Antivertiginous drug therapy does not hinder the efficacy of individualized vibrotactile neurofeedback training for vestibular rehabilitation – a randomized trial

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Vestibular rehabilitation using individualized vibrotactile neurofeedback training (IVNT) can lead to significant improvement in the postural stability of patients with vestibular symptoms of different origins. However, some of these patients have complex, severe dizziness, meaning that a pharmacological pretreatment or parallel (to vestibular rehabilitation) treatment can help them perform the rehabilitation exercises. Hence, the present study investigated the influence of a pharmacological treatment on the efficacy of vibrotactile neurofeedback training in patients with chronic, noncompensated vestibulopathies. All participants performed IVNT for ~10 min each day for 2 weeks. In addition, every second participant was selected randomly to receive oral medication (20 mg cinnarizine and 40 mg dimenhydrinate per tablet), taking three tables per day. Trunk and ankle sway and postural stability were measured. In addition, the dizziness handicap inventory was evaluated immediately before training on the last day of training and 6 months after training. After the 10-day period of IVNT, both groups showed a statistically significant improvement in all parameters tested. A follow-up analysis after 6 months showed a long-term efficacy for the IVNT, that is, the patients remained significantly improved in their postural stability. The antivertiginous therapy did not hinder the efficacy of the IVNT. The present results indicate that IVNT even in combination with an antivertiginous drug therapy is an effective treatment regime for patients with disabling vertigo of different origins. *International Journal of Rehabilitation Research* **00:000–000**

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Introduction

Vestibular rehabilitation has the primary aim of promoting vestibular habituation and, thus, improving balance function. Most rehabilitation programs should be started as early as possible and should include feedback mechanisms to speed up adaptation and sensory substitution of the impaired vestibular function (Deveze *et al.*, 2014; Lacour and Bernard-Damanze, 2015). In general, the vestibular rehabilitation protocols should be individualized to provide the best possible outcome for the patients (Tjernström *et al.*, 2016). The latest update of the Cochran Database of Systematic Reviews indicates that moderate to strong evidence exists to support vestibular rehabilitation training being applied effectively for patients with unilateral peripheral vestibular dysfunction, with the highest evidence for individualized vibrotactile neurofeedback training (IVNT) (Hillier and McDonnell, 2007; McDonnell and Hillier, 2015).

It has also been shown that vestibular rehabilitation using IVNT significantly increases postural control in almost all patient groups with chronic vertigo (Basta *et al.*, 2011; Rossi-Izquierdo *et al.*, 2013). One important prerequisite for such rehabilitation is the ability of the patient to perform complex exercises. Moreover, the patients with multitopic lesions within the vestibular system and a variety of symptoms (e.g. dizziness, nausea, vomiting, blurred vision) require additional medication to complete a vestibular rehabilitation program (Eleftheriadou *et al.*, 2012).

Two commonly used substances for this specific purpose are cinnarizine, a selective calcium channel antagonist, and dimenhydrinate, an H1 receptor antagonist antihistaminergic drug (Hain and Uddin, 2003). Cinnarizine acts mainly peripherally on the vestibular labyrinth through modulation of calcium–ion fluxes (Godfraind *et al.*, 1982; Arab *et al.*, 2004; Duwel *et al.*, 2005), whereas dimenhydrinate acts mainly centrally on neurons of the vestibular nuclei (Jaju and Wang, 1971; Soto and Vega, 2010). Because of synergetic effects, the combination of both substances was shown to be more effective in the treatment of vertigo symptoms than either substance alone (Novotny *et al.*, 1999; Scholtz *et al.*, 2004).

These two active ingredients have been used successfully as a combined low-dose drug for more than 30 years in the treatment of both central and peripheral vertigo (Schremmer *et al.*, 1999; Novotny and Kostrica, 2002; Scholtz *et al.*, 2004, 2012; Cirek *et al.*, 2005; Pytel *et al.*, 2007; Kessler *et al.*, 2012). Recently, data have suggested good tolerability and efficacy of this preparation in long-term daily use, rather than in controlled clinical trials (Scholtz *et al.*, 2016).

