Korean J Otorhinolaryngol-Head Neck Surg 2023;66(11):728-34 / eISSN 2092-6529
https://doi.org/10.3342/kjorl-hns.2023.00430

Clinical Manifestation and Prognostic Factors of Chronic Dizziness Due to Long-Term Use of Vestibular Suppressant

Younghoon Cho*, Young Chul Kim*, Jiyoung Lee, Seung Ha Oh, Sang-Yeon Lee, Jun Ho Lee, Moo Kyun Park, and Myung-Whan Suh

Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

장기간 전정억제제 사용으로 인해 발생한 만성 어지러움의 임상양상과 예후 요인에 대한 분석

조영훈* · 김영철* · 이지영 · 오승하 · 이상연 · 이준호 · 박무균 · 서명환

서울대학교 의과대학 서울대학교병원 이비인후과학교실

Received April 21, 2023
Revised May 17, 2023
Accepted May 23, 2023
Address for correspondence
Myung-Whan Suh, MD
Department of Otorhinolaryngology-Head and Neck Surgery,
Seoul National University Hospital,
Seoul National University College of Medicine,
101 Daehak-ro, Jongno-gu,
Seoul 03080, Korea
Tel +82-2-2072-2287
Fax +82-2-745-2387
E-mail drmung@naver.com

*These authors contributed equally to this work.

Background and Objectives Dimenhydrinate and benzodiazepine are widely used for the prevention of nausea and vomiting in a variety of acute vestibular diseases. Due to the prolongation of central compensatory mechanism and dependency, the long-term use of vestibular suppressants can elicit various atypical vestibular symptoms and vestibular function test (VFT) results, which result in neglect and underdiagnosis. This study aimed to investigate the effect of long-term use of vestibular suppressants and identify significant prognostic factors.
Subjects and Method Thirty-two patients diagnosed with vestibular suppressant drug associated dizziness (DAD) were enrolled. The patients were instructed to discontinue the suppressants and undergo vestibular rehabilitation therapy. The severity of dizziness, compliance to treatment, prognosis, and the results of VFT were evaluated.
Results Most of the patients (65.6%) complained of spinning vertigo while some of the patients (25.0%) complained of unsteadiness, directional pulsion, or non-vertiginous dizziness, making the diagnosis difficult. The severity of the DAD symptoms was dependent on the preceding vestibular disorder: it was significantly milder when the preceding vestibular disorder was benign paroxysmal positional vertigo. Atypical findings of VFT that cannot be fully explained based on known vestibular disorders were frequently observed (9.4%–54.5%). Preceding vestibular disorders of old age, non-compliance with vestibular rehabilitation and vestibular neuritis were found to be independent bad prognostic factors.
Conclusion Understanding and being aware of DAD as a cause of dizziness may help patients suffering from chronic dizziness without a certain diagnosis.
Korean J Otorhinolaryngol-Head Neck Surg 2023;66(11):728-34

Keywords Dizziness; Rehabilitation; Vestibular diseases.

Introduction

Pharmacological treatment is a common stratagem for symptomatic relief of dizziness as well as dizziness prophylaxis.[1-4] Dimenhydrinate and benzodiazepines are examples of the widely used vestibular suppressing medications. These drugs are usually administered in acute cases of common vestibular disorders such as vestibular neuritis (VN) or benign paroxysmal positional vertigo (BPPV). In the short-term, these

drug may be very helpful in controlling severe vertigo.[2] However, long-term intake of such vestibular suppressants may lead to poor compensation of the vestibular deficit and worsen of dizziness. Typical symptoms and physical examination findings may become indistinct after a long-term use of vestibular suppressants. Previously, the menace of over-use or misuse of vestibular suppressants has been mentioned.[5-8] For instance, patients may complain of non-specific symptoms that do not comply with the known vestibular disorders. Strange pattern of positional nystagmus that cannot be explained by VN or BPPV has also been reported.

