Original Article

Prevention of residual dizziness after repositioning maneuvers for benign paroxysmal positional vertigo with a combination of cinnarizine and dimenhydrinate

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Abstract

Backgrounds: Benign paroxysmal positional vertigo is a frequent complaint provoked by the detachment of otoconia from the utricle and their entry in a semicircular canal. Treatment is based on repositioning maneuvers; nonetheless, after successful maneuvers, some people refer an increase of instability without positioning vertigo or residual dizziness (RD).

Aims and Objectives: To decrease the number of cases of RD and duration of symptoms, different pharmacological therapies have been proposed. We assessed the efficacy of cinnarizine 20 mg and dimenhydrinate 40 mg twice a day for 1 week as treatment for RD.

Materials and Methods: We compared the presence and duration of RD in a sample of 177 patients treated with the association of cinnarizine 20 mg and dimenhydrinate 40 mg twice a day for 1 week after successful repositioning maneuvers with a sample of 118 nontreated subjects.

Results: No difference was seen in age, anxiety, duration of vertigo before treatment, and frequency of migraine between the two groups. Treated subjects had a lower rate of RD (30.5% vs. 14.1%, P = 0.0006) and duration of symptoms when present (5 ± 4 vs. 9 ± 7 days). Among treated subjects, 35 (19.8%) reported drowsiness and dry mouth at the beginning of treatment but without the need to discontinue therapy.

Conclusions: Our data support the hypothesis that this combination is useful in the prevention and therapy of RD.

Keywords: Benign paroxysmal positional vertigo, cinnarizine, dimenhydrinate, residual dizziness, therapy, vertigo

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most frequent peripheral vertigo, with a lifetime prevalence in adults of 2.4%.[1] BPPV is characterized by short episodes of vertigo provoked by a particular position of the head.[2] The episodes are normally grouped into periods of days or weeks and characterized by a tendency to relapse.[3,4] The accepted pathophysiological mechanism is the detachment of otoconial debris from the utricle macula and their entry into a semicircular canal;[5] Although head trauma, migraine, and

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autoimmune and vascular disorders have been described as possible risk factors, most cases are idiopathic.[3,4,6] Diagnosis of BPPV can be suspected based on clinical history, which mainly relies on clinical diagnostic maneuvers.[7] The treatment of BPPV involves the use of repositioning maneuvers that are specific for the semicircular canal involved.[2]

Although repositioning maneuvers are often successful, a variable percentage of patients continue to report, in the following days, a condition of persistent imbalance and unsteadiness without positional vertigo, known as residual dizziness (RD) and occurring in 30%-70% of patients.[8-10] Residual symptoms have been reported to last from days to even months.[8,10,11] Several theories have been proposed to explain the development of RD, such as the persistence of small debris in semicircular canals unable to provoke cupola deflection and nystagmus, presence of an unknown utricular dysfunction, incomplete central adaption after therapeutic maneuvers, and anxiety and emotional factors after acute vertigo.[9,11-15]

Many treatments have been proposed to approach RD, such as betahistine, polyphenol compounds, and vestibular suppressants.[16-18] Some authors have reported that dimenhydrinate at a dosage of 50 mg daily may be beneficial in the prevention of RD.[17]

In recent years, the combination of cinnarizine (20 mg) and dimenhydrinate (40 mg) has been proposed as a therapeutic measure in different vestibular disorders since it may have a synergic action on symptoms.[19]

Cinnarizine is an L-type calcium channel blocker that acts mainly on the peripheral vestibular system. It inhibits contractions of vascular smooth muscle cells with a vasodilator effect and inhibits vestibular hair cell stimulation.[20] Its efficacy in the management of peripheral vertigo and migraine prevention has been reported.[20-22] Possible side effects include drowsiness, sweating, and dry mouth.[23] Dimenhydrinate acts mainly on the central vestibular system, given its antihistaminic and anticholinergic action in preventing nausea and dizziness in motion sickness.[21]

Recent studies have evaluated the efficacy of a fixed combination of cinnarizine and dimenhydrinate in different vestibular disorders, including Meniere's disease,[9] vestibular neuritis,[24] and acute vestibular disorder.[25] The rationale for using a combination of cinnarizine and dimenhydrinate in a vestibular disorder provoked by migraine rather than cinnarizine alone relies on their synergic mechanisms of action. The combination has been proposed to be useful as a therapy in several vestibular disorders; due to its anticholinergic action, dimenhydrinate should be avoided in subjects with prostate hypertrophy and closed-angle glaucoma.[26]

The aim of our study was to assess the efficacy of the combination of cinnarizine (20 mg)/dimenhydrinate (40 mg) in the treatment of RD in a large cohort of patients.

