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Contributors All authors have made an intellectual contribution to this protocol. Li Huawei is the principal investigator of the trial, with full responsibility for the project. Wu PX, Cao WZ and Hu Yan conceived the design, developed the protocol and wrote the first draft of this manuscript. Li Huawei and Hu Yan revised and approved the final version of the study protocol and the final manuscript. Li Huawei and Hu Yan are co-corresponding authors whom contributed this paper equally.

Abstract

Introduction

Benign paroxysmal positional vertigo (BPPV) is recognized as the leading cause of periphery dizziness in adults. Canalith repositioning procedure (CRP) can effectively treat BPPV. However, a certain group of patients experience residual dizziness (RD) even after successful CRP, bringing a significantly negative impact on their daily function and quality of life. Exercise-based vestibular rehabilitation (VR) has proven to be an effective way for managing dizziness and has been applied in patients with different vestibular disorders. However, the effectiveness of VR specifically targeted RD post BPPV is unknown. This study aims to investigate the effectiveness of VR, compared with betahistine or VR plus betahistine, in patients experiencing RD after successful CRP.

Methods and analysis

A randomized single-blinded controlled trial will be carried out to determine the effectiveness of VR, compared with betahistine or VR plus betahistine, in mitigating RD and improving balance function. Patients with BPPV after successful CRP and complain of experiencing RD will be recruited. Participants will be randomized into one of three groups to receive VR or betahistine or VR plus betahistine. There will be 61 participants in each group. Primary outcomes are changes of patients' daily function measured by Vestibular Activities and Participation (VAP) questionnaire and balance ability assessed by computerized dynamic posturography (CDP). Secondary outcomes will assess quality of life, otolith function, and duration of symptoms.

Outcome measures will be taken at baseline, 4 -week, 8-week and 12-week post randomization. This study has the potential to arrive at stopping unnecessary anti-vertigo drugs prescriptions and

may lead to the consensus of using VR as the first-line treatment for RD in patients with BPPV.

Ethics and dissemination

This trial received ethics approval from Institute Review Board of Eye & ENT Hospital of Fudan University (2017046). Study results will be disseminated through peer-reviewed journals and conferences.

ClinicalTrials.gov identifier: NCT03624283

Strengths and limitations of this study

►To our knowledge, this is the first randomized controlled trial evaluating the effects of vestibular rehabilitation, compared with betahistine or VR in addition to betahistine,, on managing residual dizziness after successful CRP in patients with BPPV.

► Both subjective and objective outcome measures are comprehensively assessed with reasonable long follow-up time. In Particular, patients' activities and participation aspect based on International Classification of Functioning, Disability and Health (ICF) framework are evaluated. Such a trial will be able to fully reflect the efficacy of proposed intervention.

► For practical reason, there is no sham or placebo or no treatment as comparison group in this study; therefore, the study cannot tell whether participants improve simultaneously or how the three interventions may work in different ways to change outcomes.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the leading cause of peripheral dizziness, with a prevalence from 10.7 to 64 per 100,000 populations and a lifetime prevalence of 2.4%.[1] The onset time is most commonly between the fifth and seventh decade of life, but BPPV could occur at any age.[2] Two theories --- cupulolithiasis[3] and canalithiasis[4], are among the most widely accepted theories that elucidate the pathophysiology of BPPV. Canalithiasis has gained wider acceptance among the scientific field due to the symptoms being better explained.[5] According to the canalolithiasis hypothesis, BPPV is caused by free otoconia dislodged from the utricular macula and entering into the semicircular canal, which therefore provokes an inappropriate flow of endolymph whenever the head is rotated in the plane of the affected canal.[4] Although any of the three semicircular canals can be affected, the posterior semicircular canal BPPV is the most common, followed by horizontal canal BPPV. Treatment of BPPV is based on the performance of canalith repositioning procedure (CRP), with the aim of repositioning the displaced particles from the affected canal to their original location.[6] CRP has long emerged as a mainstay of therapy and now is well established as the gold treatment for BPPV.[7] Posterior canal BPPV can be treated by performing Epley's maneuver or Semont's liberatory maneuver. For horizontal canal BPPV, Barbecue rotation or Gufoni's maneuvers have been shown effective.

Despite the fact that CRP can provide rapid relief of vertigo sensation in BPPV patients, residual symptoms may remain even after disappearance of typical vertigo and nystagmus following a successful CRP. These residual symptoms, also referred residual dizziness (RD), imply a non-specific sensation of unsteadiness, lightheadedness, disorientation, fogginess or drowsiness.[8] The reported incidence of RD ranges from 29.6% to76.9% and the duration of RD can range from

a few days to several months.[8-12] Several Authors reported that RD symptoms may persist up to more than 3 months [13, 14], bringing adverse physical and psychological consequences to these patients.

Different pathophysiological mechanisms have been proposed to explain the presence of RD but the real cause remains unknown. Previously reported possible explanations included: (1) the persistence of debris in the canal being insufficient to provoke detectable positional nystagmus or vertigo;[11] (2) otolith dysfunction;[15, 16], (3) coexistent vestibular disease that lead to incomplete central adaptation; (4) potential autonomic dysfunction such as orthostatic hypotension[17], (5) persistent postural-perceptual dizziness (PPPD).[18]

Dizziness increases the risk of falls or fear of falling, disturbs daily life, and results in restriction of social activities. As a result, many people tend to avoid activities, limit their movement, and avoid specific circumstances because of fear of provoking dizziness and unanticipated unsteadiness attacks.[19] It is not surprised that increased postural instability was documented in patients who experiencing RD[20, 21]. Given that high prevalence of RD after successful repositioning and its negative impact on patient recovery, this impairment should be managed properly.

To date, there is no agreement on how to effectively manage RD after successful CRP in patients with BPPV. Betahistine is the most widely used medication to ameliorate dizziness, due to its effects of increasing labyrinthine microcirculation, suppressing the increased neuronal activity in vestibular receptor cells, afferent neurons, and vestibular nuclei.[11, 22] However, conflicting data exists regarding the efficacy of betahistine for preventing or treating RD. Guneri., et al. [23] evaluated the efficacy of betahistine in reducing symptoms after Epley maneuver for posterior

canal BPPV, they found 48 mg of betahistine daily intake demonstrated more effective results than Epley maneuver alone or combined with placebo in improving symptoms assessed by four different vertigo symptoms scales. On the contrary, Acar., et al.[24] carried out a randomized controlled clinical trial to investigate the efficacy of betahistine, compared with a no medication group, for the treatment of RD after successful CRP. After 3 and 5 days of treatment, the mean DHI (Dizziness Handicap Inventory) scores of the groups receiving medication did not differ from the mean DHI score of the control group, indicating betahistine did not produce any more alleviation of RD than no treatment. However, both studies have unclear randomization sequence generation, allocation concealment and only included subjective outcomes, suggesting more rigorous methodology of clinical trials that including comprehensive outcomes assessment are warranted.

