Original Article

Negative Impact of Vestibular Suppressant Drugs on Provocative Positional Tests of BPPV: A Study from the Western Part of India

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Abstract

Aims: To study the impact of vestibular suppressant drugs (VSD) on provocative positional tests (PPT) in patients with benign paroxysmal positional vertigo (BPPV). **Settings and Design:** A prospective case-control observational study. **Materials and Methods:** Patients with a history suggestive of BPPV were tested for PPT. Patients with vertiginous symptoms and with nystagmus on PPT were classified as objective BPPV (O-BPPV, control group), while those without nystagmus with no alternate diagnosis were classified as subjective BPPV (S-BPPV, case group). Details of VSD treatment were noted in all the patients. In both groups, patients were instructed to discontinue VSD and were further assigned as the VSD and non-VSD subgroups. Patients were followed for 2 months with PPT every week. PPT positive patients were treated by vestibular rehabilitation maneuvers. **Statistics:** Student t-test with two-tailed, unpaired, was used for continuous scale and Chi-square test for categorical differences between the two groups. **Results:** 295 consecutive BPPV patients were enrolled in the study, 55 in the S-BPPV group and 240 in the O-BPPV group. Significantly higher proportion of patients in the S-BPPV group were on VSD at presentation, 80.00% vs. 53.75% (OR 2.52; 95% CI: 1.30–4.86), $P = 0.006$. In an unadjusted analysis of the S-BPPV group following discontinuation of VSD, PPT became positive in 79.54% of patients as compared to 18.19% in the non-VSD group (OR 35.0; 95% CI: 6.2–197.3), $P < 0.001$. **Conclusion:** A higher proportion of S-BPPV patients were receiving VSD in comparison to O-BPPV at the initial visit. The PPT converted positive four times higher after ceasing the VSD in S-BPPV patients.

Study Design: Prospective case-control observational study.

Keywords: Dix-Hallpike test, objective BPPV, provocative position test, subjective BPPV, supine roll test, vestibular suppressant drugs

Introduction

Vertigo is one of the most common presenting symptoms in general medicine and neurology practice.[1] Peripheral vertigo is more frequent as compared to central vertigo. Of all the patients of vertigo, 20% are diagnosed as benign paroxysmal positional vertigo (BPPV) with 2.5% to 10% lifetime prevalence.[2,3] It is more common in females, and its prevalence increases with age.[1,3] BPPV impairs quality of life and is responsible for serious injuries due to falls, particularly in elderly population.[4,5]

BPPV is characterized by episodes of the spinning of surroundings or self-lasting less than a minute, provoked by the changes in the position of the head relative to gravity.[6] The otoconial debris from the utricular macula of the membranous labyrinth is detached due to age-related degeneration, head injury, or for some unknown reasons.[7] Under these circumstances, head movements that occur relative to the gravity induce an endolymph current within the semicircular canal with resultant cupular deflection leading to sudden severe asymmetry in the resting vestibular tone that generates an action potential in the ampullary nerve about a false change of head position which is transmitted to the central vestibular system.[8] During the positional test, this results in typical crescendo-decrescendo nystagmus with a fast component either toward or away from the affected ear, depending on the variant of BPPV, and is associated with typical vertigo symptoms.[9] The posterior semicircular canal (PSC) is most frequently involved (80%–90%), followed by the lateral semicircular canal (LSC) (10%–15%) and very rarely anterior semicircular canal (1%–2%).[10] The diagnostic positional tests, namely, the Dix-Hallpike test (DHT) and supine roll test (SRT), generate the diagnostic oculomotor patterns localizing and

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lateralizing the semicircular canals affected by vestibular lithiasis. In most common PSC-BPPV, the DHT elicits a typical vertical up beating torsional nystagmus with a fast component toward the lowermost ear, and in LSC-BPPV, the SRT elicits horizontal nystagmus with a fast component directed either toward (geotropic variant) or away (apogeotropic variant) from the affected ear.[11] However, some of the patients with typical vertiginous symptoms but no nystagmus on DHT or SRT are classified as subjective BPPV (S-BPPV), while those with nystagmus are classified as objective BPPV (O-BPPV).[12-14] The treating physician unaware of S-BPPV entity may subject the patients for extensive electrophysiological and neuroimaging diagnostic workup for diagnosis of vertigo.[13,15]

Vestibular suppressant drug (VSD) classes useful in the treatment of vertigo include histamine-1 receptor agonist (betahistine), antihistamines (cinnarizine, dimenhydrinate, meclizine), dopamine receptor antagonists (prochlorperazine), anticholinergics (scopolamine), and benzodiazepines (clonazepam).[16,17] These drugs may suppress the nystagmus response of BPPV during diagnostic positional tests and are speculated to contribute to patients classified as S-BPPV.[18,19] The present research aimed to study demographics and clinical profile of O-BPPV and S-BPPV as well as to find the impact of VSD on the provocative positional test (PPT) among BPPV patients.

