Original Article

Negative Effects of Betahistine on Recovery of Brainstem Oculo-motor Integration after Vestibular Rehabilitation of Benign Paroxysmal Positional Vertigo (BPPV) Patients

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ABSTRACT

Objectives: To evaluate effects of betahistine, an antihistamine, on recovery of vestibulo-ocular functions in patients with BPPV after vestibular rehabilitation (VR) therapy.
Study design: Retrospective study.
Setting: Vestibular Rehabilitation Clinic, Division of Physical Therapy, Department of Rehabilitation Medicine, Trang Hospital, Ministry of Public Health, Trang, Thailand.
Subjects: Patients with BPPV who were referred for VR; assessed with global BPPV symptom severity visual analog scale (VAS), Dix-Hallpike test (DHT), roll test (RT), head thrust test (HTT), and gaze evoked nystagmus test (GENT) before once a week of VR and one week after completing three sessions; and performed a daily home-based VR exercises (VREs) for 3 or 4 weeks.
Methods: Data of all assessments mentioned above were extracted from case record forms, and divided into two groups: those taking betahistine (81 patients) and those not taking any antihistamine (84 patients). Data from the two groups were compared and analyzed.
Results: After completing all three sessions of VR therapy, every assessment score significantly decreased ($p < 0.001$) in both groups. Before the first therapy, mean VAS scores (SD) of the betahistine and the no antihistamine groups were 9.12 (0.73) and 9.22 (0.70), respectively ($p = 0.38$); in the second assessment, were 4.17 (0.86) and 5.15 (1.21) respectively ($p < 0.001$); in the third assessment, were 3.53 (0.63) and 2.57 (3.32) ($p < 0.001$), and in the last assessment, were 1.84 (0.64) and 0.03 (0.18) respectively ($p < 0.001$). Regarding the baseline assessment of the DHT, the RT, the GENT, and the HTT, there were no significant differences ($p > 0.01$) between the two groups. However, in all subsequent assessments there were significant differences in the GENT and the HTT scores between the two groups, favoring to the no antihistamine group over the betahistine group ($p < 0.01$). The DHT and the RT scores did not reach significant differences between the two groups in the last two weeks of assessments.
Conclusion: Once a week of VR therapy and a daily home-based VREs for three or four weeks significantly decreased the BPPV symptoms. Recovery of vestibulo-ocular reflex function seemed less and not as complete in those taking betahistine.

Keywords: vestibular rehabilitation, physical therapy, benign paroxysmal positional vertigo, vestibulo-ocular reflex, betahistine

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Introduction

Benign paroxysmal positional vertigo (BPPV) is the most common cause of peripheral vertigo.[1] It is caused by displaced calcium carbonate particles called otoliths (or otoconia) inside the semicircular canals of the vestibular labyrinth of the inner ear.[2] Factors found to be correlated with increased risk of having BPPV attack are the following: elderly age,[3] vestibular artery flow impairment,[4] and cardiovascular risk factors such as diabetes, dyslipidemia, hypertension, etc.[5] Mechanical shock such as that produced during dental surgery could possibly be a precipitating cause.[6]

BPPV is clinically diagnosed by observing nystagmus and subjective vertigo during the so-called BPPV provocation tests such as Dix-Hallpike test (DHT), head thrust test (HTT), etc.[7] Each of these tests mobilizes the otoliths in one of the three semicircular canals, through a specific head movement. It is important to rule out serious diseases which mimic symptoms of BPPV such as stroke, transient ischemic attack, and posterior fossa brain pathology.[8]

Impact of BPPV ranges from mild annoyance to highly debilitating. It affects safety and falling risk. Two most commonly recommended rehabilitation methods are canalith repositioning procedure (CRP)[9] and vestibular rehabilitation exercises (VREs). Combination of CRP and VREs are expected to be more effective that either one alone,[10] especially in the long-term reduction of BPPV severity scores.[11]

Histamine receptor antagonists are the most commonly prescribed medication for BPPV,[12] but the mechanisms which this group of medication alleviates BPPV related symptoms are still unclear. In the central nervous system, the main histamine producer is within tuberomammillary nucleus which projects not only to vestibular nuclei but also thalamus,

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cortical areas, and others.[13] Recent studies suggested the role of histamine in modulation of vestibular nuclei neurotransmission, central synaptic plasticity, cognitive functions, and stress response.[13]

Anti-histaminergic compounds may probably facilitate vestibular compensation by assisting in the reduction of sensitivity to abnormal peripheral afferent.[14] For example, decreased gain of the horizontal which was reported after systemic treatment with histamine 3 (H3) reverse agonist thioperamide, as well as betahistine, another H3 receptor antagonist. If that is the case, even though this anti-histaminergic could decrease symptoms of BPPV, we suspected that such medication might impede a full recovery of vestibular function through VREs.