Despite the disabling symptoms, the effect of long-term use of vestibular suppressants on patients with dizziness has not been studied well. It may be unethical to conduct a prospective or randomized trial on the effect of long-term use of vestibular suppressants. Accordingly, all the known information on this subject is from random observations. Most of the former studies were inefficient in providing a complete picture of this patient group. For instance, the follow-up period was very short to evaluate the long-term influence and prognosis.[9,10] In other studies, the importance of mentioning the detailed medication history tends to be overlooked.[11-14] In this study, we tried to follow up a series of patients suspected of drug associated dizziness (DAD) due to long-term use of vestibular suppressant. We performed a structured history taking and a comprehensive vestibular function evaluation in these patients. We also investigated the treatment outcome and tried to distinguish significant prognostic factors.

Subjects and Methods

The study was conducted in the otology clinic of a tertiary referral center. The medical records of 42 patients who visited the clinic with a chief complaint of chronic dizziness for more than 6 months and who took dimenhydrinate and/or diazepam were considered eligible for the present study. Among 42 patients, 32 patients who underwent 1) a structured history taking, 2) comprehensive vestibular function evaluation, and 3) who were followed-up for at least a month after starting the treatment were enrolled in this study. DAD was diagnosed only when the history of vestibular suppressant intake for longer than a month was obvious and when the current dizziness symptom, sign, and vestibular function test (VFT) outcome did not agree with the known vestibular disorders. Dizziness attributed to a central cause was ruled out based on a comprehensive assessment of medical history, physical examination, and the VFT. For the 15 patients in whom exclusion was challenging, brain MRI was performed and confirmed the absence of any central causes. Ten patients were excluded for one or more reasons listed below. Seven patients refused the VFT, six patients were followed-up for less than a month, one patient underwent the VFT at another hospital, and one patient took a drug that was not clearly identified. The mean age of the patients was 58.6±15.7 years, 10 patients were male and 22 patients were female (Table 1).

All the patients had a preceding vertigo attack that was typical of peripheral origins such as BPPV, Meniere disease (MD), or VN (preceding vestibular disorder). The preceding vestibular disorder was the reason to start the vestibular suppressant. During the follow up, all the subjects were instructed to discontinue the vestibular suppressants as soon as possible. And a vestibular rehabilitation therapy (VRT) based on the Cawthorne-Cooksey method was started to facilitate the vestibular compensation process. After a session of education and rehearsal with the vestibular therapist, an illustrated booklet guided VRT program was performed every day for at least 30 minutes per day. The treatment outcome was evaluated every 1−4 months. In order to evaluate the improvement in the chronic dizziness symptom, a 100-point numerical rating scale (NRS) was used to measure the patient's sensation of dizziness during every visit:[9] 0=no vertigo and 100= worst possible vertigo ever experienced.

The severity of the dizziness symptom at first visit, compliance to treatment, and the prognosis was dichotomized into two categories as follows: 1) The severity of the dizziness symptom at first visit was considered mild if the dizziness was bothersome but did not cause any impairment to the patient's daily activity. It was considered severe if the dizziness caused

Table 1. Demographics (n=32)

	Value
Age, years	58.6±15.7
Male	10 (31.3)
Duration of illness (months)	44.4±47.3
Preceding vestibular disorder (BPPV:MD:VN)	15:8:9
Vestibular suppressant used	
Dimenhydrinate	29 (90.6)
Benzodiazepine	6 (18.8)
Both dimenhydrinate and benzodiazepine	3 (9.4)
Mean duration of drug intake (months)	20.0±20.9

Data are presented as mean±standard deviation or n (%). BPPV, benign paroxysmal positional vertigo; MD, Meniere disease; VN, vestibular neuritis

impairment to the patient's daily activity: everyday life head movement, occupational motions, or recreation activity. 2) To evaluate the compliance to treatment, complete discontinuation of the vestibular suppressant was checked. Also, compliance with the treatment and proficiency of performing the VRT was checked by a single doctor and graded during every visit. Compliance with treatment was considered good if the patient kept up with the daily VRT program and fulfilled each step of the program. It was considered poor if the patient did not perform the VRT program or the patient did not comply with the correct head and eye movement protocol. 3) The prognosis was categorized as good or unsatisfactory according to the NRS score of the last visit. If the NRS score on dizziness decreased by 50% or more, the prognosis was considered good. If it decreased to less than 50%, the prognosis was considered unsatisfactory. Only the patients who underwent VRT for ≥2 month were included in the prognosis analysis (n=29).