MATERIALS AND METHODS

In this retrospective study, 295 subjects were recruited at our university center between 2014 and 2017. Patients were included if they had a final diagnosis of BPPV; patients were diagnosed with a video-Frenzel (Interacoustics – Assens – Denmark). The study was approved by our Ethics Committee (103/INT/2020) and was performed in accordance with the Declaration of Helsinki. All patients underwent routine repositioning maneuvers. A Semont or Epley maneuver was performed for the posterior canal, and a barbecue or Gufoni maneuver for both the geotropic or apogeotropic forms involving the lateral canal. Repositioning maneuvers were performed every 2–3 days until the complete resolution of the BPPV. In all, 210 patients had a complete resolution after the first maneuver, 81 after the second, and 4 patients after the third maneuver. Repositioning maneuvers were performed at least 1 h after the previous one; they were suggested to start therapy in order to prevent or at least reducing RD only if the further diagnostic maneuvers were negative.

No other experimental procedure was performed. Data from the study were presented at a meeting in Halle in 2018.

Inclusion criteria were the presence of primary BPPV and age between 20 and 80 years. Patients were excluded if reported previous BPPV, vestibular neuritis, posttraumatic or postneuritis BPPV, Menière's disease, a central nervous system disease other than migraine, diabetes, alcohol or drug addiction, uncontrolled hypertension, hypotension, thyroid disease, severe coronary artery disease, severe renal and/or hepatic impairment, antiplatelet and/or anticoagulant therapy, pregnant or breastfeeding, chronic instability of any kind preexisting at the onset of BPPV, or known intolerance to cinnarizine or dimenhydrinate. Drug therapy was also avoided in subjects with prostate hypertrophy and closed-angle glaucoma.

The main outcome was the presence and duration of RD, defined as the sensation of imbalance or unsteadiness or light heavy-headedness, without rotational or positional vertigo.

To minimize possible RD, after successful maneuvers, patients were proposed therapy with cinnarizine/dimenhydrinate for at least 10 days, and informed about possible side effects of the drug combination. One hundred and seventy-seven accepted the therapy (Group T, therapy), while 118 decided not to use it (Group N). All patients were asked to provide information on the presence and duration of RD in the following days through E-mail replying to the question "do you feel imbalance or heavy lightheadedness? If yes, how long does this symptom lasted?" after 10 and 20 days. Patients were asked to take one tablet twice daily for at least 7 days; it was also suggested to continue therapy if they did not have complete recovery from symptoms. We decided on a reduced dose of the combination to limit side effects (drowsiness above all).

The following data were collected during the first consultation with patients in both the groups:

- Duration of symptoms before consultation
- Number of maneuvers
- A visual analog scale (VAS) scale for the question "how much do you feel anxious for your vertigo?," where 0 is no anxiety and 100 the greatest anxiety
- Lifetime history of migraine according to the International Headache Society (HIS) criteria.[27]

Statistical analyses

A repeated measure analysis of variance was carried out to compare the number of vertigo attacks and the number of headaches between the two groups and the change over time. Continuously distributed variables were compared with a *t*-test for independent samples. The Chi-square test was used to assess differences for nominal values.

RESULTS

No difference was seen in age (56.2 ± 7 in Group T and 58 ± 11 in Group N, $P = 0.08$) and sex between the two groups (89/177, 50.2% of females in Group T vs. 61/118, 51.6% in Group N, P = not significant [ns]).

RD was reported in 25 of 177 subjects of Group T (14.1%) and in 36/118 (30.5%) in Group N ($P = 0.0006$) after a demonstrated complete resolution of BPPV.

Migraineurs were equally represented in the two groups and 27 of 177 (15%) in Group T and 16/118 (13.6%) in Group N had a lifetime history of migrainous headaches (ns).

There was no significant difference in VAS anxiety in the two groups (35 ± 15 in Group T vs. 32 ± 10 in Group N).