At Trang Hospital patients with BPPV were treated by otolaryngologist who prescribed medication and referred them for VR therapy. A BPPV rehabilitation clinic was established in 2007. Since then, there has been an average of 140 BPPV patients received VR therapy per year. Before therapy, each patient was assessed with the global BPPV symptoms (vertigo, dizziness and balance problem) severity assessment using a VAS (visual analog scale) diagram and a set of BPPV provocation test and vestibulo-ocular function tests as follows: the Dix-Hallpike test (DHT), the roll test (RT), the head thrust test (HTT) and the gaze evoked nystagmus test (GENT) (Appendix 1). All were carried out and recorded by physical therapist, the first investigator. The first assessment took place immediately befoe the beginning of the first therapy session. The second and the third assessments took place just before each weekly therapy session. The last assessment took place one week after the third therapy session. All assessments were carried out by the first investigator. According to our VR therapy (Appendix 2), the patients underwent one or another CRP technique, depending on an identified location of otolith in the semicircular canal. Then, they were guided through a series of VREs[15] which consisted of vestibulo-|ocular reflex (VOR) training with fixed target, VOR training with moving target and a side lying exercise (Brandt and Daroff exercise). All exercises were demonstrated by physical therapist, and the patients were informed to complete 4 sets of 3 repetitions of each exercise per day at home. All data of the assessments and the therapy were recorded in the case record forms.

In our previous retrospective pilot study, we have found that patients who took antihistamine medication showed less improvement of BPPV symptoms as measured with VAS. Betahistine has been the most commonly antihistamine prescribed for the treatment of BPPV symptoms at Trang Hospital.[16] To our best knowledge, there had never been a study focusing on the effect of betahistine on the recovery of these VOR related oculo-motor functions in those with BPPV. Therefore, the objective of this study was to investigate whether betahistine had a negative effect on recovery of brainstem VOR integration after completing three sessions of VR therapy and a daily home-based VREs for three weeks.

Methods

After obtaining the approval from the Trang Hospital Ethical Review Board (certification letter number 030/10-2562) the research was conducted as per the following details.

Participants

Data from medical records and case record forms (CRFs) of all patients who were referred to the BPPV clinic, the Division of Physical Therapy, for vestibular rehabilitation therapy, during October 2017 until August 2018 were retrospectively reviewed and analyzed.

Based on our pilot study which showed standard deviation of 7.99 and defining mean difference of 6.4, a sample size was calculated with software PS sample size: online available: www.Power-Analysis.com. As the result, 38 patients from each group (a group of taking betahistine and a group of not taking any antihistamine) in order to achieve statistical power of 0.8 and statistical significance at $p < 0.01$

Study protocol

From a total 525 medical records reviewed, 360 patients were excluded: 56 cases took other antihistamine medicine other than betahistine and 304 had incomplete data making them useless for analysis.

The BPPV assessment and the VR therapy case record forms (CRFs) of the recruited patients were selected and divided into two groups, those taking betahistine and those not taking any antihistamine. Then, the relevant data of the BPPV assessments/tests (Annex 1) before, during and after the therapy were retrospectively reviewed and extracted for analysis.

Statistical analysis

Demographic data were analyzed with descriptive statistic. Because the distribution of scores was not normally distributed, a non-parametric statistic test was used. Changes of BPPV tests scores across the course of VR therapy for each group were calculated with Friedman test. The difference of each assessment score between the betahistine and the no antihistamine groups were analyzed using Mann-Whitney test. Statistic calculations were done using MedCalc Statistical Software version 19.1 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org; 2019)

Results

Of the 165 patients (37 males and 128 females) who completed the VR therapy and received all four BPPV assessments sessions necessary for analysis, there were 81 patients in the betahistine group and 84 in the no antihistamine group. Mean age was 58.26 (SD 13.15) years. Mean duration of BPPV symptoms was 34.71 (SD 34.05) days prior to the first visit. Table 1 shows comparisons of demographic data of the patients in the betahistine and the no antihistamine groups.

