International Tinnitus Journal. 2010;16(1):32-6.

Effect of treatment with betahistine dihydrochloride on the postural stability in patients with different duration of benign paroxysmal positional vertigo

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Abstract

The effect of betahistine dihydrochloride on the postural stability after repositioning Epley's maneuver (EM) in patients with BPPV was evaluated by static posturography in open and closed eyes conditions. Ninety patients were divided into four groups by duration (less and above 60 days of BPPV) and by treatment (with and without treatment with betahistine). The investigation was made one hour after the positive Dix-Hallpike test, 10 and 20 days after the treatment with EM. "Sway velocity" (SV) was calculated to evaluate postural stability. The results show dependence between efficacy of treatment with betahistine applied after EM and duration of BPPV. Betahistine normalized postural stability of patients with duration of BPPV less than 60 days after 10 days of treatment and had less effect on patients with duration of BPPV above 60 days. We assume that after removing the otoconia betahistine plays an important role for improving blood flow in the inner ear. The short presence of otoconia didn't damage sensory receptor, and restoring the normal function of motion-sensitive hairs cells and stabilizing the posture was observed.

Keywords: Paroxysmal, vertigo, BPPV, postural, betahistine.

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Acknowledgments: The study was supported by the National Fund for Scientific Research, Grants #TN 1522

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common cause for peripheral vestibular vertigo. The onset age of the disorder occurs mostly between the age of 50 to 70 years. BPPV is characterized by brief repeated episodes of mild to intense dizziness provoked by specific changes in the position of the head, and accompanied by imbalance, and nausea[1,2]. The most common hypothesis for the BPPV is the presence of small crystals of calcium carbonate, named 'otoconia', derived from the utricular and saccular macula in the semicircular canal. This particle cause a change of the endolymph flow in the semicircular canal and thus leads to abnormal excitability of vestibular receptors. Posterior semicircular canal is affected in approximately 85 to 95 percent of BPPV patients[3]. Most of the patients complain of loss of equilibrium and unstable gait during and between the paroxysmal vertigo attacks. BPPV is diagnosed from patient history (feeling of vertigo with sudden changes in positions) and by performing the classic diagnostic maneuver of Dix-Hallpike and a clinical practice guideline criteria proposed by *Bhattacharyya* et al.[2,4]. The test involves a reorientation of the head to align the posterior canal with the direction of gravity. During a movement in the vertical plane, the otoconia shifts and affects the motion-sensitive receptors situated in the semicircular canal. This leads to a typical nystagmus and positional vertigo. The principal therapy of BPPV is the removal of the otoconias by physical treatment with liberating maneuvers[5,6] or Brandt-Daroff exercises[7]. That is a noninvasive procedure for repositioning of the head, clearing of the crystals out of the canal and depositing them back into the part of the inner ear where they belong.

The pharmacological therapies applied to BPPV patients are directed to suppress the vertigo. The most commonly used are benzodiazepines and antihistamines. These medications often have multiple actions. In addition they can modify the intensity of symptoms or affect the underlying disease process. Vestibular suppressants and antiemetic drugs are still the basis of the acute treatment of vertigo, but are not effective for BPPV[8-10]. Betahistine dihydrochloride is a histamine analogue which was introduced in the treatment of vertigo, motion sickness and various peripheral and central vestibular disorders of different origins[11-13]. It has a very strong affinity for histamine H_3 receptors and a weak affinity for histamine H_1 receptors. Betahistine seems to dilate the blood vessels within the inner ear, improve the microcirculation of the labyrinth, relieve pressure from endolymphatic fluid and act on the smooth muscle[12-15]. Betahistine dihydrochloride is effective in reducing the number of vertigo attacks, their intensity score and their duration after 30-days treatment of BPPV with dosage of 16 mg twice a day[16]. In another study of patients with BPPV the application of a Betahistine dihydrochloride two weeks after a physical treatment showed better results for restoring vestibular function compared to the only physical treatment group[17]. Several reports have suggested that repositioning maneuver was effective for treatment the BPPV, but the symptoms relief and the postural stability was restored in different degree after physical treatment[6,18,19,20]. Patients with BPPV showed impaired equilibrium and significantly higher postural sway parameters as sway velocity and amplitude, than healthy subjects when the visual and proprioceptive inputs were changed[21,22]. After the repositioning Epley maneuver the positioning vertigo and the typical nystagmus of patients with BPPV of the posterior semicircular canal (BPPV-PSC) disappeared, but the postural instability remained[18,23-25]. Our earlier results showed that the postural maintenance in BPPV-PSC patients depended on the disease duration. One week after the Epley maneuver patients with duration of BPPV symptoms less than 60 days after the first attack do better in postural stability than those patients with more than 60 days duration of BPPV however without reaching normal values[25].

