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Review Article

Expert opinions regarding neuro-microcirculatory, vestibular and labyrinthine dynamics in benign paroxysmal positional vertigo

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ABSTRACT

Benign paroxysmal positional vertigo (BPPV) is a common vestibular disorder and a leading cause of peripheral vertigo in adults. The current treatment with repositioning maneuvers still leaves some residual dizziness in a significant proportion of patients with BPPV. The role of neuro-microcirculatory, vestibular, and labyrinthine dynamics needs to be evaluated. Eighty leading neurologists and otolaryngologists from across India participated in advisory board meetings to debate on altered neuro-microcirculatory, vestibular, and labyrinthine dynamics in BPPV. Betahistine when used in conjunction with Epley maneuver was considered to be a safe treatment. Betahistine can be used as monotherapy in patients with BPPV who are deemed unfit to undergo canalolith repositioning maneuvers. Betahistine provides short-term relief from acute symptoms associated with BPPV by improving microcirculation in the labyrinth and improves vestibular compensation, thereby providing long-term benefit. Betahistine also improves outcomes in combination with canalolith repositioning maneuvers. Experts unanimously agreed upon the role of betahistine in providing better vestibular health and in-turn, recovery from vertigo.

Keywords: Betahistine, Epley maneuver, Dizziness, Vestibular compensation

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV), a common vestibular disorder, is a leading cause of peripheral vertigo in adults. The reported prevalence of BPPV is about 10.7-64 per 1,00,000 people, and BPPV has a lifetime prevalence of 2.4%.[1] A multicenter study conducted in India reported that BPPV accounted for a considerable percentage of the overall burden of vertigo. It was reported that peripheral causes were predominant in majority of patients (74%), with BPPV being the most frequent (68%).[2] Idiopathic BPPV is commonly observed in patients in the age group of 50 to 70 years.[3] A higher prevalence is observed in elderly patients. BPPV may be idiopathic, but may occur after head trauma and in association with other vestibular disorders such as Meniere's disease, vestibular neuritis, and vascular disorders.[4] BPPV is typified by the sudden onset of brief episodes of severe vertigo, persisting for a few seconds to minutes, but there are no auditory symptoms. Vertigo is triggered by change in head position such as lying down/turning in bed, bending over and neck extension. Posterior canal BPPV is the most common (85.2%) type of vertigo, while horizontal canal BPPV is less common (13.6%). Patients with BPPV are often very anxious and may not be amenable to have their symptoms provoked with a Dix-Hallpike maneuver.[5] Dizziness increases the risk of falls or fear of falling, disturbs daily life, and restricts social activities, which eventually having an adverse effect on the patient's quality of life.[5-7]

The current treatment with repositioning maneuvers still leaves residual dizziness in a proportion of patients with BPPV.[1] This residual dizziness may be attributed to persistent debris in the canal, otolith dysfunction presence of vestibular disease resulting in inadequate central adaptation, autonomic dysfunction, or presence of persistent postural-perceptual dizziness.[1,5]

The way to address this dilemma with the currently available drugs needs to be investigated so that treatment outcomes can be improved significantly.

There is a paucity of data and a divided belief regarding use of drugs such as betahistine for the management of BPPV. Hence, there was a need to have an opinion-based consensus on the role of betahistine in patients with BPPV treated with or without repositioning maneuvers.

A group of 80 experts (neurologists and otolaryngologists) from across India participated in virtual advisory board meetings to debate on altered neuro-microcirculatory, vestibular, and labyrinthine dynamics in BPPV and frame recommendations for current practice and management in India. Key concepts regarding the role of neuro-micro-circulatory, vestibular and labyrinthine dynamics in BPPV were discussed with the panel members. A literature search using PubMed was conducted using the key words, BPPV and residual dizziness. Recommendations for the management of BPPV patients with or without repositioning maneuvers were made based on literature evidence and expert consensus.

REPOSITIONING MANEUVERS IN BPPV

Currently, there are two hypotheses proposed to explain BPPV pathogenesis namely cupulolithiasis and canalolithiasis. According to the more popular canalolithiasis hypothesis, BPPV is caused by free otoconia which consist of calcite, a mixture of calcium and carbonates. These otoconia dislodge from the utricular macula and enter the semicircular canal.[8] This free-floating debris in the canal moves together with the endolymph causing displacement of the cupula away from the ampulla, initiating a nystagmus. The posterior semi-circular canal is most affected, followed by the horizontal canal. Cupulolithiasis alludes to crystals that have become stuck or attached to the cupula in one of the three semi-circular canals, usually the posterior canal. BPPV caused by cupulolithiasis may be responsible for the more persistent cases of BPPV that do not respond well to positioning treatments. Neither the canalolithiasis nor the cupulolithiasis theories address why the crystals become dislodged. There are several theories about the conditions that can cause crystals to become dislodged and enter the semi-circular canals.[8]

Consensus statement 1

Clinicians must diagnose posterior semi-circular canal BPPV in patients with vertigo associated with torsional, up-beating nystagmus using the Dix Hallpike maneuver, which is performed by bringing the patient from an upright to supine position with the head turned 45° to one side and the neck extended 20° with the affected ear down. The maneuver should be repeated with the opposite ear down if the initial maneuver is negative.