Recently, non-pharmacological interventions, such as vestibular rehabilitation (VR), are recommended as the first line of treatment for chronic vertigo.[22] VR, which has been available since 1940s, is an exercise-based treatment consisting of varied eye, head, and body movements designed to stimulate the vestibular system and optimize vestibular compensation.[25] Current VR approach typically includes a combination of three different exercise components to address the impairments or functional limitations identified during evaluation: (1) gaze stability exercises, (2) habituation exercises, including optokinetic exercises, (3) balance and gait training in different conditions.[26] The aim of VR is to improve the visual-vestibular interaction and increase balance ability. It is also evidenced to contribute to an improvement in daily function and a reduction of symptoms of dizziness.[26] The mechanism for its effectiveness is thought to rely on the following three aspects: (1) compensation/habituation, which is a central process, refers to that

repeated exposure to a provocative stimulus will result in a reduction in the symptomatic response to that treatment[27]; (2) adaptation, which is the recovery of the dynamic vestibulo-ocular responses due to the ability of the vestibular system to make long-term changes in the neuronal response to input; and (3) substitution, which is the use of other strategies to replace the lost function.[28]

An updated evidence-based clinical guideline by American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HSNF) points out that the clinician should offer VR in treatment of BPPV, stating that although movement/ habituation-based VR should not be first-line treatment modality for BPPV, it is indicated for patients who have persistent disability following CRP.[29] VR is particularly indicated in subjects with additional impairments, such as nonspecific dizziness and those patients with heightened fall risk.[7] A Cochrane review [30] has been undertaken to assess the effectiveness of VR in people with symptomatic unilateral peripheral vestibular dysfunction (UPVD) which included eight studies investigated VR in BPPV specifically, supporting the thought that the primary intervention for BPPV should be CRP that directly treat the condition, but movement/habituation-based VR will further aid and benefit long-term functional recovery. A more recent review by Bressi et al.[31] proposes that a hierarchy of interventions should be offered to people with BPPV, starting with CRP followed by post-treatment exercises. They also indicate that CRP and VR seem to have a synergic effect in patients with BPPV.[31]

While previous studies shed light on the great beneficial of VR in BPPV patients, to date, no randomized clinical trial has been conducted to specifically investigate VR, with or without betahistine, in dealing with RD following CRP in patients with BPPV. This study has been

designed with the broad aim of verifying VR as the first-line option in treating RD, which is conformed to the current recommendations for best clinical practice with respect to the implementation of VR for persons with impairments and functional limitations related to the vestibular deficit.[26] Moreover, the present study has the potential to arrive at stopping unnecessary anti-vertigo drugs prescriptions in BPPV patients.

Aims of the study

This study will investigate the effects of VR, compared with betahistine or VR plus betahistine, on managing RD after successful CRP in patients with BPPV.

We hypothesize that participants in VR group, compared with participants in betahistine group, will display fewer activities and participation restrictions and less balance inability. Moreover, we expect that participants in VR group would experience shorter duration of residual dizziness, better quality of life and enhanced recovery of otolith dysfunction (if any).

We also hypothesize that the effects of VR alone will be non-inferior to a combination of VR and betahistine, in terms of outcome measures mentioned above.

METHODS AND ANALYSIS

Study design, setting, and participants

This study is designed as a randomized controlled prospective single-blinded trail. Outcome assessment will be conducted by two researchers who are blinded to group allocation.

The study setting is the largest ENT-specialized hospital in China. The hospital serves a population of about 23 million of Shanghai. It also serves as a referral center accepting patients from all over the country.

The eligibility criteria are as follows: (1) diagnosed as unilateral BPPV (unilateral posterior

semicircular canal BPPV or horizontal semicircular canal BPPV) according to the clinical practice guideline by AAO-HNSF in 2017[29], (2) aged 18~80 years, (3) reporting residual symptoms after successful repositioning maneuvers. Participants will be excluded if they are: (1) confirmed as anterior semicircular canal BPPV or multicanal BPPV, (2) recurrent BPPV, (3) with coexisting vestibular disorders, including Meniere disease, vestibular neuritis, labyrinthitis, and peripheral vestibular loss, (4) with severe cervical spine disease, (5) with severe cardiovascular diseases, (6) with known cerebral vascular disease like carotid stenosis, (7) suspected of significant depression or anxiety as defined as a score of ≥ 8 for each respective scale of Hospital Anxiety and Depression Scale, (8) pregnant/ lactating or planning to become pregnant during the study period, (9) those who had taken vestibulosupressant, antihistamines, and/ or ototoxic medications in the previous 3 months.

Procedure

The study protocol was reviewed and approved by the Institutional Review Board of the Eye & ENT Hospital of Fudan University (Reference Number:2017046). Patients who are suspected of having BPPV and visit ENT specialist are possibly eligible for this study. They will undergo Dix–Hallpike test, roll test, and anterior canal provoking test to confirm as suffering from solely unilateral posterior canal or horizontal canal involved. After diagnosis by ENT specialist, posterior canal BPPV will be treated using Epley's maneuver or Semont's liberatory maneuver, while horizontal canal BPPV will be treated with Barbecue rotation maneuvers. The same physiotherapist applies both testing procedure and CRP maneuver. CRP is repeated up to three times during one day. Conversion from a positive to a negative Dix-Hallpike is considered as successful. Patients who failed when up to three CRPs have been performed will not be included

in this study.

On the second day following successful CRP, a lead investigator will contact the patient by either telephone or Wechat. Patients will be asked whether they are experiencing residual symptoms. If yes, they will be initially screened through telephone interview and those who meet the inclusion criteria will be invited to participate in the study. A face-to-face interview will be arranged for patients who express an interest in the trial, and formal written consent will be obtained from candidates who agree to participate. Participants then are asked to fill out Hospital Anxiety and Depression Scale (HADS), only those scored less than 8 for each respective subscale of anxiety or depression will be considered eligible. After obtaining written consent form, the principal investigator (Li HW) will fully review the participant's medical history, execute physical examination and perform videonystagmography (VNG) to record nystagmus, to rule out any central nervous system pathologies or other vestibular diseases. Whenever necessary, imaging exam such as CT scan or MRI is supplemented to exclude inner ear and pontocerebellar lesions. After eligibility screenings, participants then will be randomly allocated into one of three groups: participants in Group A will perform VR exercises; Group B will be described with betahistine; and Group C will be offered with both VR and betahistine. Outcome measures will be taken at baseline, four-week, eight-week, and 12-week post randomization. Outcome measurements will be executed by two independent research staff, one is responsible for apparatus-based measures and another in charge of subjective data collecting, both of whom are unaware of the treatment assignment until the end of the study. See figure 1 for a study flow chart.