Material and Methods

This observational prospective case-control study was conducted at a tertiary hospital in western India from January 2018 to February 2019. Consecutive patients aged between 18 and 70 years, who presented with brief episodes of vertigo lasting less than 60 s due to the change of head position, provisionally diagnosed as BPPV, were included in the study. Patients with morbid obesity, severe cervical spine diseases, acute stroke, and significant carotid artery stenosis were excluded. A complete neuro-otological examination of patients included carrying out DHT and SRT on either side using takeaway Michael glasses. The Michael glasses are a substitute for Frenzel goggles designed for nystagmus study having advantage of visual axis fixation and magnification of the eyeballs movements. The patients with vertiginous symptoms without any nystagmus with Michael glasses examination during either of the PPT were classified as S-BPPV and included as cases. Patients with vertiginous symptoms and with classical nystagmus (upbeat torsional nystagmus in PSC-BPPV and horizontal geotropic or apogeotropic nystagmus in LSC-BPPV) during the PPTs were classified as O-BPPV and constituted the control group of the study. Neuroimaging and electrophysiological studies were undertaken in selected patients, if indicated, to rule out other causes of vertigo. The study protocol was approved by the institutional ethics committee. The written consent was obtained from each participant regarding the study objectives and publication of the research data as per Helsinki guidelines.

A history of VSD exposure was obtained from all patients. Patients in either group who were taking VSD in the past 24 h were instructed to discontinue it and were assigned to the VSD-group. Patients with no history of VSD intake in the past 24 h were assigned to non-VSD group. The control group was treated with the recommended vestibular rehabilitation maneuvers.[20] Patients in the case group were advised to report immediately, should the symptoms of positional vertigo recur; otherwise, were followed up weekly. Patients were followed for 2 months and PPTs were repeated at each weekly visit. Patients whose PPT converted positive in cases (S-BPPV) were treated by the same rehabilitation treatment as the control group (O-BPPV).

Statistics

The latest SPSS software was used to analyze the obtained data. Student t-test with two-tailed, unpaired, was used to find the significance of study parameters for continuous scale (mean values) and Chi-square test for categorical differences (percentages) between the two groups. The sample size was calculated as per the standard statistical formula for 80% power and 0.05 alpha error of the proposed study.

Results

Out of 311 patients, 16 patients were excluded from the final analysis (10 patients did not meet inclusion criteria and 6 patients were lost to follow-up, 2 from the S-BPPV group and 4 from the O-BPPV group). In the S-BPPV group, two patients were excluded; one had features of left Horner's syndrome with left face and right-sided hemi-sensory loss and magnetic resonance imaging (MRI) brain revealed left lateral medullary infarction, and the second patient had bilateral papilledema and MRI brain revealed right cerebellopontine angle tumor. Eight patients were excluded from the O-BPPV group. Among them, one had a new-onset mild headache with projectile vomiting and during DHT had downbeat nystagmus, with MRI revealing pontomedullary junction space occupying lesion and other had mild daily headache with MRI detected midline cerebellar tumor. One patient with posterior canal BPPV had subtle unilateral upper motor neurone facial weakness was diagnosed as lower pons infarction. Three patients denied for written consent and two patients with cervical spine spondylosis were also excluded.

Total of 295 patients, 55 cases and 240 controls have been included in the study. More patient in the S-BPPV group were on VSD at initial visit (80.00% vs. 53.75%, P=0.006). Age, gender, duration of vertigo, associated comorbid medical illness, or history of head injury had no significant effect in the comparison between the case and the control group by Chi-square test. The posterior canal was involved in 85% of patients in each group, while none of the patients had anterior canal involvement. Single VSD was prescribed in most patients, though some patients were on two or three different drugs [Table 1].

Table 2 shows the number of patients in the S-BPPV group in whom PPT became positive after stopping VSD

therapy during 2-month follow-up, and were compared to the non-VSD subgroup. During the first 7-day follow-up, PPT converted positive in 27.27% in the VSD group, while none in the non-VSD group. Additional (14.54% vs. 9.09%) during the 14 days, (16.36% vs. none) during the 30 days, and (5.45% vs. 9.09%) during the 60 days follow-up in VSD vs. non-VSD patients PPT converted positive in the S-BPPV group, respectively. Overall, in S-BPPV patients, after discontinuing VSD, PPT converted positive in 79.54% of the VSD subgroup, while only in 18.19% of the non-VSD subgroup with a *P* value of less than 0.001.