All the possible data were expressed as a mean±standard deviation. Continuous variables were analyzed using non-parametric Mann-Whitney U test. Chi-squared test was used for dichotomized categorical variables. As there were more than two categories, the preceding vestibular disorders that lead to long-term vestibular suppressant use were analyzed using Cramer's V test and ANOVA test. SPSS version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A p-value<0.05 was considered to indicate statistical significance.

The Seoul National University Hospital IRB approved waiver of consent for this study (IRB No. 2309-108-1467).

Results

Subjective perception of vestibular symptom

Approximately two third of the DAD patients complained of a spinning vertigo but the other one-third of the DAD patients complained of indefinite vestibular symptom that was not vertigo. In detail, according to the 2009 Barany classification, 21 patients (65.6%) described their DAD symptoms as "spinning vertigo". Three patients (9.4%) described their DAD as "postural symptoms": "unsteadiness" in 2 patients and "directional pulsion" in one patient. Five patients (15.6%) described their DAD symptoms as "non-vertiginous dizziness." Three patients (9.4%) failed to describe their subjective perception of vestibular symptom, even after repeated history taking by two doctors.

Severity of the dizziness symptom

The severity of the dizziness symptom was significantly different, according to the preceding vestibular disorder of DAD (p=0.028) (Table 2). When the preceding vestibular disorder was BPPV, the dizziness symptom was mild in most of the patients (53.3%). The dizziness symptom was mild in 37.5% and severe in 62.5% when the preceding vestibular disorder was MD. The dizziness symptom was observed to be always severe (100%) when the preceding vestibular disorder was VN. The severity of the dizziness symptom was not related to any of the VFT results.

Typical VFT outcomes demonstrating unilateral vestibulopathy

The VFT outcomes are summarized in Table 3. Despite the

Table 2. The severity of the dizziness symptom and prognosis according to the preceding vestibular disorder that leads to long-term vestibular suppressant use

	BPPV (n=15)	MD (n=8)	VN (n=9)	p-value
Duration of medication, months	17.3±15.0	25.4±30.4	19.4±21.1	0.691
Severity of the dizziness symptom*				0.028
Mild	8 (53.3)	3 (37.5)	0	
Severe	7 (46.7)	5 (62.5)	9 (10.00)	
Compliance with VRT				0.600
VRT compliant group	9 (60.0)	3 (37.5)	5 (55.6)	
VRT non-compliant group	2 (13.3)	1 (12.5)	4 (44.4)	
Prognosis†				0.049
Good prognosis	11 (84.6)	4 (57.1)	3 (33.3)	
Unsatisfactory prognosis	2 (15.4)	3 (42.9)	6 (66.7)	

Data are presented as mean±standard deviation or n (%). *Cramer's V=0.472, p-value=0.028; †Cramer's V=0.456, p-value=0.049.
BPPV, benign paroxysmal positional vertigo; MD, Meniere disease; VN, vestibular neuritis; VRT, vestibular rehabilitation therapy

Table 3. Vestibular function test results

	Negative outcome	Typical unilateral vestibulopathy	Atypical outcome	Atypical findings
Caloric test (n=25)				
Canal paresis >20%	14 (56.0)	11 (44.0)		
Rotation chair test (n=25)				
SHA gain	12 (48.0)	13 (52.0)		
SHA asymmetry	18 (72.0)	7 (28.0)		
SHA phase	17 (68.0)	8 (32.0)		
Head impulse test				
bHIT (n=23)	8 (34.8)	9 (39.1)	6 (26.1)	Corrective saccade not in agreement with the caloric test (n=6)
vHIT (n=11)	1 (9.1)	4 (36.4)	6 (54.5)	
VIN (n=22)	3 (40.6)	16 (50.0)	3 (9.4)	Direction changing VIN (n=3)
Video nystagmography (n=32)	7 (21.9)	17 (53.1)	8 (25.0)	DCPN with (n=2)/without (n=6) SN