The aim of the current study was to determine the effect of treatment with Betahistine dihydrochloride on the postural stability after repositioning Epley's maneuver in patients with different duration of BPPV – PSC, evaluated by static posturography.

PATIENTS AND METHODS

Participants

Ninety patients with "idiopathic" BPPV, aged between 50 and 64 years (mean 55.8 with a standard deviation (SD ±6.5) and 20 controls of healthy subjects (mean age 54.2 ± 7.9 years) without any history of vestibular disorders were investigated. The diagnosis BPPV - PSC was based on the patient's complaints of presence of episodes of transient attacks of rotational vertigo induced by sudden head movements without auditory symptoms and the positive Dix-Hallpike positioning test (inducing the typical torsional transient positioning nystagmus)[2,4].

All participants did not take antivertigo drugs, antihistamines, calcium antagonists, antiaggregants, thiazide diuretics, corticosteroids and benzodiazepines. Patients with head injury, ear infection, vestibular neuritis or Ménière's disease were excluded from the investigation. All patients were instructed to restrain from alcohol use and any kind of medication for 24 hours before testing. All participants signed an informed consent form following approval by the Ethic Committee of the Institute of Neurobiology, Sofia, in conformity with the Declaration of Helsinki.

The patients with BPPV – PSC were divided into four groups depending on the duration of symptoms of vertigo and of treatment (Table 1).

Table 1. Groups of patients with BPPV of the posterior semicircular canal

Group	Duration of the symptoms of vertigo	Drug
1	< 60 day after the first attack of postural vertigo (n= 25; aged 54.4±4.6)	-
2	< 60 day (n= 23; aged 56.1±2.9)	Betahistine dihydrochloride
3	>60 day (n=22; aged 57.3±6.2)	-
4	>60 day (n=20; aged 55.5±7.1)	Betahistine dihydrochloride

Apparatus

A static posturographic system designed in the Institute of Neurobiology, Sofia, was used to measure the balance ability[26,27]. Briefly, the displacements of foot pressure center in both medio-lateral (ML) and anterior-posterior (AP) directions were registered. Two analogue signals were digitized with a sampling interval of 10 ms and filtered with a digital Hamming low-pass filter with cut-off frequency of 10 Hz in order to remove the high frequency noise and discretization error[29].

Treatment

For removal of the otoconias from posterior semicircular canal we used the repositioning maneuver described by Epley[6]. The maneuver was performed several times until the vertigo and the nystagmus disappeared - the negative Dix-Hallpike positioning test. After a successful physical treatment, patients were requested to stick to postural restrictions for some days, e.g., to avoid sudden head movements in the vertical plane and they were asked to sleep in a semi-seated position.

Betahistine dihydrochloride was administered 20 days after the physical treatment with the Epley's repositional maneuver (EM) at a daily dose of 48 mg (16 mg tree times or 24 mg two times a day, after meals, at 8 a.m., 12 a.m. and 8 p.m. or at 8 a.m. and 8 p.m.). The pharmacological treatment patients groups were randomly selected (groups 2 and 4).

Procedure

Postural stability of patients was evaluated before treatment, one hour after the negative Dix-Hallpike test, 10 and 20 days after the physical treatment with the EM. Static balance was measured in two conditions: (1) stance on the stable platform with open eyes (OE), targeting at a distance of 2 m at the eye's plane and (2) with closed eyes (CE). The participants were informed to stand upright on the platform with separated heels of 3 cm distance and feet splayed at an angle of 30°.

Data analysis

The postural stability was evaluated by means of "Sway velocity" (SV) calculated for each subject and each experimental condition. The differences between SV of two patients groups as well as between SV of patients and SV of healthy control were analyzed with Mann-Whitney test. A possible effect of Betahistine dihydrochloride on the postural stability of two BPPV patients groups was evaluated by repeated-measures ANOVA with four factors. The between-subject factor "drug" with two levels (with Betahistine dihydrochloride and without Betahistine dihydrochloride) and three within subject factors: "time" with three levels (1 hour, 10 day, 20 day after treatment), ''direction'' (ML and AP) and ''condition'' (open and closed eyes). Bonferroni's tests were applied where appropriate as post-hoc analysis. The statistical analyses were performed with Statistica 7.0 (Stat Soft Inc., USA, 2004), and statistical significance was set as $P<0.05$.