In the entire sample, the median for the VAS scale was 34, and higher anxiety levels were associated with a longer duration of RD (8.4 ± 2.1 days vs. 5.2 ± 1.9, $P = 0.01$). Duration of vertigo before repositioning maneuvers was similar in the two groups (13.8 ± 4.2 days in Group T and 14 ± 3.8 days in Group N).

The number of maneuvers did not differ between the two groups (1.3 ± 0.2 in Group T and 1.2 ± 0.3 in Group N).

The duration of RD in Group T was 5 ± 4 days compared to 9 ± 7 in the Group N ($P = 0.001$). The results are summarized in Table 1.

Among treated patients, 35 (19.8%) reported drowsiness and/or dry mouth during therapy, but normally decreased in 2–3 days, and discontinuation of therapy was not needed in any patient.

DISCUSSION

RD after repositioning maneuvers for BPPV is very common, reported in almost 50% of cases,[8] although in a previous invastigation it was found in about 30% of patients with idiopathic BPPV.[15] Patients often describe the sensation of imbalance or unsteadiness in the absence of the positional vertigo characterizing BPPV.

Several possibilities have been considered for the persistence of symptoms:

a. The presence of a small quantity of debris, *per se* insufficient to provoke symptoms

Table 1: Results

	Treated (*n*=177)	Not-treated (*n*=118)	*P*
Age	56±7	58±11	NS
Sex/female, *n* (%)	89 (50.2)	61 (51.6)	NS
Subjects with RD at day 10, *n* (%)	25 (14.1)	36 (30.5)	0.0006
Duration of RD (days)	5±4	9±7	0.01
Migraine	27/177 (15)	16/118 (13.6)	NS
VAS anxiety	35±15	32±10	NS
Duration of vertigo before maneuvers (days)	13.8±4.2	14±3.8	NS
Number of maneuvers	1.3±0.2	1.2±0.3	NS

NS: Not significant, RD: Residual dizziness, VAS: Visual Analogue Scale

b. The necessity of compensation of the vestibular system after successful repositioning maneuvers
c. The anxiety developed by the patient (in this case the duration of symptoms before repositioning maneuver may play a role)
d. The presence of another disorder of the peripheral vestibular system (i.e., a primitive utricular disorder) that may be involved in RD.

Regarding point c, in our sample anxiety was evaluated with a simple VAS scale and duration of BPPV before repositioning maneuvers were similar in the two groups.

In addition, migraine did not play a role in our cohort since there was no difference between the two groups.

However, the finding of a reduced number of subjects reporting RD in the 10 following days after successful repositioning maneuvers and duration of symptoms underline the possibility of a pharmacological benefit. Above all, the efficacy of the combination is not inconsistent with the possibility that after repositioning maneuvers a compensation of the vestibular system is required as well as an undiagnosed macular disorder may play a role in the development of symptoms.

Moreover, cinnarizine and in particular the combination of cinnarizine and dimenhydrinate has been proposed in several conditions in the spectrum of vertigo – instability. Among these, it was demonstrated to be useful in different peripheral vestibular disorders[19-26,28,29] and in motion sickness.[30] It can be postulated that active therapy may, on the one hand, reduce symptoms and, on the other hand, promote vestibular compensation.[31]

The presence of calcium channel blockers has been demonstrated in the inner ear; for example, the saccular region has at least two different types of calcium channels; although the role of these drugs has been postulated in the regulation of maculae, the mechanism of calcium sequestration from endolymph through calcium pores is partially unknown.[32]

Dimenhydrinate, on the other hand, is a first-generation histamine antagonist that is active on H1 receptors. It is among the most used drugs in the treatment and prevention of motion sickness or symptoms of nausea and dizziness.[28]

A synergic action may be postulated, possibly by decreasing the dose of each drug. Cinnarizine exerts its action on the peripheral vestibular system by inhibiting calcium influx into vestibular hair cells, thus regulating their afferent transmission. Dimenhydrinate acts mainly on the central vestibular system with antihistaminergic and anticholinergic action, and prevents nausea by acting on the vomiting center and reducing motion sickness.[25]

In our opinion, the main limitation of our work is the lack of a placebo control group, making it impossible to evaluate the placebo effect.

CONCLUSIONS

RD is a frequent condition whose manifestation, in many cases disabling, is a long-lasting imbalance. The combination of cinnarizine and dimenhydrinate appears to be useful to prevent and shorten RD; at the dose adopted herein, side effects were limited, and the drug was generally well tolerated.

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Conflicts of interest
There are no conflicts of interest.

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