Table 1. Comparisons of demographic data of the patients in the betahistine and the no antihistamine groups

	Betahistine (n=81)	No antihistamine (n=84)
Gender[1]		
- Male	20 (24.7)	17 (20.2)
- Female	61 (75.3)	67 (79.8)
Age[2]	55.58 (13.14)	60.85 (12.81)
Duration of sickness[2] (days)	30.44 (32.64)	38.86 (34.69)
Comorbidities		
- Dyslipidemia (DLP)	5	6
- Diabetes mellitus (DM)	0	6
- Hypertension (HT)	5	8
- HT and DLP	8	9
- HT, DM, and DLP	1	12
- Others	8	10
- No comorbidities	54	33

[1]Number (%), [2]mean (SD)

BPPV, benign paroxysmal positional vertigo

Table 2. Data of median (IQR) of the scores from the four assessments sessions

Test		Betahistine		No antihistamine		*p*-value[b]
		Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]	
BPPV symptoms severity VAS	Pre	9 (9.00 to 10.00)		9 (9.00 to 10.00)		0.371
	Post 1	4 (3.00 to 5.00)	< 0.001	5 (4.00 to 6.00)	< 0.001	0.001
	Post 2	4 (3.00 to 4.00)		2 (2.00 to 3.00)		< 0.001
	Post 3	2 (1.00 to 2.00)		0.00 (0.00 to 0.00)		< 0.001
Dix-Hallpike test (DHT)	Pre	1 (1.00 to 1.00)		0.238 (0.00 to 0.00)		0.004
	Post 1	1 (0.00 to 1.00)	< 0.001	0.107 (0.00 to 0.00)	< 0.001	0.002
	Post 2	0.222 (0.00 to 0.00)		0.035 (0.00 to 0.00)		0.087
	Post 3	0 (0.00 to 0.00)		0.035 (0.00 to 0.00)		0.087
Roll Test (RT)	Pre	0.074 (0.00 to 0.00)		0.238 (0.00 to 0.00)		0.004
	Post 1	0 (0.00 to 0.00)	< 0.001	0.107 (0.00 to 0.00)	< 0.001	0.002
	Post 2	0 (0.00 to 0.00)		0.035 (0.00 to 0.00)		0.087
	Post 3	0 (0.00 to 0.00)		0.035 (0.00 to 0.00)		0.087
Gaze evoked nystagmus Test (GENT)	Pre	2 (2.00 to 2.00)		2 (1.00 to 2.00)		0.018
	Post 1	2 (2.00 to 2.00)	< 0.001	0 (0.00 to 0.00)	< 0.001	< 0.001
	Post 2	2 (2.00 to 2.00)		0 (0.00 to 0.00)		< 0.001
	Post 3	2 (1.00 to 2.00)		0 (0.00 to 0.00)		< 0.001
Head thrust Test (HTT)	Pre	2 (2.00 to 2.00)		2 (1.00 to 2.00)		0.010
	Post 1	2 (2.00 to 2.00)	< 0.001	0 (0.00 to 0.00)	< 0.001	< 0.001
	Post 2	2 (2.00 to 2.00)		0 (0.00 to 0.00)		< 0.001
	Post 3	2 (1.00 to 2.00)		0 (0.00 to 0.00)		< 0.001

BPPV, benign paroxysmal positional vertigo; VAS, visual analog scale; NT, not testable

Pre, before the first therapy session; post 1, before the second session; post 2, before the third session; and post 3, one week after the third session

[a]Friedman test comparing repeated measurement of the same group over time

[b]Mann-Whitney test comparison between the two groups: the betahistine and the no antihistamine groups

Table 2 shows median (IQR) of the scores from the four assessments sessions (pre - before the first therapy session, post 1 – before the second session, post 2 – before the third session, and post 3 – one week after the third session). There were significant improvements of every assessment score ($p < 0.001$) in both groups. Before the first therapy session, the BPPV symptoms severity VAS score (SD) of the betahistine and the no antihistamine groups, were 9.12 (0.73) and 9.22 (0.70) (p=0.38); however, in the second assessment were 4.17 (0.86) and 5.15 (1.21) ($p < 0.001$); in the third assessment were 3.53 (0.63) and 2.57 (3.32) ($p < 0.001$), and in the last assessment were 1.84 (0.64) and 0.03 (0.18), respectively ($p < 0.001$).