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Central compensation of vestibular deficits is essentially a physiological process, re-evaluating remaining, nonimpaired, or nonvestibular stimuli (e.g. the postural muscles, vision, and proprioception) to maintain balance (Deveze *et al.*, 2014). The treatment of vertigo with vestibulosuppressant drugs might negatively affect central vestibular compensation (Rascol *et al.*, 1995; Hain and Uddin, 2003). In animal models, dimenhydrinate has a negative effect on the speed of vestibular compensation (Peppard, 1986). This might be disadvantageous for an effective rehabilitation program. Randomized studies in healthy volunteers showed no significant impairment in vigilance after taking the combination of dimenhydrinate and cinnarizine compared with betahistine [which is considered nonsedating (Schneider *et al.*, 2003)] and placebo (Philipova *et al.*, 2004).

The aim of this study was therefore to investigate the influence of an antivertiginous drug therapy (fixed combination of cinnarizine/dimenhydrinate) on the efficacy of IVNT for vestibular rehabilitation.

Patients and methods

Patients

All participants reported dizziness and instability under daily life conditions. Those with otolith disorders suffered more than all other types of vestibular disorder from increased instability on soft surfaces. Patients with presbyvertigo reported an enhanced fear-to-fall, especially in twilight.

The total sample included 42 participants who had chronic, noncompensated vestibular dysfunction: 24 with presbyvertigo, 14 with unilateral horizontal semicircular canal loss, and four with unilateral saccular disorders. The required sample size was determined using the GPower 3.1 software (University of Kiel, Kiel, Germany). Using a parallel study design, the study population was divided randomly into two groups of 21 participants, each group having a similar distribution of pathologies (12 with presbyvertigo, seven with unilateral horizontal semicircular canal function loss, and two with unilateral saccular disorders). Thus, each group consisted of 21 participants. Group 1 received a combined treatment with medication and IVNT and included 12 female patients and nine male patients with a mean age of 63.3 ± 13.1 years. Group 2 received only IVNT treatment and included nine women and 12 men, with a mean age of 68.3 ± 13.3 years. The two groups did not differ significantly with respect to sex ($P = 0.537$) or age ($P = 0.223$).

Vestibular testing to clearly differentiate between the semicircular canal and otolith disorders was performed just before treatment began. The test battery included caloric testing (horizontal semicircular canal function), recording of cervical vestibular evoked myogenic potentials (cVEMP, saccular function), and analysis of subjective haptic vertical (utricular function).

None of the participants showed severe nonvestibular sensory deficits (e.g. polyneuropathy), an acute vestibular disorder, or medication that would actively influence the vestibular system. No other treatment was provided for balance disorder during the study period.

Interventions

Individualization of the rehabilitation program started with a body sway analysis (mobile posturography) using the diagnostic tool of the VertiGuard System (Zeisberg GmbH, Metzingen, Germany). The device was mounted with a belt at the hip close to the center of mass. Patients performed the standard balance deficit test (SBDT) (Basta *et al.*, 2011, 2013), a set of 14 different everyday life stance and gait conditions. The results of the body sway analysis were compared with age-related and sex-related normative values.

Participants older than 59 years performed the geriatric standard balance deficit test (gSBDT). Here, difficult tasks, such as standing on one leg with eyes closed or standing on one leg with eyes open on foam, were replaced by the tasks 'stand up' and 'sit down' (Basta *et al.*, 2011, 2013). For all stance tasks, the measurement time was 20 s and as long as required for gait tasks. The SBDT composite score, a risk-of-falling indicator, was calculated as the sum of ratios of all SBDT/gSBDT task scores to their age-related and sex-related normative values in anterior/posterior and lateral directions.

The individualized training program consisted of up to six tasks including the SBDT or gSBDT tasks with the most prominent deviations from normative control values (Basta *et al.*, 2011; Rossi-Izquierdo *et al.*, 2013). Individualized training was performed daily under supervision over 2 weeks, resulting in 10 sessions as the weekend was excluded. A training session consisted of five repetitions of each selected training task. Each repetition took a maximum of 20 s. During training, participants received a vibrotactile feedback signal for those directions that showed a higher body sway than preset individual thresholds. The preset threshold for each training task was based on the age-related and sex-related normative values and could be modified in a limited range to adjust the feedback on the participant's performance. No vibrotactile feedback was applied if the participant's sway was below a preset threshold.