Randomization and blinding

Participants will be randomized into three groups of 61 each. The randomization process will be

carried out by an internet-based randomization tool provided by China clinical trial registration center. The website is accessible to public via http://www.medresman.org/login.aspx. The randomization sequence will be generated automatically when the administrator logins on the website asking for the allocation number once an eligible patient is recruited. Participants will be randomly allocated at a ratio of 1:1:1 with stratified by sex and age (≤60 years, >60 years). As the randomization is on-line and automatic, neither the researchers nor the patients can manipulate which treatment the patients are receiving, therefore to ensure group allocations are randomly assigned.

Since VR is an operational intervention, it is not possible for either patients or the physiotherapists and physicians to be blind to allocation. However, two independent research staff will contact patients to collect both subjective and apparatus-based data. The statistician of our trial team will remain blind until statistical analyses are complete.

Interventions

Following eligible screening, participants are randomly assigned to one of three intervention groups.

Participants in Group A (VR group) will perform vestibular rehabilitation exercises twice a day, 5 days per week, over a period of four weeks. The exercise protocol was developed based on clinical experience and adapted from the previous studies. [32, 33] in which vestibular stimulated exercise applied were shown to improve balance ability and functional performance among BPPV patients who had undergone CRP. A dedicated physiotherapist (Wu PX) drafted the initial protocol. The content was then reviewed by three experts with expertise in caring for patients with chronic dizziness, and was piloted with two female and two male patients who have experienced RD post

BPPV. Participants reported no difficulties in practicing these exercises. The protocol primarily consists of three categories: oculomotor exercises, head movement exercises, gait and balance training, which is described in table1.

Table 1 Overview of the VR program

Components	Movements	Rational
Oculomotor exercises	VORx1 VORx2 Smooth pursuits Saccades	Improve gaze stability and vestibulo-ocular (VOR) gain adaptation
Head movement exercises	Shaking the head right and left, nodding the head up and down, and circumducting the head clockwise and counterclockwise; while maintaining focus on a visual target	Habituate vestibular responses and to relieve symptoms
Gait and balance training	Static standing on varied base of support (feet apart, feet together, semi-tandem, Tandem) Static standing with different arm positions (arms away from body, arms close to body, arms reaching forward, arms tossing a ball) Sitting to stand up Sitting upright then bending down to pick up objects	Facilitate the vestibulospinal response, improve postural stability, and help regain balance and physical function

Walking with yaw head movement
Walking with pitch head movement
Tossing a ball above the eye level while walking
Tandem walking on a level surface
Tandem walking on a foam surface

The difficulties of the tasks in each session are different according to each participant's balance performance (as measured by computerized dynamic posturography, CDP) or tolerance to vestibular stimulus. We intend to make the tasks progressively challenging. The approaches used to increase task challenge will be: (1) performing the exercises from a generally slow speed to an increased velocity; (2) change target distance (near to far) while performing VOR x1; (3) placing target in a distracting visual pattern; (4) performing the exercises with eyes open to with eyes shut; (5) with altered surface from solid surface to foam surface; (6) carrying out dual tasks such as doing math or talking on cell phone while walking.

The VR protocol consists of one office-based session each week by a skilled physiotherapist (Wu PX) at the clinic, and the other four days of home-based exercise. Compliance will be assessed during home exercise only. An exercise diary outlining the time and duration of each time exercise is required to be filled out every week. A video and booklet have been developed illustrating the program and are used as guides when participants carry out exercise at home. Figure 2 and figure 3 present the screenshots of the training video. During the first clinical visit sessions, the physiotherapist will provide adequate supervised vestibular rehabilitation for the patients to help them understand the goals of the program and ways to manage and progress themselves

independently. Patients are also instructed not to start any new physical activity during the study period.

Participants in Group B (betahistine group) will be prescribed with betahistine 12mg (manufactured by Wei Cai China Pharmaceutical Co., Ltd.), two tablets two times daily for 7 days. Participants are asked not to take any other types of antivertiginous medicine in the course of the study, or in case that scenario occurs, they should inform his/her ENT specialist. The pharmacy department of the study hospital is responsible for dispensing betahistine to each participant. There are 30 tablets in one prescription package. During the first follow-up visit (4-week post randomization), participants are asked to bring their medicine package and the specialist will count the tablets left, if the participant fully adheres to the protocol, then 2 tablets should be left. Participants allocated in Group C (VR plus betahistine group) will receive a combination of VR and betahistine protocol as described above.

Adverse events

Adverse events are rare while performing VR. However, patients are instructed to report any complaints or symptoms during or after performing the exercises. The following symptoms are considered as signs to stop or modify VR protocol: vomiting, nausea or muscle soreness, a feeling of sharp or prolonged pain in the neck, arms or legs, a feeling of ear fullness, hearing loss or tinnitus, double vision, fainting with experience of unconsciousness or blacking out. Adverse events will be reported to Institute of Review board of Eye & ENT Hospital of Fudan University within 48 hours.

The tolerability judgments for betahistine were reported as good.[34] Major possible side effects include gastrointestinal system disturbances and headache.[35] In current study, participants are

encouraged to report spontaneously of any event after betahistine intake. The investigator will routinely contact the participant once a week and ask if there are any unexpected symptoms coming up. Any adverse events likely caused by betahistine during the trial will be recorded and reported to the Adverse Drug Reaction (ADR) administration of Eye & ENT Hospital of Fudan University within 48 hours.

Withdrawal/ retention of participants

Participation is voluntary in this study and the participants have the right to withdraw at any time. However, we will use approaches as recommended by Dziura et al.[36] to improve adherence to the intervention protocols and minimize attrition rates. These include data collection not requiring clinical appointments, a reimbursement mechanism for extra auxiliary examination fees that encourages study completion, and the provision of weekly phone-call contact during the trial. Any concerns, such as unexpected symptoms, as well as logistic issues such as travelling to clinic or parking issue will be evaluated during each telephone consultation. In rare cases, participants may be withdrawn owing to unforeseen circumstances. Every reason for withdrawal will be recorded.