Regarding the DHT, the RT, the GENT and HTT, in the baseline assessment mean scores in the betahistine group were not significantly different from the no antihistamine groups ($p > 0.01$). However, there were significant differences between groups in the GENT and the HTT scores in all subsequent assessments, favoring the no antihistamine group over the betahistine group ($p < 0.01$). However, in the first week assessment, the DHT and the RT scores were significant differences between the two groups, favoring the

no antihistamine group; but in the last two weeks of assessments the between group differences did not reach significant level (see Table 2).

Discussion

This study showed improvements in all assessments of BPPV symptoms after VR therapy, compatible with known facts that BPPV symptoms remit spontaneously with time, and that the CRP and the VREs shorten the recovery time. [10-12] However, the difference between the betahistine group and the no antihistamine group has never been mentioned previously. In the second assessment the VAS was significantly lower in the betahistine group but thereafter the no antihistamine group had instead lower VAS scores, and BPPV symptoms free was found only in the no antihistamine group at the end of the therapy. This suggests that perhaps antihistamine could initially help to alleviate the symptoms but possibly reduce the positive effects of vestibular rehabilitation in the longer run.

When looking at tests that challenge VOR and voluntary gaze control and stabilization such as the GENT and the HTT, the no antihistamine group seemed to have a faster recovery than the betahistine group. Therefore, it is suspected that antihistamine medication may reduce the adaptive response to benefit neurological adaptation. However, such medication may have no significant effect on the sensitivity of provocation test as the DHT and the RT scores in the last two assessment sessions showed no between group differences. This is not surprising because these two tests serve to provoke BPPV symptoms in cases with free moving otolith inside the semicircular canal. But over time the otoliths might have been resorbed and the vestibular organ and nuclei might have developed a lower sensitivity to the remaining bits already.

There were few limitations of this study. Firstly, it was a retrospective study of the VR therapy guideline for BPPV at Trang Hospital which was a part of routine-to-research to improve the management. Although the CRFs were set from the beginning, all the assessments and therapy were carried out by the first investigator only. Other limitations were that patients' compliance to medication (duration and dose of betahistine) and patients' adherence to the home-based VREs, were not controlled or recorded. To prove that betahistine really impedes the vestibulo-ocular functions, one should conduct an assessor-blinded, randomized controlled trial. Indeed, there has been a research proposal published about such a research being planned.[17] Besides, a longer-term follow-up should be carried out so that effects of medication on prevention of recurrence could be studied.

In conclusion, betahistine seems helpful for BPPV symptoms reduction in the first one or two weeks of vestibular rehabilitation therapy. One should consider discontinuation of the medication to promote more effective vestibular rehabilitation as it demonstrated significantly less global symptom reduction, and less recovery of vestibulo-ocular reflex functions, than those not receiving any antihistamine.

Disclosure

Watcharin Tayati and Assistant Prof. Parit Wongphaet declare no conflict of interest of any kind.