In unadjusted analysis, VSD exposure was 1.5 times more common in the S-BPPV group as compared to the O-BPPV group (OR 2.52, 95% CI: 1.30–4.86). The results were indistinguishable even after multidiscipline adjustment (OR 2.50, 95% CI: 1.26–4.30). In S-BPPV group, PPT converted positive 3.5 times higher after discontinuing the drugs in the VSD subgroup, as compared to non-VSD subgroup in unadjusted analysis (OR 35.0, 95% CI: 6.20–197.3), and results were significant even after multivariable adjustments (OR 34.0, 95% CI: 6.4–190.3).

Table 1: Demographic and clinical characteristics of the case (S-BPPV) and control (O-BPPV) groups

Characteristics n (%)	S-BPPV (%) 55 (21.24)	O-BPPV (%) 240 (78.76)	*P*
Mean age ± SD (Years)	44.15±12.30	42.32±11.45	0.578
Female	35 (63.64)	159 (66.25)	0.754
H/o Hypertension	08 (14.54)	42 (17.50)	0.218
H/o Diabetes mellitus	10 (18.19)	51 (21.25)	0.661
H/o Chronic Kidney injury	01 (01.81)	09 (03.75)	0.423
H/o Ischemic heart disease	07 (12.72)	33 (13.75)	0.863
H/o Head injury	06 (10.90)	26 (10.83)	0.330
Nausea, vomiting	12 (21.81)	60 (25.00)	0.669
Vertigo duration <7 days	34 (61.81)	162 (67.50)	0.496
Vertigo duration ≥7 days	21 (36.37)	78 (32.50)	0.642
H/o Recurrent vertigo	13 (23.63)	63 (26.25)	0.118
Posterior canal BPPV	47 (85.45)	201 (83.75)	0.788
Horizontal canal BPPV	08 (14.55)	39 (16.25)	0.788
H/o VSD treatment	44 (80.00)	129 (53.75)	0.006
Single drug	24 (43.63)	71 (29.58)	-
Dual drugs	12 (21.82)	35 (14.58)	-
Triple drugs	08 (14.54)	23 (09.58)	-

S-BPPV: Subjective BPPV, O-BPPV: Objective BPPV

Discussion

Globally, most of vertigo patients initially carry a nonspecified diagnosis of "vertigo syndrome" at primary care, and VSD are frequently prescribed for 1 to 4 weeks to the vast majority of such patients.[20,21] Almost 25% to 50% of cases have confirmed or probable BPPV as the cause of vertigo, and hence their VSD therapy is not evidence-based.[22,23] In our study, 58.64% (173/295) patients with BPPV were receiving VSD at the time of enrolment in the study, which is comparable to the study of Kameswaran *et al*., where around 60% of patients with BPPV were initially prescribed the drugs.[23] Guidelines recommend treatment with canalith repositioning maneuver (CRM) which has class 1-A evidence.[24] VSD therapy has no role in the management of BPPV, except as an antiemetic agent before CRM in individuals who have persistent nausea and vomiting.[18,19]

González *et al*., Tan *et al*., and Balatsouras *et al*. reported an incidence of S-BPPV of 24.71%, 34.28%, and 25%, respectively, in their studies.[5,14,19] The incidence of S-BPPV in our study was 21.24%, which is comparable to other studies. Both the varieties of BPPV were twice more common in females similarly to other studies.[25-30] However, the mean age of the patients in our study was in the early fourth decade in contrast to western countries' BPPV studies, where the mean age was in the late fifth decade of life.[25,26] We observed that the history of hypertension, diabetes mellitus, and head injury were significant risk factors for S-BPPV as well as O-BPPV. However, age, gender, hypertension, diabetes mellitus, history of head injury, and either duration or recurrence of vertigo were not having significant differences in the comparison of both the groups.