Data are presented as n (%). SHA, sinusoidal harmonic acceleration; bHIT, bedside head-impulse test; vHIT, video head-impulse test; VIN, vibration induced nystagmus; DCPN, direction changing positional nystagmus; SN, spontaneous nystagmus

long history of chronic dizziness in all the subjects (44.4±47.3 months), a typical unilateral peripheral vestibulopathy was identified only in half of the subjects in general. In detail, unilateral vestibulopathy was identified in only 44.0% of the patients by the caloric test, in 52.0% by the rotation chair test sinusoidal harmonic acceleration (SHA) gain parameter, in 28.0% by SHA asymmetry parameter, and in 32.0% by SHA phase parameter. Typical findings implying unilateral vestibulopathy were found in 42.9%–51.8% by head impulse test (HIT) and in 50.0% by vibration induced nystagmus. As for video nystagmography, typical findings implying unilateral vestibulopathy (direction fixed positional nystagmus and/or post-head shake nystagmus) was found in 53.1% of the patients. In summary, typical unilateral vestibulopathy was identified in approximately half of the subjects.

Atypical VFT outcomes that do not comply with peripheral vestibular disorder

Direction changing positional nystagmus (DCPN) mimicking horizontal canal BPPV was found in 8 patients, however, the dizziness symptom was not consistent with BPPV in all these patients. Direction changing vibration induced nystagmus (VIN) (direction of nystagmus was different between the left and right mastoid vibrator application) was found in 3 patients. The corrective saccade found in HIT was not in agreement with the caloric test results in 6 patients. That is, no catch-up saccade was found and the gain was normal even though the caloric test canal paresis value was larger than 20% in one patient. On the contrary, definite catch up saccades was detected in one ear in 5 patients, while the caloric test canal paresis value was smaller than 20%. In summary, atypical VFT outcomes that do not comply with the known peripheral vestibular disorders was found in 9.4%–54.5%.

Table 4. Comparison between the good prognosis group and the unsatisfactory prognosis group

	Good prognosis group (n=18)	Unsatisfactory prognosis group (n=11)	*p*-value
Male	5 (27.8)	5 (45.5)	0.432
Age, years	54.3±14.9	65.2±15.4	0.047
Good compliance to VRT	13 (81.3)	4 (40.0)	0.046
Vestibular suppressant used			
Dimenhydrinate	17 (94.4)	10 (90.9)	>0.999
Benzodiazepine	2 (11.1)	3 (27.3)	0.339
Medication duration (months)	17.6±15.0	17.6±19.0	0.450
Vestibular function test results			
Atypical findings in vHIT	6 (66.7)	3 (27.3)	>0.999
Atypical findings in VIN	2 (11.1)	1 (9.1)	>0.999
Atypical findings in VNG	5 (29.4)	2 (18.2)	0.668

Data are presented as n (%) or mean ± standard deviation. Good prognosis group, numeric rating scale on dizziness decreased by 50% or more; poor prognosis group, numeric rating scale on dizziness decreased to less than 50%; only the patients who underwent VRT for ≥2 month were included in the prognosis analysis (n=29). VRT, vestibular rehabilitation therapy; vHIT, video head-impulse test; VIN, vibration induced nystagmus; VNG, video nystagmography

Prognostic factor analysis

The prognosis was good in 62% (18 patients) and unsatisfactory in 37.9% (11 patients). The difference between the good prognosis group and unsatisfactory prognosis group is summarized in Table 4. The unsatisfactory prognosis group was significantly older (65.2±15.4 years old) than the good prog-

Table 5. Improvement in dizziness NRS score in accordance with the treatment compliance

	VRT compliant group (n=17)	VRT non-compliant group (n=7)	*p*-value
Age, years	60.5±14.3	62.9±15.4	0.396
Duration of medication (months)	17.8±17.2	20.4±19.2	0.757
Severity of symptom			>0.999
Mild	5 (29.4)	2 (28.6)	
Severe	12 (70.6)	5 (71.4)	
Improvement in NRS (points)	69.8±39.6	37.4±33.6	0.034