For all participants, IVNT was performed daily (10 min) over 2 weeks with the VertiGuard system (Zeisberg GmbH). Over the same period, participants in group 1 received additional treatment with a fixed combination of 20 mg cinnarizine and 40 mg dimenhydrinate (Arlevert, Hennig Arzneimittel, Floersheim am Main, Germany) three times daily. Participants in group 2 received no additional medication during the training period.

Outcome measures

Outcome measures were calculated immediately before and after the rehabilitation, as well as 6 months after the training period.

The primary outcome measure was the SBDT composite score, recorded after the last training session and without any feedback signal. This score is scaled between 0 and 100, where 100 represents the highest risk of falling and thus represents the lowest stability.

Furthermore, each participant underwent the sensory organization test (SOT) on the ankle sway reference platform BalanceMaster (Nicolet Biomedical, Clackamas, Oregon, USA). Measurements were taken during three repeated 20 s runs under six sensorimotor standing conditions (Nashner, 2001). The SOT composite score is scored between 0 and 100, with the highest score indicating maximal stability.

All participants were also asked to fill in the dizziness handicap inventory (DHI) questionnaire (Kurre *et al.*, 2009). This questionnaire characterizes disability resulting from balance impairment, with scores ranging between 0 and 100. The maximum score represents the greatest disability.

Statistical analysis

δScores were calculated by subtracting the pretraining from the post-training value (pre–post change score). The Kolmogorov–Smirnov test was chosen for testing the data distribution. Normally distributed data were analyzed using the *t*-test for independent samples (δ scores) or dependent samples (mean), whereas for non-normally distributed data, the Mann–Whitney *U*-test (independent samples) or Wilcoxon's test (dependent samples) was used. The level for significance of all tests was *P* value less than 0.05. Bonferroni α corrections were applied for multiple comparisons.

Both the study and the manuscript were prepared in accordance with the CONSORT 2010 guideline and checklist for randomized clinical trials.

The Institutional Review Board approved the study protocol and the study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

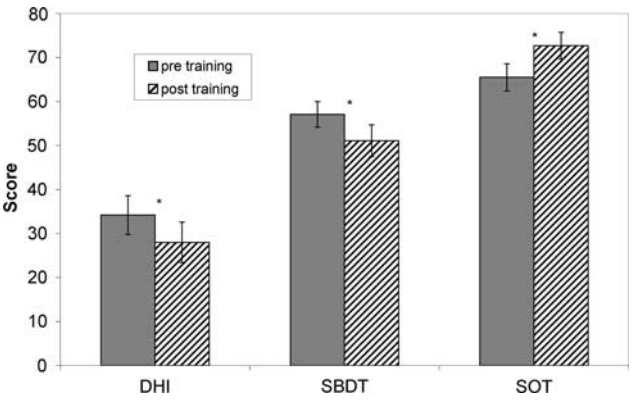
Results

Group 1

Objective parameters such as SBDT and SOT scores as well as subjective parameters such as DHI scores were calculated before and after the training period for the group receiving IVNT and medication interventions (Fig. 1).

The group 1 SBDT composite score before training was 57.1 ± 2.9, decreasing to 51.1 ± 3.6 after training. This improvement was statistically significant. A significant improvement in the SOT composite score was found when comparing pretraining and post-training results: 65.5 ± 3.1 and 72.7 ± 3.0, respectively. DHI scores following training were decreased: 34.2 ± 4.4 pretraining and 28.0 ± 4.6 post-training, this change representing a significant improvement.

Fig. 1



Mean ± SEM values of the dizziness handicap inventory (DHI, $P = 0.001$, paired *t*-test), the standard balance deficit test (SBDT, $P = 0.014$, paired *t*-test), and the sensory organization test (SOT, $P = 0.006$, paired *t*-test) before and after an individualized vibrotactile neurofeedback training for group 1, which received additional medication (cinnarizine 20 mg and dimenhydrinate 40 mg). *Significant differences. The level for significance was *P* less than 0.05.

The post-training results were compared with measurements that were performed 6 months later (Fig. 2). The DHI score after 6 months was 27.3 ± 0.7. This was not statistically significantly different compared with the post-training level. The SBDT composite score was 50.2 ± 3.3 and the SOT score was 71.8 ± 2.9. Neither of these scores was significantly different from post-training results.