Outcome measures

Evaluating therapy success in patients suffering from vestibular disorder is often difficult due to the complexity of this condition and the lack of specific apparatus-based parameters. Various measurements have been utilized; however, no consensus was reached as to what aspects should be addressed. An international group of investigators and health care providers developed a core set, based on the International Classification of Functioning, Disability and Health (ICF) framework, illustrating key aspects of functioning that should be measured when assessing patients with vertigo, dizziness, and imbalance.[37] Of which, two main domains are included: (1)

body function and structure; (2) activity and participation. Recently published evidence-based clinical practice guideline made recommendations for specific rehabilitation outcome assessment by using recommended measures across the ICF domains.[26] In current study, both ICF-based activity and participation aspect and apparatus-based measures will be included to capture the whole picture of effectiveness of VR on managing RD after successful repositioning in BPPV patients.

Primary outcomes

Primary outcomes are focused on patients' daily functional aspects and balance ability, which include:

1. Participant's activity and participation, quantified by Vestibular Activities and Participation (VAP) measure. The VAP is a 34-item self-report questionnaire based on ICF framework to evaluate the effect of dizziness and/or balance problem on the ability to perform activity and participation tasks.[38] The difficulty of each task is rated without assistance of other persons. Each item of the VAP is set as a five-point scale indicating the level of difficulty; 0 refers to none difficulty and 4 represents unable to do. Total score is obtained by calculating the average item scores after excluding the "not applicable" responses. Previous study established cross-cultural validity of VAP.[39] We recently have completed the translation and validation work of Chinese version of VAP.

2. Balance function, measured by computerized dynamic posturography (CDP, Equitest, NeuroCom International, Inc.). The Sensory Organization Test (SOT) of CDP evaluates the ability of subjects to utilize vision, vestibular and somatosensory for maintaining their balance.[40] Six increasingly challenging conditions (from SOT 1 through SOT6) that disrupt portions of balance

sensory input or visual surrounding are carried out to fulfill balance evaluation. An Equilibrium Score (ES) for each condition is calculated by comparing the angular difference between the subject's calculated maximum and minimum sagittal plane body sway to a theoretical maximum displacement (12.5°). In terms of overall performance, a Composite Score (CS) is given as an estimate of postural stability, a CS score near 100% indicates little sway, while scores approaching 0% indicate evidenced instability or fall. Both ES in each test condition from SOT 1 to SOT 6 and the CS will be used for analysis in this study. The values are considered as abnormal when the score is lower than the age-specific norm data.

Secondary outcomes

Secondary outcomes include quality of life, recovery of otolith dysfunction, and duration of symptoms.

1. Quality of life measured by DHI. DHI has been widely used as a reliable tool for evaluating the self-perceived handicap effects imposed by vestibular system disease and has been translated and standardized for the Chinese by Ding et al. [41] The DHI consists of 25 self-assessment items which can be broken down into three subscales: physical, emotional, and functional. Total scores of DHI range from 0 to 100 with increasing scores indicating greater perception of handicap because of dizziness. It has been widely used as a reliable and valid tool for assessing the harmful effects of dizziness on QoL of patients including BPPV.[42]

2. Otolith function, analyzed by Vestibular Evoked Myogenic Potentials (VEMPs). VEMPs is now established as clinical test of otolith function. Cervical VEMP (cVEMP) is used to assess inferior nerve otolith function (test mainly saccular function) and ocular VEMP (oVEMP) is believed to exam superior nerve otolith function (test mainly utricular function). Previous studies[43,

44]identified that, in patients with BPPV underwent successful CRP, the occurrence of residual symptoms was correlated to the abnormalities of oVEMP, suggesting that utricular dysfunction is responsible for RD presence. Controversially, another study found that BPPV patients with saccular dysfunction were more than those with utricular dysfunction[42]. Therefore, in present study, both cVEMP and oVEMP will be recorded by using Bio-Logic Naviator Pro 9.0 (Natus Medical Inc., San Carlos, USA) system. The procedure will be performed in a sound-proof room. The methodology is reported in detail elsewhere.[45] Otolith dysfunction in our patients is defined as the lack of unilateral responses in cVEMP or oVEMP.

3. Duration of symptoms reported by patients. During the trial period, a researcher contacts the participants once a week to probe how many days do they experience symptoms in the previous week. By the end of the study, the reported symptoms' day of each week will be added together representing the whole duration of symptoms.

Timepoint of outcome measures

Outcome measures are applied at baseline and at three follow-ups. Baseline assessments occur on the second day following successful CRP. Participants will repeat the same battery of tests conducted at baseline and 4 weeks, 8 weeks and 12 weeks post allocation, with the exception of CDP and VEMPs, which will only be repeated when the previous exam shows abnormal.

Schedule of enrollment, interventions and outcome assessments are presented in table2.

Table 2 Schedule of enrollment, interventions and outcome assessments

	Study period						
	Screening and eligibility	Allocation	Post allocation				Close-out
Timepoint	−T1	T0	T1	T2	T3	T4	
(D=day, W=week)		D2	D2-8	W4	W8	W12	
Eligibility screen	✓	✓					
Medical history reviewing	✓						
Physical and VNG examination	✓						
HADS	✓						
Informed consent	✓						
Allocation		✓					
Interventions							
VR (group A)			←	→			

Betahistine (group B)			✓				
VR plus Betahistine (group C)			←	→			
Assessments							
Outcome variables							
VAP		✓		✓	✓	✓	
CDP		✓		✓/#	✓/#	✓/#	
DHI		✓		✓	✓	✓	
oVEMP		✓		✓/#	✓/#	✓/#	
cVEMP		✓		✓/#	✓/#	✓/#	
Symptom duration		✓		✓	✓	✓	✓

Abbreviations. VNG, videonystagmography; HADS, Hospital Anxiety and Depression Scale; VR, vestibular rehabilitation; VAP, the Vestibular Activities and Participation measure; CDP, computerized dynamic posturography; DHI, Dizziness Handicap Inventory; VEMP, Vestibular Evoked Myogenic Potential.

Statistical analysis

Sample size calculation

The study sample size was based on one of the primary outcomes--- VAP measure, which is a useful clinical tool to assess a patient's limitation in activities and participation due to vertigo, dizziness, and unsteadiness. The validation study of VAP in patients who complained about dizziness or imbalance showed the minimum detectable change (MDC) for the VAP was 0.58, with a standard error of 0.21[39]. In this study, a 0.6 difference of VAP score is considered clinically meaningful. Thus, to detect an MDC of 0.6 for the VAP with 80% power (alpha level of 0.05, two-sided test), 55 per group will be required. Although there are three groups in this study, controlling for type 1 error rate is not needed because our hypotheses are: (1) VR will be better than betahistine (Group A versus Group B) and (2) VR will be non-inferior to VR plus betahistine (Group A versus Group C); therefore, only two comparisons will be executed. Allowing a 20% loss to follow-up, a total sample of 183 (61 per group) will be required for the current study.