VRT, vestibular rehabilitation therapy; NRS, numerical rating scale

nosis group (54.3±14.9 years old, p=0.047). Also, the number of patients with good VRT compliance (40.0%) was significantly less in the unsatisfactory prognosis group compared to the good prognosis group (81.3%, p=0.046). To differentiate between the effect of age and VRT compliance, the results were re-stratified based on the compliance of VRT (Table 5). The patient's age was similar in the VRT compliant group (60.5±14.3 years old) and VRT non-compliant group (62.9±15.4 years old, p=0.396). The dizziness NRS improvement was significantly greater in VRT compliant group (69.8±39.6 points) compared to the VRT non-compliant group (37.4±33.6 points, p=0.034). The prognosis was also significantly different, according to the preceding vestibular disorder (p=0.049) (Table 2). When the preceding vestibular disorder was BPPV, the prognosis was good in most of the patients (84.6%). The prognosis was unsatisfactory in the majority of the patients (66.7%) when the preceding vestibular disorder was VN.

Discussion

In this study, we focused on patients with chronic dizziness placed on long-term vestibular suppressant medications. It is known that long-term use of vestibular suppressants can be a cause of chronic dizziness, but the specific clinical presentation and prognosis have not been clearly elucidated. We found that the subjective perception of vestibular symptom can be diverse in DAD patients. Contrary to our expectation, 65.6% of the patients complained of spinning vertigo. Only 25.0% of the patients complained of unsteadiness, directional pulsion, or non-vertiginous dizziness. It seems that subjective perception of vestibular symptom alone cannot be a clue for the diagnosis or suspicion of DAD. The VFT findings in DAD patients did not reveal a consistent pattern. Unilateral vestibulopathy was identified only in 36.4%−53.1% of the patients. Atypical VFT were frequently (9.4%−54.5%) observed. The severity of the DAD symptom was dependent on the preceding vestibular disorder: it was significantly milder if the preceding vestibular disorder was BPPV. The prognosis of DAD was poor (in 37.9%) when the patients were old and not compliant to VRT. When the preceding vestibular disorder was VN, the severity of DAD was more severe and the prognosis was poor.

The most problematic medication that was suspected to be the cause of DAD was dimenhydrinate (90.6%) and diazepam (18.8%) in our patients. Dimenhydrinate is a histamine receptor antagonist with a phosphodiesterase inhibitor. It is widely used for short-term treatment of dizziness with nausea and vomiting in acute vestibular disorders.[2] A randomized controlled study reported that dimenhydrinate is more effective than other medications for the treatment of acute peripheral vertigo in patients in the emergency department.[15] Due to its good effect on acute dizziness symptoms, misuse for longer durations have been reported.[5] Long-term use of dimenhydrinate can lead to a separate category of chronic dizziness, which is presumed to be due to the prolongation of central compensatory mechanisms.[2] It should be noted that, in our patients, dimenhydrinate/diazepam was prescribed for 20.0±20.9 months at the primary and secondary healthcare services. It seems that doctors who are not specialized in vestibular disorders tend to rely on dimenhydrinate as a quick fix solution for all types of dizziness. Surprisingly, 46.9% of our patients started the vestibular suppressant due to BPPV, which should have been managed by canalith repositioning maneuver instead of medication. This problem can be more severe in countries where dimenhydrinate is classified as an over-the-counter medication.[5,8,16]

Many of the DAD patients presented with an atypical VFT finding such as DCPN or direction changing VIN. This may be a problem because atypical VFT findings can lead to obscure diagnosis and be confused with central vertigo. It has been reported that brainstem lesions in the inhibitory pathways from the cerebellum to the prepositus hypoglossi nucleus may elongate the post-rotatory nystagmus.[17] Consequently, small positional changes may augment the post-rotatory nystagmus resulting in DCPN. Lesions in the vestibular cerebellum may also cause dysfunction of the central adaptive mechanism, eliciting DCPN.[18] The reason why direction changing nystagmus was found in our patients is unclear. However, considering that vestibular suppressants can restrain the correc-

tion of vestibular tone imbalance, it may have impaired the central adaptive mechanism of the vestibular cerebellum. Although the exact pathophysiology of DCPN in DAD cannot be elucidated based on this study, we believe that the main site of drug action was the brainstem and/or vestibular cerebellum (not the peripheral vestibular apparatus).