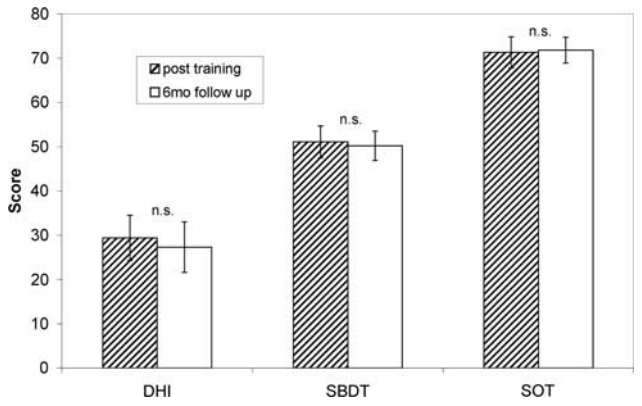
Group 2

Pretraining and post-training results were compared for the group that performed individualized training only, without medication intake. Significant changes were found for SBDT, SOT, and DHI scores (Fig. 3).

The SBDT composite score before training was 59.6 ± 3.5 and decreased to 52.3 ± 2.5 after training. This difference was statistically significant. The SOT composite score showed a significant improvement on comparing pretraining and post-training results: 65.4 ± 3.0 and 69.4 ± 3.3, respectively. DHI scores were statistically significantly improved on comparing pretraining and post-training results: 38.0 ± 4.3 before training and 28.9 ± 4.2 after training.

No statistically significant differences were observed when group 2 post-training results were compared with the 6-month follow-up results (Fig. 4). After 6 months,

Fig. 2



Mean ± SEM values of the dizziness handicap inventory (DHI, $P = 0.504$, paired t-test), the standard balance deficit test (SBDT, $P = 0.63$, paired t-test), and the sensory organization test (SOT, $P = 0.741$, paired t-test) directly after the individualized vibrotactile neurofeedback training and 6 months after the training period for group 1, which received additional medication (cinnarizine 20 mg and dimenhydrinate 40 mg). The level for significance was P less than 0.05.

Fig. 3

Mean ± SEM values of the dizziness handicap inventory (DHI, $P = 0.01$, paired t-test), the standard balance deficit test (SBDT, $P = 0.003$, paired t-test), and the sensory organization test (SOT, $P = 0.022$, Wilcoxon's test) before and after an individualized vibrotactile neurofeedback training for group 2, which received no additional medication. *Significant differences. The level for significance was P less than 0.05.

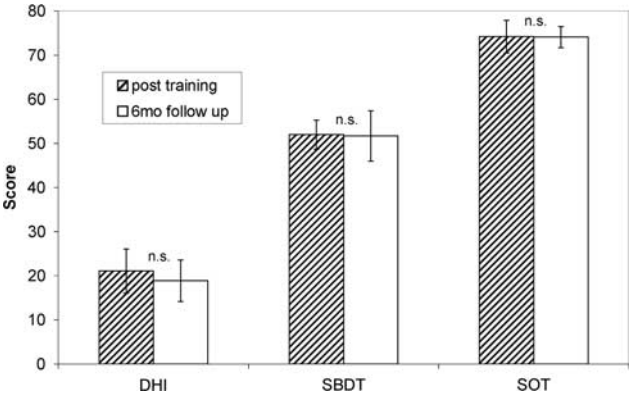
the composite score of SBDT was 51.7 ± 5.7. This change in the score was not statistically significantly different compared with the post-training level. After 6 months, the SOT composite score was 74.1 ± 2.4 and the DHI score was 18.9 ± 4.7. The changes in these scores were also not statistically significantly different compared with the post-training scores.

Intergroup comparison

δ scores for outcome parameters were calculated to examine possible effects of the pharmacological treatment with cinnarizine/dimenhydrinate on the efficacy of the IVNT. No statistically significant between-group differences were found for the DHI questionnaire, the SBDT, and the SOT (Fig. 5). For group 1, δ scores before were -6.2 ± 1.7 for DHI, -5.9 ± 2.1 for SBDT, and 7.2 ± 2.1 for SOT. In group 2, the δ scores reached values of -9.1 ± 3.1 for the DHI, -7.3 ± 2.2 for the SBDT, and 4.0 ± 1.6 for the SOT.