Data Analysis

Statistical analyses will be completed using IBM SPSS Statistics for Windows (SPSS V.22.0) and the level of significance will be set at $p<0.05$. Firstly, descriptive analysis will be conducted to determine outliers and distributions of the data. Then, the intervention group and control group will be analyzed for baseline comparability with respect to the baseline variables. Analysis of the outcome measures will be based on the conservative intention-to-treat (ITT) approach; moreover, as a secondary analysis, a per protocol analysis will also be performed. Drop-out / attrition is anticipated. We will examine the structure and pattern of missing data and, if appropriate, multiple imputation methods will be used in both ITT and the per-protocol analyses.

The main analysis of change in the primary outcomes (VAP score and SOT composite) will use mixed-model with repeated measures (MMRM) models, with fixed effects for group and time and a random effect for subject. Mathematical transformation or categorization of raw scores will be undertaken to meet distributional assumptions that required in MMRM models. Models will adjust for age, gender and other baseline potential confounders. Secondary outcomes include both continuous data (DHI score, duration of symptoms) and dichotomous data (otolith function, defined as normal or abnormal). Analysis of secondary outcomes will be conducted using mixed model with repeated measures for continuous outcomes or logistic regression for dichotomous data, again controlling for baseline potential confounders. Statistical analysis will be carried out by a statistician from Fudan University Medical School, who is blinded to group allocation and study hypothesis. To achieve that blinding, all participants are anonymized and study arms are coded as A, B, C.

Trail status and recruitment

Protocol V.2.0, 10 August, 2018. Planned date of first enrolment is September 1, 2018. The estimated time required for recruitment is 15 months. The total duration of this study is expected to be 23 months, including statistical analysis and study results drafting.

Data management

Data Safety and Monitoring Board (DSMD) has already been set up. DSMD will monitor day-to-day running of the trial, review the accumulation data, check database integrity, and be responsible for carry out interim analyses. DSMD consists of five persons: a chair, a statistician, a methodologist experienced in research with BPPV, a clinical expert, and a patient representative. All members are independent from the study sponsor and report no competing interest. The

DSMD meets approximately every month from the start of the trial. Trial sponsor compensate DSMD members for their time and effort, similar to the compensation provided to other trial support personnel.

For data collection, an electronic case report form (CRF) has been designed to record all the data from the baseline and the three follow-ups during the trial. Electronic data are stored on a public platform at www.medresman.org sponsored by China clinical trial registry center. The database uses standard techniques to provide security. Access to database is controlled by user names and encrypted passwords. Individual participant data (IPD) will be made public in 6 months after the completion of the study through the IPD sharing platform.

Patient and public involvement

Patients and the public were not involved in the design of this study. However, we have consulted with a patien representative about his views on how best to involve patients throughout the proposed project. His views have been incorporated in our revised protocol. Patients and the public will be informed of the study results via peer-reviewed journals or academic conference.

Dissemination of the study findings

We plan to publish the study findings in peer-reviewed academic journals. We also intend to deliver presentation of this study at local, national and international conferences where possible. Furthermore, we will draft a summary of the study results on website of Eye & ENT hospital that can be accessed by all trial participants as well as relevant interest groups.

Competing interests

No competing interests exist.

Funding

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Ethics approval

Institute Review Board of Eye & ENT Hospital of Fudan University (reference number.2017046).

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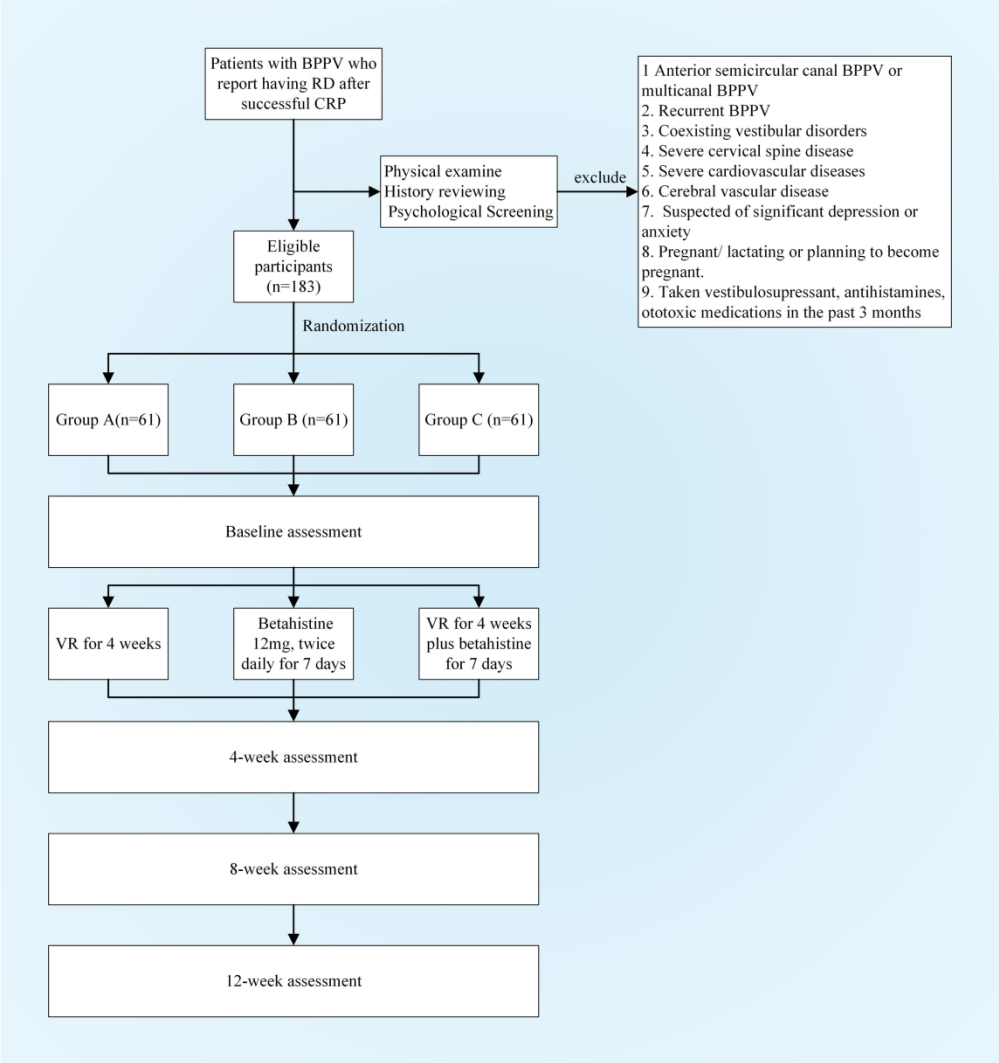
Figure 1 Study flow chart.