We found the aging and VRT performance are independent prognostic factors of DAD. Old age is known to have a negative effect on the vestibular system. For instance, aging may cause degeneration and progressive loss of nerve cells in the peripheral and central vestibular system.[19] Also, the central compensation process deteriorates with aging. The central compensation determined by rotating chair responses was reduced in the elderly, resulting in slower balance control after an acute unilateral peripheral vestibular loss.[20] The prognosis of DAD in our elderly patients may also have been unsatisfactory due to the senile changes in the peripheral and central vestibular system, which is responsible for central compensation. Another possibility may be that the elderly patients were unable to perform the VRT efficiently, which could be due to lack of understanding or physical strength. We investigated this factor by comparing the age between the VRT compliant group (60.5±14.3) and the VRT non-compliant group (62.9±15.4), but found no difference, implying that compliance to VRT may be a separate and independent prognostic factor. Several systemic reviews and meta-analysis have reported that VRT is an effective management of vestibular dysfunction with moderate to strong evidence.[21-23] We believe that VRT provided a resolution of symptoms and improvement in functioning, even in our DAD patients.

The prognosis was good when the preceding vestibular disorder was BPPV, but unsatisfactory when it was VN. Why would the prognosis be different depending on the preceding vestibular disorder? One hypothesis may be that BPPV patients developed chronic dizziness due to the drug-induced central decompensation while the preceding vestibular disorder (BPPV) has been resolved. On the contrary, VN patients developed chronic dizziness due to the drug-induced central decompensation as well as the remaining asymmetry of the vestibular tone. That is, the reason for dizziness is central (DAD) plus peripheral (VN) in VN patient, while it is only central (DAD) in BPPV patients. This may also in part explain the high severity of symptom when the preceding vestibular disorder was VN.

To the best of our knowledge, this is the first study that focused on the prognostic factors of chronic dizziness due to long-term vestibular suppressant use. However, there are some limitations in the study that need clarification. This study was a retrospective review of medical records, so the causal relationship between the vestibular suppressant medication and symptoms/prognosis may not be certain. Due to the characteristic of chronic dizziness and long history, it was not sure if the patients truly constituted a homogeneous group. Furthermore, the patients in this study may not represent entire DAD patients. Structured history taking was always performed to control this limitation, but it may not be perfect. There was no control group employed in the present study. Further study with a proper control group may be needed to understand the sole clinical features and treatment outcomes of DAD.

Acknowledgments

This work was supported by the Materials/Parts Technology Development Program (Development of industry process of a new hyaluronic acid, 200 Pa·s or more, of more than 20 times compared to the existing for sustained-release DDS, 1415184765, 20016715) funded By the Ministry of Trade, Industry & Energy (MOTIE, Korea).

Author Contribution

Conceptualization: Myung-Whan Suh. Data curation: Younghoon Cho, Young Chul Kim, Jiyoung Lee, Myung-Whan Suh. Formal analysis: all authors. Investigation: Younghoon Cho, Young Chul Kim, Jiyoung Lee, Myung-Whan Suh. Methodology: Younghoon Cho, Young Chul Kim, Jiyoung Lee, Myung-Whan Suh. Project administration: Myung-Whan Suh. Resources: Myung-Whan Suh. Supervision: Seung Ha Oh, Sang-Yeon Lee, Jun Ho Lee, Moo Kyun Park, Myung-Whan Suh. Validation: Seung Ha Oh, Sang-Yeon Lee, Jun Ho Lee, Moo Kyun Park, Myung-Whan Suh. Writing—original draft: Younghoon Cho, Young Chul Kim, Jiyoung Lee. Writing—review & editing: Younghoon Cho, Young Chul Kim, Jiyoung Lee, Myung-Whan Suh.

ORCIDs

Younghoon Cho	https://orcid.org/0000-0002-9542-3916
Young Chul Kim	https://orcid.org/0000-0001-9123-3368
Seung Ha Oh	https://orcid.org/0000-0003-1284-5070
Sang-Yeon Lee	https://orcid.org/0000-0003-3566-8708

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