RESULTS

Before treatment with LM the SV of postural sways in two patient groups are significantly higher than that in healthy subjects ($P < 0.001$). (Figure.1). With eyes open in both directions (ML and AP) BPPV patients with less than 60 days duration showed significantly greater SV than those with duration over 60 days ($P < 0.001$). In eyes closed conditions, this group of patients demonstrated decreasing of SV significantly in AP direction ($P < 0.001$). In the other group of patients (duration >60 days) the deprivation of vision did not change significantly the SV of postural sways (Figure 1).

The changes of patients SV in comparison with SV of healthy subjects (dotted line) is presented in Figure 2 (a-d). All patients demonstrated significantly higher SV in the first hour after EM. Twenty days after the physical treatment without drug therapy the typical nystagmus and vertigo disappear in 71% of the patients with BPPV – PSC and a negative Dix-Hallpike test was observed, but in 96% of them the sense of postural instability persisted. The SV decreased but stayed significantly higher than that in healthy subjects, most expressed in patients group above 60 days duration of BPPV (Figure 2 a-d). ANOVA

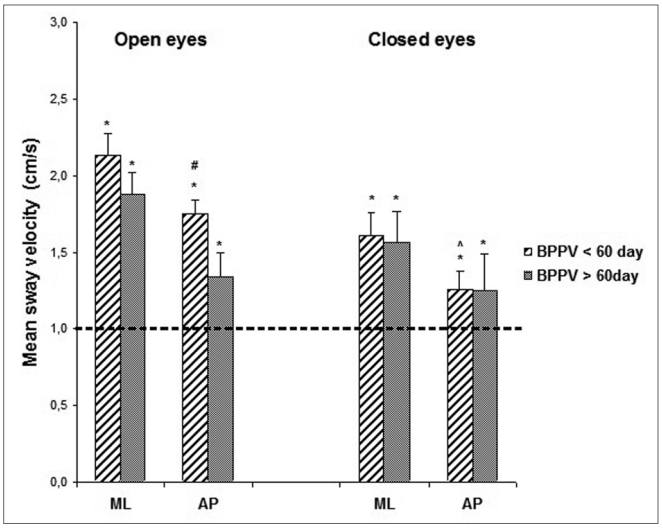

Figure 1. Changes of mean sway velocity (SV) for two groups of BPPV-PSC patients (less than 60 days and more than 60 days after the first vertigo attack) compared to SV of healthy subjects ($SV_{patient}$ / $SV_{healthy}$) in medio-lateral (ML) and anterior-posterior (AP) directions, during quiet upright stance with open and closed eyes before course of treatment. The data are presented in relative values ± SD. A broken line shows level of the healthy control. Significant difference of Mann-Whitney test, $p<0.01$ is noted by: * significant difference between healthy subjects and patients; # - between two patient groups; ^ - between open and closed eyes conditions.

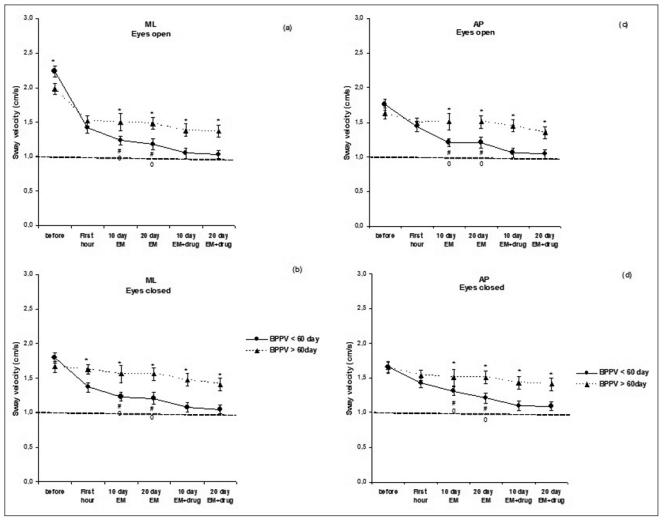

Figure 2. Time related changes of mean sway velocity (SV) after applied Epley maneuver for two groups of BPPV-PSC patients (less than 60 days and above 60 days after the first vertigo attack) as against to SV of healthy subjects ($SV_{patient}$ / $SV_{healthy}$) with and without treatment with Betahistine dihydrochloride. The changes of SV were presented as follows: (a) and (b) the SV in medio-lateral (ML) direction, (c) and (d) the SV in anterior-posterior (AP) direction, (a) and (c) on open eyes condition and (b) and (d) on closed eyes condition. The data are presented in relative values ± SD. A broken line shows level of the healthy control. Significant difference Bonferroni's post hoc test, $p<0.01$ is noted by: * significant difference between two patient groups; # - 10 days treatment Betahistine dihydrochloride and without treatment; with ; 0 - 20 days treatment Betahistine dihydrochloride and without treatment.