If the patient has a history compatible with BPPV, and the Dix Hallpike test exhibits horizontal or no nystagmus, the clinician should perform supine roll test to assess for lateral semicircular canal BPPV.

Treatment for BPPV consists of the canalith repositioning procedure (CRP) that facilitates movement of the displaced particles from the affected canal to their original location. CRP have been the mainstay therapy for BPPV. Posterior canal BPPV is treated by performing the Epley maneuver or Semont maneuver.[9] For horizontal canal BPPV, barbecue rotation or the Gufoni maneuver is effective. These particle-repositioning maneuvers may help clear the debris from the posterior semi-circular canal and move them into the utricle. However, BPPV has a high rate of recurrence, and in approximately 50% of patients, symptoms will recur within 40 months after treatment.[5]

Consensus statement 2

Clinicians must treat patients with posterior canal BPPV with a canalith repositioning procedure.

Clinicians should not recommend post procedural postural restrictions after canalith repositioning procedure for posterior canal BPPV.

RESIDUAL DIZZINESS AFTER REPOSITIONING MANEUVERS IN BPPV

Although CRP can offer rapid relief from vertigo in patients with BPPV, residual symptoms may remain even after the disappearance of typical vertigo and nystagmus. Some patients report imbalance without positional vertigo for a certain period after CRP, which is termed as residual dizziness (RD). RD presents as non-specific sensation of unsteadiness, light headedness, disorientation, fogginess, or drowsiness. The incidence of RD ranges from 29.6% to 76.9%, and its duration ranges from a few days to several months resulting in adverse physical and psychological consequences. RD is a common condition among the elderly. RD is associated with significant anxiety, disabling dizziness even after the resolution of the acute vertigo and in the absence of otolithic or vestibular dysfunction.[1]

The cause of RD remains unknown, but it has been proposed that otolith dysfunction or co-existing vestibular disease may lead to incomplete central adaptation. The movement of otoconia, returning to the utricle, has also been postulated to be the cause of RD after CRP. The otoconia may act like acceleration transducers and affect the sensory cells resulting in vertigo or dizziness after physical therapy. The early occurrence of RD (within 48-72 h after CRP) might be due to the new position acquired by the otoconial mass after otoconial detachment. After the CRPs, otoconia return to the utricular macula, the debris re-attaches to the otolithic membrane of the utricle changing otolith pressure. The

new signal leads to an altered stimulation of the sensory epithelium of the utricle, provoking dizziness. Another postulate for RD is that there is persistence of a small amount of residual debris into the semi-circular canal, which is insufficient to provoke cupular deflection leading to RD. Other postulated causes include potential autonomic dysfunction such as orthostatic hypotension and persistent postural perceptual dizziness and the presence of a pathology involving both the semicircular canals and otolith.[1] Degeneration of neural elements with a consequent altered interaction with otolithic and canalicular receptors may also be responsible for RD.[1]

Consensus statement 3

In patients with BPPV, factors that modify management, such as central nervous system disorders, impaired mobility, or balance, and/or increased risk for falling should be assessed

Patients should be reassessed within one month after an initial period of observation or treatment to document resolution or persistence of symptoms

Clinicians should evaluate patients with persistent symptoms for unresolved BPPV and/or with underlying peripheral vestibular or central nervous system disorders

Clinicians must educate patients about the impact of BPPV, with respect to patient safety and potential for disease recurrence

EXERCISE-BASED VESTIBULAR REHABILITATION FOR RD

Exercise-based vestibular rehabilitation (VR) is an effective method for managing dizziness associated with vestibular disorders. Currently, three different exercise components are used for VR: (1) gaze stability exercises; (2) habituation exercises, including optokinetic exercises, and (3) balance and gait training in different conditions. The postulated effects of these exercises on VR mechanism include the following: (1) compensation/habituation or repeated exposure to a provocative stimulus that will lead to reduction in the symptomatic response to treatment, (2) adaptation or recovery of dynamic vestibulo-ocular responses due to the inherent ability of the vestibular system to make long-term changes in the neuronal response to input, and (3) the use of alternative strategies to replace the lost function.[1] A Cochrane review has indicated that the primary intervention for BPPV should be CRP but movement/habituation-based VR will aid in long-term functional recovery.[1]

Consensus statement 4

Canalith repositioning procedure (CRP) and vestibular rehabilitation (VR) may have a synergistic effect in patients with BPPV, especially in elderly patients

VR does not reduce the recurrence rate, but it seems to reduce unpleasantness

VR can substitute CRP when spine comorbidities contraindicate CRP and can reduce the uptake of anti-vertigo drugs post CRP