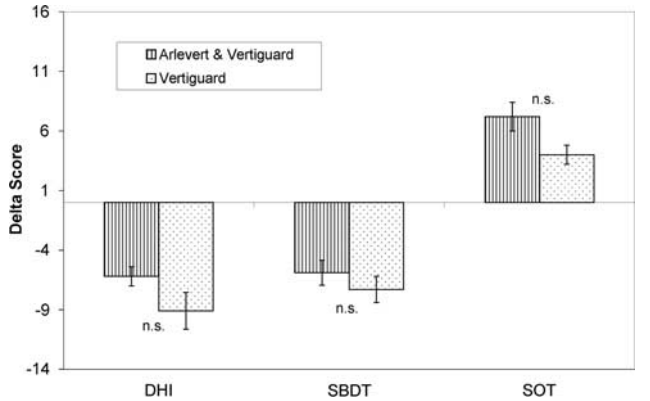
Comparing scores between 6 months after training with the scores recorded immediately after training, δ scores for objective and subjective tests between groups did not differ significantly (Fig. 6). In group 1, δ scores were -2.1 ± 3.1 for

Fig. 4



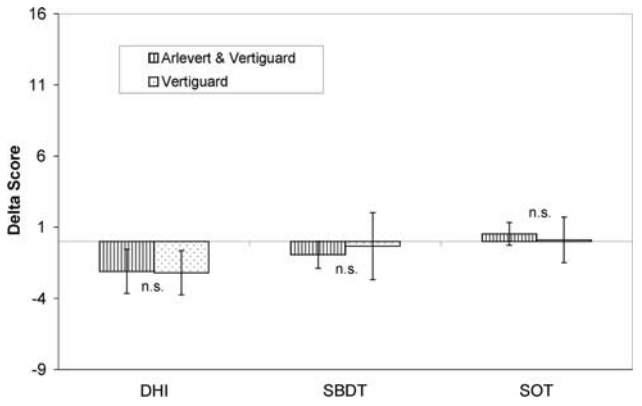
Mean ± SEM values of the dizziness handicap inventory (DHI, $P = 0.499$, paired t-test), the standard balance deficit test (SBDT, $P = 0.946$, paired t-test), and the sensory organization test (SOT, $P = 0.97$, Wilcoxon's test) directly after an individualized vibrotactile neurofeedback training and 6 months after the training period for group 2, which received no additional medication. The level for significance was P less than 0.05.

Fig. 5



δ-Scores (post-training minus pretraining value) of the dizziness handicap inventory (DHI, $P = 0.421$, t-test), the standard balance deficit test (SBDT, $P = 0.662$, t-test), and the sensory organization test (SOT, $P = 0.263$, U-test) before and after an individualized vibrotactile neurofeedback training for group 1 (with additional medication of cinnarizine 20 mg and dimenhydrinate 40 mg) compared with group 2 (without additional medication). The level for significance was P less than 0.05.

Fig. 6



δ-Scores (post-training minus pretraining value) of the dizziness handicap inventory (DHI, $P = 0.984$, t-test), the standard balance deficit test (SBDT, $P = 0.894$, t-test), and the sensory organization test (SOT, $P = 0.84$, U-test) directly after an individualized vibrotactile neurofeedback training and 6 months after the training period for group 1 (with additional medication of cinnarizine 20 mg and dimenhydrinate 40 mg) compared with group 2 (without medication). The level for significance was P less than 0.05.

the DHI, $-0.93.2 \pm 1.9$ for the SBDT, and 0.53 ± 1.6 for the SOT. δ-Scores for group 2 were -2.2 ± 3.1 for DHI, -0.33 ± 4.7 for SBDT, and 0.11 ± 3.2 for SOT.

Discussion

In this paper, the influence of an antivertiginous drug therapy on the efficacy of IVNT has been analyzed. The application of the fixed low dose of cinnarizine/dimenhydrinate medication was shown to be effective in the suppression of vertigo-associated adverse effects such as nausea, vomiting, or blurred vision during the training period. The positive effects of IVNT, quantified by a set of specific outcome parameters, (DHI, SBDT, and SOT), were not significantly different between groups. This suggests that the concomitant intake of cinnarizine/dimenhydrinate at dosages applied in the present study did not significantly compromise the central compensation processes that are considered important for the full efficacy of the IVNT.