showed significant effects of factor "Drug" ($F_{1,45}$= 11.04, $p<0.001$) and factor "Time" ($F_{1,45}$= 9.28, $p<0.001$) for group of patients with BPPV duration less than 60 days. Therapy with Betahistine dihydrochloride helped to restore the postural stability of this patients group. Ten days after treatment the SV was normalized and did not differ from that in healthy subjects (Figure 2 a-d). For other patients group (>60 days) the effects of all factors were not statistically significant. Ten day after pharmacological treatment the SV didn't change significantly than that in the first hour after EM. In the eyes open condition the SV of both patient groups decreased significantly ($P<0.05$) in the first hour after physical treatment compared with SV before treatment in both direction (ML and AP) (Figure 2 a, c). The reduction of vision (eyes closed) decreased the SV of patients with duration of BPPV less than 60 days only and a significant difference between two groups was observed (Figure 2 b, d). This patient group showed the significant difference between SV 10 and 20 days after EM and SV 10 and 20 days after EM and therapy with Betahistine dihydrochloride, especially in condition with eyes open (Figure 2 a, c). For other patients group (>60 days) a difference between values of SV with and without pharmacological treatment no observed.

DISCUSSION

The beneficial effect of the most popular liberatory maneuver of Semont[5], Epley maneuver[6] or Brandt-Daroff exercises[7] for treating Benign Paroxysmal Postural Vertigo is well known. The therapy with Betahistine dihydrochloride used after applying Semont liberatory maneuver and Brandt-Daroff exercises demonstrated the better results evaluated by Epley criteria[6] 14 days after treatment, independently of age of patients[17]. In our previous study we determined the difference in the process of recovery after treatment with Eplay maneuver in patients with duration of BPPV – PSC less and more than 60 days[25]. The patients with duration of BPPV – PSC less than 60 days improved their postural stability, while posture of other patients (>60 days) was not influenced significantly by EM. The present study shows the beneficial effect of Betahistine dihydrochloride on the postural stability parameters when administered 20 days after physical treatment with Eplay maneuver. Betahistine dihydrochloride normalized faster (at the 10th day of treatment) the postural stability of the patients with duration of BPPV less than 60 days and had less effect (statistically insignificant) on patients with duration of BPPV more than 60 days. The Epley maneuver removed otoconias in the affected semicircular canal and get them into a different part of the ear where they will be less likely to cause vestibular disturbance. We suggest that after removing the otoconias the acute sensory conflict between the vestibular system and the vision probably

diminished. This leads to disappearance of nystagmus, to restoration of the normal action of vestibulo-ocular reflex and to decrease of postural instability. We assume that the long presence of otoconias in the lumen or in the cupula of the semicircular canal permanently damaged the normal function of motion-sensitive hairs cells in the inner ear, because of that the therapy with EM and with Betahistine dihydrochloride 20 days after EM have a weak effect on the postural stability of patients with duration of BPPV above 60 days. We suggest that a long lasting abnormality in the peripheral vestibular system activates some adaptation processes in central nervous system connected with mechanisms participating in the maintenance of posture and take a form of new pattern of postural stability in patients with duration of BPPV above 60 days, and the treatment with Betahistine dihydrochloride after EM is not effective. For the other group of patients (less than 60 day duration of BPPV) the treatment with Betahistine dihydrochloride after EM is effective and ten days after treatment postural stability of patients was normalized. We assume that Betahistine dihydrochloride accelerates the recovery of function of vestibular system, by improving blood flow in the inner ear and normalization of the function of motion-sensitive hair cells is faster.

In conclusion, the results of this study show the dependence between efficacy of treatment with Betahistine dihydrochloride applied after EM and duration of BPPV. The treatment with Betahistine dihydrochloride at a daily dose of 48 mg had beneficial effect on the 10th day after EM in BPPV with duration of disease less than 60 days of the first symptom of vertigo.

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