr Dis Treat 4:441–453
27. Strupp M, Hupert D, Frenzel C, Wagner J, Hahn A, Jahn K, Zingler VC, Mansmann U, Brandt T (2008) Long-term prophylactic treatment of attacks of vertigo in Menière's disease—comparison of a high with a low dosage of betahistine in an open trial. Acta Otolaryngol 128:520–524
28. Allum JH, Keshner EA, Honegger F, Pfaltz CR (1988) Indicators of the influence a peripheral vestibular deficit has on vestibulo-spinal reflex responses controlling postural stability. Acta Otolaryngol 106:252–263