This finding is in line with the results of other clinical studies. In patients with vestibular neuritis, the cessation of spontaneous nystagmus within a few weeks is modulated through vestibular compensation (Halmagyi *et al.*, 2010). Similar effects were observed in patients with vestibular neuritis treated with a combination of cinnarizine (20 mg) and dimenhydrinate (40 mg) (Scholtz *et al.*, 2012). After 4 weeks, a nearly complete cessation of spontaneous nystagmus was observed, indicating that the use of this medication did not interfere with the central compensation processes. In accordance with these findings Vanspauwen *et al.* (2011), a statistically significant effect on the sacculocollic reflex arch (cVEMP parameters p1-latency and p1/n1-interpeak-latency) was observed. This effect was observed only after the intake of promethazine and D-amphetamine, but not for cinnarizine (20 mg) and dimenhydrinate (40 mg). Furthermore, the administration of scopolamine accelerated the sacculocollic reflex by decreasing cVEMP p1-latency, whereas cinnarizine (25 mg) or dimenhydrinate (100 mg) did not (Tal *et al.*, 2016).

However, Holtmann *et al.* (1989) reported that, compared with a placebo, a high dose of dimenhydrinate (100 mg) significantly interfered with the vestibulo–ocular reflex, reducing the nystagmus slow-phase velocity during caloric irrigation or after rotational testing, and with the optokinetic reflex. This indicates an attenuation of processing of vestibular and visual stimuli in the central nervous system which represents the primary mechanism involved in the antivertiginous effect of dimenhydrinate. In addition, a reduced excitability of peripheral vestibular receptors was also found in these experiments. An effect on peripheral vestibular receptors is expected more for cinnarizin than for dimenhydrinate. Shupak *et al.* (1994) showed that reflex gain values in response to sinusoidal oscillations on a rotatory chair were significantly reduced compared with placebo after the intake of 25 mg cinnarizine. This dosage is close to that applied in the present study. In contrast, the dosage of dimenhydrinate was much lower than that in the study of Holtmann *et al.* (1989) mentioned above. Thus, the attenuation of central nervous system processing that impairs vestibular compensation appears to be very limited at low dosage as the rehabilitation results in the present study were excellent and not different for the group taking medication compared with the group receiving only IVNT rehabilitation.

The present study could not prove whether this holds true for other, less effective methods of vestibular rehabilitation that largely consist of vestibular physiotherapy.

Vestibular rehabilitation using IVNT significantly improved balance recovery in patients treated in parallel with cinnarizine/dimenhydrinate as well as in patients without medication. Body sway and dizziness symptoms decreased similarly in both groups. On the one hand, the high efficacy of the IVNT is based on the individualized training. Individualized vestibular rehabilitation alone was shown to be more efficient in improving quality of life than performing general balance exercises (Morozetti *et al.*, 2011; Lacour and Bernard-Damanze, 2015). On the other hand, the very intuitively directed tactile feedback signal significantly improves the training effect through motor learning (Lacour *et al.*, 2016).

Follow-up analysis after 6 months showed long-term stability of the positive effects of IVNT in both intervention groups. This observed long-term effect is in line with earlier studies in patients with chronic severe vestibular disorders or with Parkinson's disease, where only a small number of supervised sessions were sufficient to obtain a long-lasting improvement in postural stability (Rossi-Izquierdo *et al.*, 2009, 2013; Basta *et al.*, 2011).

The present results indicate that the IVNT in combination with a fixed low-dose combination of cinnarizine/dimenhydrinate can be applied effectively in participants with severe vertigo symptoms. Significant improvements in objective parameters such as SBDT or SOT score and subjective parameter such as the DHI questionnaire might reflect the success of the IVNT even while taking cinnarizine (20 mg) and dimenhydrinate (40 mg) three times daily.

Patients gain an additional benefit from the medication, and so can perform the IVNT rehabilitation program without limitations or impairment of central compensation. No additional beneficial effect of the pharmacotherapy on the IVNT efficacy was found, either directly after the rehabilitation program or at the 6-month follow-up visit.

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Conflicts of interest

There are no conflicts of interest.

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