Customized VR can adequately reduce symptoms and improve quality of life

ROLE OF BETAHISTINE IN IMPROVING MICROCIRCULATION IN BPPV

Histamine plays an important role in the peripheral vestibular system regulating the sensory coding. Histamine increases the activity of the afferent neurons of semi-circular canals and regulates the intracellular calcium ion concentration in the vestibular periphery. Betahistine is postulated to reduce the functional asymmetry of vestibular organs, increase the microcirculation of the labyrinth by causing dilation of blood vessels, and relieve the pressure from endolymphatic fluid.[10]

Betahistine is approved in more than 115 countries for the treatment of peripheral vertigo. It is a structural analogue of histamine and has pleiotropic actions due to its weak agonist activity at the histamine H_1 receptors and antagonist activity at the H_3 receptors.[11,12]

Betahistine is a centrally acting drug, which enhances histamine synthesis within tuberomammillary nuclei of the posterior hypothalamus and histamine release within vestibular nuclei by causing antagonism of H(3) autoreceptors.[13,14] Laurikainen et al demonstrated that betahistine causes a selective increase in the inner ear blood flow by dilation of the micro vessels in the inner ear but has only weak vasodilation effects in the other areas. Selective vasodilation of the inner ear without systemic effects prevents hypotensive effects. This is an important differential of betahistine from other vasodilators since they are non-selective in their action and dilate all the blood vessels in the body.[15] This vasodilatory effect of betahistine is attributed partially to the stimulation of the H_1 histamine receptors in the inner ear blood vessels and partially to the release of histamine, which stimulates the H_1 receptors of the inner ear blood vessels resulting in vasodilatation and increased blood flow to inner ear.[15]

The cochlea has a strong autoregulatory capacity that easily compensates for small changes in cochlear circulation. Betahistine is likely to also have an effect on vestibular circulation by increasing cochlear blood flow (54% increase observed in animal studies).[16-18] By improving circulation in the cochlear stria vascularis via an action on the precapillary sphincter with an associated reduction in excessive endolymphatic pressure, it improves the function of vestibular hair cells. The central action of betahistine leads to an enhancement of

histamine synthesis in tuberomammillary nuclei and its subsequent release within the vestibular nuclei. Betahistine is also postulated to regulate alertness via cerebral H_1 receptors. Betahistine enhances the process of vestibular compensation and reduces the spontaneous activity of peripheral vestibular receptors.[11,19] This results in improved recovery and the quality of life of patients with BPPV.

CLINICAL BENEFITS OBSERVED WITH BETAHISTINE

Stambolieva et al. demonstrated that treatment with betahistine dihydrochloride helped to restore the postural stability, normalized sway velocity in patients treated with betahistine and canal repositioning maneuvers such as Semont maneuver and Brandt Daroff exercises independently of age of patients with a significant difference with respect to the with comparators ($p<0.01$).[12,20] Several clinical trials have demonstrated that betahistine is effective in reducing the frequency and severity of vertigo, and in improving vertigo-associated symptoms, including nausea and vomiting.[11]

In a study conducted by Cavaliere et al two physical maneuvers with and without betahistine were compared, and it was observed that the group treated with betahistine showed better improvement as compared to the group receiving physical therapy alone.[21]

Guneri et al evaluated the efficacy of betahistine in reducing symptoms after Epley maneuver for posterior canal BPPV and found that 48 mg of daily betahistine with maneuvers was more effective than Epley maneuver in improving symptoms as evaluated by four different vertigo symptoms scales.[21,22] Studies have demonstrated that treatment with Epley maneuver and betahistine causes better improvement in the mean visual analog scale (VAS) score at 1 and 4 weeks of follow-up. A greater improvement in mean post treatment VAS score was observed in patients treated with the combination of Epley maneuver with betahistine as compared to patients treated with betahistine monotherapy.[21]

Betahistine dihydrochloride facilitated an accelerated recovery of the function of vestibular system, secondary to improved microcirculation in the inner ear and faster normalization of the function of motion sensitive hair cells. The cumulative effect of particle repositioning and pharmacotherapy was statistically significant as compared to baseline. Patients had faster recovery, lesser recurrence, and longer relief of symptoms.

Consensus statement 5

The vasodilatory effect of betahistine can increase blood flow to the inner ear and improve outcomes with BPPV treatment

Betahistine can lead to an accelerated recovery of vestibular system function due to improved microcirculation in the inner ear.

CONCLUSION

BPPV is an incapacitating and recurring condition. Patients require reassurance regarding the benign nature of the condition and the available treatment options. Amongst the various vestibular rehabilitation exercises for the treatment of BPPV, Epley maneuver with betahistine is more effective in management of patients of BPPV, and it is helpful in reducing symptoms to a tolerable level. Betahistine when used in conjunction with Epley maneuver is a safe treatment. Betahistine can be used as monotherapy in patients of BPPV who are deemed unfit to undergo canalith repositioning maneuvers. Betahistine provides short-term relief for acute symptoms associated with BPPV by improving microcirculation in the labyrinth and improves the vestibular compensation, thereby providing long-term benefit too by working towards vestibular recovery. Betahistine improves outcomes in combination with canalith repositioning maneuvers. Thus, betahistine plays a critical role in bettering vestibular health and in-turn recovery from vertigo.

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