The exact pathophysiology of subjective BPPV is unknown, but various theories have been suggested.[8,23] Most of the researchers agree with the hypothesis of S-BPPV as a mild form of BPPV where the force generated by the movement of the otoconial debris is weaker in comparison to O-BPPV; hence, it produces vertigo symptoms, but not nystagmus.[8] Another theory is that VSD therapy prescribed to BPPV patients at the onset of symptoms may suppress central and peripheral vestibular compensation by various mechanisms.[19] The study by Tan *et al*. shows that VSDs were prescribed to 25% higher number of S-BPPV patients compared to O-BPPV at the level of primary care before the specialist referral for final diagnosis. More than half of these S-BPPV patients converted to O-BPPV

Table 2: Positive PPT conversion over time in cases (S-BPPV)

VSD Treatment	7 Days	14 Days	30 Days	60 Days	Overall
Single VSD *n*=24 (%)	8 (33.33)	4 (16.67)	5 (20.83)	1 (04.17)	18 (75.00)
Dual VSD *n*=12 (%)	5 (41.67)	2 (16.67)	3 (25.00)	1 (08.33)	11 (91.67)
Triple VSD *n*=08 (%)	2 (25.00)	2 (25.00)	1 (12.50)	1 (12.50)	6 (75.00)
Over all VSD *n*=44 (%)	15(34.09)	8 (18.18)	9 (20.45)	3 (06.82)	35 (79.54)
Non-VSD *n*=11 (%)	Nil	1 (09.09)	Nil	1 (09.09)	02 (18.19)
P	0.003	0.025	0.015	<0.001	<0.001

within 10 days of discontinuing the VSD therapy.[19] In our study, one-third of all S-BPPV patients converted to O-BPPV in the 1 week and near 60% within 30 days of stopping VSD therapy. During follow-up visits, a significantly higher number of patients' PPT converted positive after discontinuing the drugs in the VSD subgroup in comparison to non-VSD subgroup in S-BPPV patients. A statistically significantly higher number of S-BPPV patients were receiving VSD therapy at the initial visit in comparison to O-BPPV patients ($P < 0.001$) in our study. These observations support the hypothesis of VSD therapy as one of the contributing factors for negative PPT in BPPV patients exposed to the drug therapy instead of rehabilitation treatment.

Our study has certain limitations. We have used Michael glasses for nystagmus study of DHT instead of nystagmography, and it is possible that subtle nystagmus may have been missed and some of the patients may have been wrongly categorized as S-BPPV. Diagnosis of S-BPPV was based on clinical characteristics. Some central vertigo causes very rarely may mimic S-BPPV, which could have been included in our study as neuroimaging studies were not performed in all patients except when clinically indicated. In addition, we have included only patients with vertigo in prior 4 weeks of presentation, and many chronic and recurrent cases were not included. The strength of our study was statistically sufficient sample size and objective findings such as the presence of classical nystagmus for diagnosing conversion of S-BPPV to O-BPPV.

In summary, BPPV is the commonest cause of vertigo, and VSD is mistakenly prescribed to many BPPV patients at the initial visit with a syndromic diagnosis of "acute vertigo under investigation." VSD treatment may be a contributing factor for negative PPT in BPPV patients, especially for subjective variety. Therefore, proper classification is essential in all patients with complaints of vertiginous symptoms. No patients with a provisional diagnosis of BPPV should be prescribed VSD unless used as an antiemetic therapy. Our study results should be validated by further large-scale trials.

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Conflicts of interest

There are no conflicts of interest.