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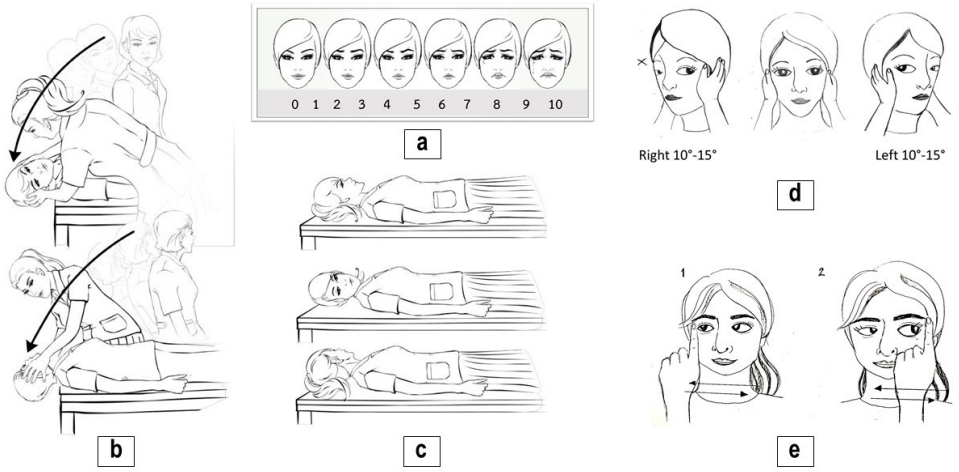
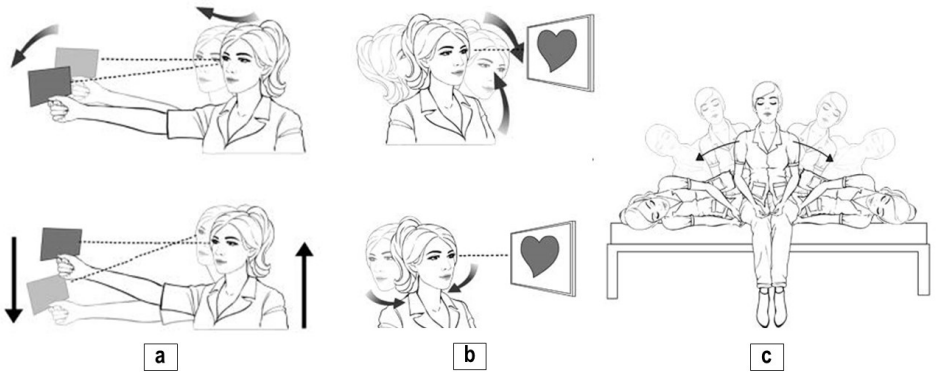
Appendix 1. BPPV assessments



a) Visual analog scale (VAS) diagram for global BPPV symptom severity, b) Dix-Hallpike test (DHT), c) Roll test (RT), d) Head thrust test (HTT), and e) Gaze evoked nystagmus test (GENT)

Visual Analog Scale: VAS score of zero indicates no problem at all and ten means the worst possible imaginable troublesome.
Dix Hall Pike test (DHP): A seated patient with neck turned 45 degree to one side is lowered quickly to a supine position with the neck extended 30 degrees below horizontal. The purpose of this test is to provoke symptom if there is otolith inside the anterior or posterior semicircular canal. (Score of 0,1, or 2 is given for each test when no, one sided, or bilateral nystagmus respectively.)
Roll test (RT): The neck of a supine lying patient is turned to one side, and then to the other side. The purpose of this test is to provoke symptoms if there is otolith inside the horizontal semicircular canal. (Score of 0,1, or 2 is given for each test when no, one sided, or bilateral nystagmus respectively.)
Head thrust test (HTT): A tester instructs a seated patient to fix his/her gaze on a target in front, then quickly rotate the head of the patient to one side about 10-15 degree, and then to another side. (Score of 0,1, or 2 is given for each test when no, one sided, or both eyes lose fixation to the target due to the passively induced quick short head turning respectively.)
Gaze evoked nystagmus test (GENT): A tester asks the seated patient to keep his/her head steady and fixes his/her gaze on a midline visual target which then was moved about 30 degree to one side, and then to another side.(Score of 0,1, or 2 is given for each test when no, one sided, or both eyes lost fixation to the target at any time.)

Appendix 2. Vestibular rehabilitation therapy program



a) Vestibulo-ocular reflex (VOR) training with a moving target, b) VOR training with a fixed target, and c) Side lying exercise (Brandt and Daroff Exercise)

Vestibulo-ocular reflex (VOR) training with a fixed target: starting from a straight sitting position with eyes fixing on a target in front. Then practice turning head back and forth horizontally or vertically while always keep looking at the target. The speed and amplitude of movement should be systematically and carefully increased without provoking a dizziness or vertigo.
Vestibulo-ocular reflex (VOR) training with a moving target: similar with the previous exercise, except that the target is being moved in the opposite direction with head turning. For example, when patient is turning the head from left to right the target is moved from right to left. This exercise aims to normalize influence of VOR on voluntary gaze control.
Side lying exercise (Brandt and Daroff Exercise): This exercise aims to desensitize the semicircular canal to the irritation of the otolith. Starting from a seated position facing the side of a bed then gently reposition into side lying position and remain in the position for 30 seconds.