Figure 2 Screenshot of head movement exercises in the training video.

Figure 3 Screenshot of gait exercise in the training video.



223x238mm (300 x 300 DPI)

Figure 2 Screenshot of head movement exercises in the training video

285x160mm (300 x 300 DPI)

Figure 2 Screenshot of gait exercises in the training video

528x297mm (96 x 96 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	22
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	In title page
	5b	Name and contact information for the trial sponsor	In title page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	In title page
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-8
	6b	Explanation for choice of comparators	-
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8,11
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14,15
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	19-20
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	22
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	22,23

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14,15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Informed consent (annex)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23

	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	annex
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effects of vestibular rehabilitation, with or without betahistine, on managing residual dizziness after successful repositioning maneuvers in patients with benign paroxysmal positional vertigo : protocol for a randomized controlled trial

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Primary Subject Heading:	Ear, nose and throat/otolaryngology
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The effects of vestibular rehabilitation, with or without betahistine, on managing residual dizziness after successful repositioning maneuvers in patients with benign paroxysmal positional vertigo：protocol for a randomized controlled trial

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Contributors All authors have made an intellectual contribution to this protocol. Li Huawei is the principal investigator of the trial, with full responsibility for the project. Wu PX, Cao WZ and Hu Yan conceived the design, developed the protocol and wrote the first draft of this manuscript. Li Huawei and Hu Yan revised and approved the final version of the study protocol and the final manuscript. Li Huawei and Hu Yan are co-corresponding authors whom contributed this paper equally.

Abstract

Introduction

Benign paroxysmal positional vertigo (BPPV) is recognized as the leading cause of periphery veritgo in adults. Canalith repositioning procedure (CRP) can effectively treat BPPV. However, a certain group of patients experience residual dizziness (RD) even after successful CRP, bringing a significantly negative impact on their daily function and quality of life. Exercise-based vestibular rehabilitation (VR) has proven to be an effective way for managing dizziness and has been applied in patients with different vestibular disorders. However, the effectiveness of VR specifically targeted RD post BPPV is unknown. This study aims to investigate the effectiveness of VR, compared with betahistine or VR plus betahistine, in patients experiencing RD after successful CRP.

Methods and analysis

A randomized single-blinded controlled trial will be carried out to determine the effectiveness of VR, compared with betahistine or VR plus betahistine, in mitigating RD and improving balance function. Patients with BPPV after successful CRP and complain of experiencing RD will be recruited. Participants will be randomized into one of three groups to receive VR or betahistine or VR plus betahistine. There will be 61 participants in each group. Primary outcomes are changes of patients' daily function measured by Vestibular Activities and Participation (VAP) questionnaire and balance ability assessed by computerized dynamic posturography (CDP). Secondary outcomes will assess dizziness-related handicap, otolith function, and duration of RD symptoms.

Outcome measures will be taken at baseline, 2-week, 4-week and 8-week post randomization. This study has the potential to arrive at stopping unnecessary anti-vertigo drugs prescriptions and may lead to the consensus of using VR as the first-line treatment for RD in patients with BPPV.

Ethics and dissemination

This trial received ethics approval from Institute Review Board of Eye & ENT Hospital of Fudan University (2017046). Study results will be disseminated through peer-reviewed journals and conferences.

ClinicalTrials.gov identifier: NCT03624283

Strengths and limitations of this study

►To our knowledge, this is the first randomized controlled trial evaluating the effects of vestibular rehabilitation, compared with betahistine or VR in addition to betahistine, on managing residual dizziness after successful CRP in patients with BPPV.

► Both subjective and objective outcome measures are comprehensively assessed with reasonable long follow-up time. In Particular, patients' activities and participation aspect based on International Classification of Functioning, Disability and Health (ICF) framework are evaluated. Such a trial will be able to fully reflect the efficacy of proposed intervention.

► For practical reason, there is no sham or placebo or no treatment as comparison group in this study; therefore, the study cannot tell whether participants improve simultaneously or how the three interventions may work in different ways to change outcomes.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the leading cause of peripheral vertigo, with a prevalence from 10.7 to 64 per 100,000 populations and a lifetime prevalence of 2.4%.[1] The onset time is most commonly between the fifth and seventh decade of life, but BPPV could occur at any age.[2] Two theories --- cupulolithiasis[3] and canalithiasis[4], are among the most widely accepted theories that elucidate the pathophysiology of BPPV. Canalithiasis has gained wider acceptance among the scientific field due to the symptoms being better explained.[5] According to the canalolithiasis hypothesis, BPPV is caused by free otoconia dislodged from the utricular macula and entering into the semicircular canal, which therefore provokes an inappropriate flow of endolymph whenever the head is rotated in the plane of the affected canal.[4] Although any of the three semicircular canals can be affected, the posterior semicircular canal BPPV is the most common, followed by horizontal canal BPPV. Treatment of BPPV is based on the performance of canalith repositioning procedure (CRP), with the aim of repositioning the displaced particles from the affected canal to their original location. [6] CRP has long emerged as a mainstay of therapy and now is well established as the gold treatment for BPPV.[7] Posterior canal BPPV can be treated by performing Epley's maneuver or Semont's liberatory maneuver. For horizontal canal BPPV, Barbecue rotation or Gufoni's maneuvers have been shown effective.

Despite the fact that CRP can provide rapid relief of vertigo sensation in BPPV patients, residual symptoms may remain even after disappearance of typical vertigo and nystagmus following a successful CRP. These residual symptoms, also referred as residual dizziness (RD), imply a non-specific sensation of unsteadiness, lightheadedness, disorientation, fogginess or drowsiness.[8] The reported incidence of RD ranges from 29.6% to76.9% and the duration of RD can range from

a few days to several months.[8-12] Several Authors reported that RD symptoms may persist up to more than 3 months [13, 14], bringing adverse physical and psychological consequences to these patients.

Different pathophysiological mechanisms have been proposed to explain the presence of RD but the real cause remains unknown. Previously reported possible explanations included: (1) the persistence of debris in the canal being insufficient to provoke detectable positional nystagmus or vertigo;[11] (2) otolith dysfunction;[15, 16] (3) coexistent vestibular disease that lead to incomplete central adaptation; (4) potential autonomic dysfunction such as orthostatic hypotension;[17] (5) persistent postural-perceptual dizziness (PPPD).[18]

Dizziness increases the risk of falls or fear of falling, disturbs daily life, and results in restriction of social activities. As a result, many people tend to avoid activities, limit their movement, and avoid specific circumstances because of fear of provoking dizziness and unanticipated unsteadiness attacks.[19] It is not surprised that increased postural instability was documented in patients who experiencing RD[20, 21]. Given that high prevalence of RD after successful repositioning and its negative impact on patient recovery, this impairment should be managed properly.