References

1. Strupp M, Brandt T. Diagnosis and treatment of vertigo and dizziness. Dtsch Arztebl Int 2008;105:173-80.
2. von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, Lempert T, *et al*. Epidemiology of benign paroxysmal positional vertigo: A population based study. J Neurol Neurosurg Psychiatry 2006;78:710-5.
3. Agrawal Y, Carey JP, Della Santina CC, Schubert MC, Minor LB. Disorders of balance and vestibular function in US adults: Data from the National health and nutrition examination survey, 2001–2004. Arch Intern Med 2009;169:938-44.
4. Chen Z-J, Chang C-H, Hu L-Y, Tu M-S, Lu T, Chen P-M, *et al*. Increased risk of benign paroxysmal positional vertigo in patients with anxiety disorders: A nationwide population-based retrospective cohort study. BMC Psychiatry 2016;16:238
5. Balatsouras DG, Koukoutsis G, Fassolis A, Moukos A, Apris A. Benign paroxysmal positional vertigo in the elderly: Current insights. Clin Interv Aging 2018;13:2251-66.
6. Marom T, Oron Y, Watad W, Levy D, Roth Y. Revisiting benign paroxysmal positional vertigo pathophysiology. Am J Otolaryngol 2009;30:250-5.
7. Walther LE. Procedures for restoring vestibular disorders. GMS Curr Top Otorhinolaryngol Head Neck Surg 2005;4:Doc05.
8. Hornibrook J. Benign paroxysmal positional vertigo (BPPV): History, pathophysiology, office treatment and future directions. Int J Otolaryngol 2011;2011:835671.
9. Balatsouras DG, Koukoutsis G, Ganelis P, Korres GS, Kaberos A. Diagnosis of single- or multiple-canal benign paroxysmal positional vertigo according to the type of nystagmus. Int J Otolaryngol 2011;2011:483965.
10. Ibekwe TS, Rogers C. Clinical evaluation of posterior canal benign paroxysmal positional vertigo. Niger Med J 2012;53:94-101.
11. Parnes LS, Agrawal SK, Atlas J. Diagnosis and management of benign paroxysmal positional vertigo (BPPV). CMAJ 2003;169:681-93.
12. You P, Instrum R, Parnes L. Benign paroxysmal positional vertigo. Laryngoscope Investig Otolaryngol 2018;4, 116-23.
13. Jung JY, Kim SH. Comparison between objective and subjective benign paroxysmal positional vertigo: Clinical features and outcomes. Acta Otolaryngol 2016;136:1267-72.
14. González-AguadoR,Domènech-VadilloE,Álvarez-MorujodeSandeMG, Guerra-Jiménez G, Domínguez-Durán E. Subjective benign paroxysmal positional vertigo in patients with osteoporosis or migraine. Braz J Otorhinolaryngol 2020;86:83-90.
15. Palmeri R, Kumar A. Benign Paroxysmal Positional Vertigo (BPPV) [Last updated on 2019 Mar 08]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470308/.
16. Scholtz A-W, Ilgner J, Loader B, Pritschow BW, Weisshaar G. Cinnarizine and dimenhydrinate in the treatment of vertigo in medical practice. Wien Klin Wochenschr 2016;128:341-7.
17. Bird JC, Beynon GJ, Prevost AT, Baguley DM. An analysis of referral patterns for dizziness in the primary care setting. Br J Gen Pract 1998;48:1828-32.
18. Chimirri S, Aiello R, Mazzitello C, Mumoli L, Palleria C, Altomonte M, *et al*. Vertigo/dizziness as a Drugs' adverse reaction. J Pharmacol Pharmacother 2013;4(Suppl 1):S104-9.
19. Tan J, Yu D, Feng Y, Song Q, You J, Shi H, *et al*. First-referral presentations of patients with benign paroxysmal positional vertigo who were negative on positional testing and who lacked nystagmus. Eur Arch Otorhinolaryngol 2015;272:3247-51.
20. Patel DM, Gurumukhani JK, Patel MV, Patel GR. Phenytoin induced chorea: A rare adverse effect of the drug. Curr Drug Saf 2019;14:51-2
21. Parfenov VA, Golyk VA, Matsnev EI, Morozova SV, Melnikov OA, Antonenko LM, *et al*. Effectiveness of betahistine (48 mg/day) in patients with vestibular vertigo during routine practice: The VIRTUOSO study. PLoS One 2017;12:e0174114.
22. von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, Lempert T, *et al*. Epidemiology of benign paroxysmal positional vertigo: A population based study. J Neurol Neurosurg Psychiatry 2007;78:710-5.
23. Kameswaran M, Pujari S, Singh J, Basumatary LJ, Sarda K, Pore R. Clinicoetiological pattern and pharmacotherapy practices in patients with new onset vertigo: Findings from a prospectivemulticenter registry in India. Int J Otorhinolaryngol Head Neck Surg 2017;3:404-13.
24. Hilton M, Pinder D. The epley (canalith repositioning) manoeuvre for benign paroxysmal positional vertigo. Cochrane Database Syst Rev 2004;2:CD003162.
25. Yetiser S, Ince D. Demographic analysis of benign paroxysmal positional vertigo as a common public health problem. Ann Med Health Sci Res 2015;5:50-3.

26. Liu D-H, Kuo C-H, Wang C-T, Chiu C-C, Chen T-J, Hwang D-K, *et al*. Age-related increases in benign paroxysmal positional vertigo are reversed in women taking estrogen replacement therapy: A population-based study in Taiwan. Front Aging Neurosci 2017;9:404.
27. Ogun OA, Janky KL, Cohn ES, Büki B, Lundberg YW. Gender-based comorbidity in benign paroxysmal positional vertigo. PLoS One 2014;9:e105546.
28. Tari AD, Kumar S. The effect of postural stability exercises in benign paroxysmal positional vertigo: Pre–post experimental study. Physiother-J Indian Assoc Physiother 2017;11:66-70.
29. Byun H, Chung JH, Lee SH, Park CW, Kim EM, Kim I. Increased risk of benign paroxysmal positional vertigo in osteoporosis: A nationwide population-based cohort study. Sci Rep 2019;9:3469.
30. Balatsouras DG, Koukoutsis G, Fassolis A, Moukos A, Apris A. Benign paroxysmal positional vertigo in the elderly: Current insights. Clin Interv Aging 2018;13:2251-66.