To date, there is no agreement on how to effectively manage RD after successful CRP in patients with BPPV. Betahistine is the most widely used medication to ameliorate dizziness, due to its effects of increasing labyrinthine microcirculation, suppressing the increased neuronal activity in vestibular receptor cells, afferent neurons, and vestibular nuclei.[11, 22] However, conflicting data exists regarding the efficacy of betahistine for preventing or treating RD. Guneri et al[23] evaluated the efficacy of betahistine in reducing symptoms after Epley maneuver for posterior

canal BPPV, they found 48 mg of betahistine daily intake demonstrated more effective results than Epley maneuver alone or combined with placebo in improving symptoms assessed by four different vertigo symptoms scales. On the contrary, Acar et al [24] carried out a randomized controlled clinical trial to investigate the efficacy of betahistine, compared with a no medication group, for the treatment of RD after successful CRP. After 3 and 5 days of treatment, the mean DHI (Dizziness Handicap Inventory) scores of the groups receiving medication did not differ from the mean DHI score of the control group, indicating betahistine did not produce any more alleviation of RD than no treatment. However, both studies have unclear randomization sequence generation, allocation concealment and only included subjective outcomes, suggesting more rigorous methodology of clinical trials that including comprehensive outcomes assessment are warranted.

Recently, non-pharmacological interventions, such as vestibular rehabilitation (VR), are recommended as the first line of treatment for chronic vertigo.[22] VR, which has been available since 1940s, is an exercise-based treatment consisting of varied eye, head, and body movements designed to stimulate the vestibular system and optimize vestibular compensation.[25] Current VR approach typically includes a combination of three different exercise components to address the impairments or functional limitations identified during evaluation: (1) gaze stability exercises, (2) habituation exercises, including optokinetic exercises, (3) balance and gait training in different conditions.[26] The aim of VR is to improve the visual-vestibular interaction and increase balance ability. It is also evidenced to contribute to an improvement in daily function and a reduction of symptoms of dizziness.[26] The mechanism for its effectiveness is thought to rely on the following three aspects: (1) compensation/habituation, which is a central process, refers to that

repeated exposure to a provocative stimulus will result in a reduction in the symptomatic response to that treatment[27]; (2) adaptation, which is the recovery of the dynamic vestibulo-ocular responses due to the ability of the vestibular system to make long-term changes in the neuronal response to input; and (3) substitution, which is the use of other strategies to replace the lost function.[28]

An updated evidence-based clinical guideline by American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HSNF) points out that the clinician should offer VR in treatment of BPPV, stating that although movement/ habituation-based VR should not be first-line treatment modality for BPPV, it is indicated for patients who have persistent disability following CRP.[29] VR is particularly indicated in subjects with additional impairments, such as nonspecific dizziness and those patients with heightened fall risk.[7] A Cochrane review [30] has been undertaken to assess the effectiveness of VR in people with symptomatic unilateral peripheral vestibular dysfunction (UPVD) which included eight studies investigated VR in BPPV specifically, supporting the thought that the primary intervention for BPPV should be CRP that directly treat the condition, but movement/habituation-based VR will further aid and benefit long-term functional recovery. A more recent review by Bressi et al.[31] proposes that a hierarchy of interventions should be offered to people with BPPV, starting with CRP followed by post-treatment exercises. They also indicate that CRP and VR seem to have a synergic effect in patients with BPPV.[31]

While previous studies shed light on the great beneficial of VR in BPPV patients, to date, no randomized clinical trial has been conducted to specifically investigate VR, with or without betahistine, in dealing with RD following CRP in patients with BPPV. This study has been

designed with the broad aim of verifying VR as the first-line option in treating RD, which is conformed to the current recommendations for best clinical practice with respect to the implementation of VR for persons with impairments and functional limitations related to the vestibular deficit.[26] Moreover, the present study has the potential to arrive at stopping unnecessary anti-vertigo drugs prescriptions in BPPV patients.

Aims of the study

This study will investigate the effects of VR, compared with betahistine or VR plus betahistine, on managing RD after successful CRP in patients with BPPV.

We hypothesize that participants in VR group, compared with participants in betahistine group, will display fewer activities and participation restrictions and less balance inability. Moreover, we expect that participants in VR group would experience shorter duration of RD, less dizziness-related handicap and enhanced recovery of otolith dysfunction (if any).

We also hypothesize that the effects of VR alone will be non-inferior to a combination of VR and betahistine, in terms of outcome measures mentioned above.

METHODS AND ANALYSIS

Study design, setting, and participants

This study is designed as a randomized controlled prospective single-blinded trail. Outcome assessment will be conducted by two researchers who are blinded to group allocation.

The study setting is the largest ENT-specialized hospital in China. The hospital serves a population of about 23 million of Shanghai. It also serves as a referral center accepting patients from all over the country.

The eligibility criteria are as follows: (1) diagnosed as unilateral BPPV (unilateral posterior

semicircular canal BPPV or horizontal semicircular canal BPPV) according to the clinical practice guideline by AAO-HNSF in 2017[29], (2) aged 18~80 years, (3) reporting residual symptoms after successful repositioning maneuvers. Participants will be excluded if they are: (1) confirmed as anterior semicircular canal BPPV or multicanal BPPV, (2) recurrent BPPV, (3) with coexisting vestibular disorders, including Meniere disease, vestibular neuritis, labyrinthitis, and peripheral vestibular loss, (4) with severe cervical spine disease, (5) with severe cardiovascular diseases, (6) with known cerebral vascular disease like carotid stenosis, (7) pregnant/ lactating or planning to become pregnant during the study period, (8) those who had taken vestibulosupressant, antihistamines, and/ or ototoxic medications in the previous 3 months.

Procedure

The study protocol was reviewed and approved by the Institutional Review Board of the Eye & ENT Hospital of Fudan University (Reference Number:2017046). Patients who are suspected of having BPPV and visit ENT specialist are possibly eligible for this study. They will undergo Dix–Hallpike test, roll test, and anterior canal provoking test to confirm as suffering from solely unilateral posterior canal or horizontal canal involved. After diagnosis by ENT specialist, posterior canal BPPV will be treated using Epley's maneuver or Semont's liberatory maneuver, while horizontal canal BPPV will be treated with Barbecue rotation maneuvers. The same physiotherapist applies both testing procedure and CRP maneuver. CRP is repeated up to three times during one day. After successful repositioning maneuver, patients are asked to complete a DHI test. Patients who failed when up to three CRPs have been performed will not be included in this study.

On the second day following successful CRP, a lead investigator will contact the patient by either

telephone or Wechat. Patients will be asked whether they are experiencing residual symptoms. If yes, they will be initially screened through telephone interview and those who meet the inclusion criteria will be invited to participate in the study. A face-to-face interview will be arranged for patients who express an interest in the trial, and formal written consent will be obtained from candidates who agree to participate. After obtaining written consent form, the principal investigator (Li HW) will fully review the participant's medical history, execute physical examination and perform videonystagmography (VNG) including caloric test, to rule out any central nervous system pathologies or other vestibular diseases. Diagnostic test for BPPV will be repeated to make sure findings are negative. Pure-tone audiometry and tympanometry will be checked. Gait and balance will also be assessed (Romberg, sharpened Romberg). Whenever necessary, imaging exam such as CT scan or MRI is supplemented to exclude cerebellar disorders. The purpose of above-mentioned examinations is to confirm the diagnosis and validate the homogeneity of all participants who take part in current study. After eligibility screenings, participants then will be randomly allocated into one of three groups: participants in Group A will perform VR exercises; Group B will be described with betahistine; and Group C will be offered with both VR and betahistine. Outcome measures will be taken at baseline, two-week, four-week, and eight-week post randomization. Outcome measurements will be executed by two independent research staff, one is responsible for apparatus-based measures and another in charge of subjective data collecting, both of whom are unaware of the treatment assignment until the end of the study. See figure 1 for a study flow chart.

Randomization and blinding

Participants will be randomized into three groups of 61 each. The randomization process will be

carried out by an internet-based randomization tool provided by China clinical trial registration center. The website is accessible to public via http://www.medresman.org/login.aspx. The randomization sequence will be generated automatically when the administrator logins on the website asking for the allocation number once an eligible patient is recruited. Participants will be randomly allocated at a ratio of 1:1:1 with stratified by sex and age (≤60 years, >60 years). As the randomization is on-line and automatic, neither the researchers nor the patients can manipulate which treatment the patients are receiving, therefore to ensure group allocations are randomly assigned.

Since VR is an operational intervention, it is not possible for either patients or the physiotherapists and physicians to be blind to allocation. However, two independent research staff will contact patients to collect both subjective and apparatus-based data. The statistician of our trial team will remain blind until statistical analyses are complete.

Interventions

Following eligible screening, participants are randomly assigned to one of three intervention groups.

Participants in Group A (VR group) will perform vestibular rehabilitation exercises twice a day,7 days per week, over a period of four weeks. The exercise protocol was developed based on clinical experience and adapted from the previous studies.[32, 33] in which vestibular stimulated exercise applied were shown to improve balance ability and functional performance among BPPV patients who had undergone CRP. A dedicated physiotherapist (Wu PX) drafted the initial protocol. The content was then reviewed by three experts with expertise in caring for patients with chronic dizziness, and was piloted with two female and two male patients who have experienced RD post

BPPV. Participants reported no difficulties in practicing these exercises. The protocol primarily consists of three categories: oculomotor exercises, head movement exercises, gait and balance training, which is described in table1.

Table 1 Overview of the VR program

Components	Movements	Rational
Oculomotor exercises	VORx1 VORx2 Smooth pursuits Saccades	Improve gaze stability and vestibulo-ocular (VOR) gain adaptation
Head movement exercises	Shaking the head right and left, nodding the head up and down, and circumducting the head clockwise and counterclockwise; while maintaining focus on a visual target	Habituate vestibular responses and to relieve symptoms
Gait and balance training	Static standing on varied base of support (feet apart, feet together, semi-tandem, Tandem) Static standing with different arm positions (arms away from body, arms close to body, arms reaching forward, arms tossing a ball) Sitting to stand up Sitting upright then bending down to pick up objects	Facilitate the vestibulospinal response, improve postural stability, and help regain balance and physical function

Walking with yaw head movement
Walking with pitch head movement
Tossing a ball above the eye level while walking
Tandem walking on a level surface
Tandem walking on a foam surface

The difficulties of the tasks in each session are different according to each participant's balance performance (as measured by computerized dynamic posturography, CDP) or tolerance to vestibular stimulus. We intend to make the tasks progressively challenging. The approaches used to increase task challenge will be: (1) performing the exercises from a generally slow speed to an increased velocity; (2) change target distance (near to far) while performing VOR x1; (3) placing target in a distracting visual pattern; (4) performing the exercises with eyes open to with eyes shut; (5) with altered surface from solid surface to foam surface; (6) carrying out dual tasks such as doing math or talking on cell phone while walking.

The VR protocol consists of one office-based session each week by a skilled physiotherapist (Wu PX) at the clinic, and the other six days of home-based exercise. Compliance will be assessed during home exercise only. An exercise diary outlining the time and duration of each time exercise is required to be filled out every week. A video and booklet have been developed illustrating the program and are used as guides when participants carry out exercise at home. Figure 2 and figure 3 present the screenshots of the training video. During the first clinical visit sessions, the physiotherapist will provide adequate supervised vestibular rehabilitation for the patients to help them understand the goals of the program and ways to manage and progress

themselves independently. Patients are also instructed not to start any new physical activity during the study period.

Participants in Group B (betahistine group) will be prescribed with betahistine 12mg (manufactured by Wei Cai China Pharmaceutical Co., Ltd.), two tablets two times daily for four weeks. Participants are asked not to take any other types of antivertiginous medicine in the course of the study, or in case that scenario occurs, they should inform his/her ENT specialist. The pharmacy department of the study hospital is responsible for dispensing betahistine to each participant. There are 30 tablets in one prescription package. Four packages will be prescribed at the commencement of treatment. During the first two follow-up visits (2-week and 4-week post randomization), participants are asked to bring their drug packages and the specialist will count the tablets left, if the participant fully adheres to the protocol, then 8 tablets should be left by the 4-week follow-up.

Participants allocated in Group C (VR plus betahistine group) will receive a combination of VR and betahistine protocol as described above.

Adverse events

Adverse events are rare while performing VR. However, patients are instructed to report any complaints or symptoms during or after performing the exercises. The following symptoms are considered as signs to stop or modify VR protocol: vomiting, nausea or muscle soreness, a feeling of sharp or prolonged pain in the neck, arms or legs, a feeling of ear fullness, hearing loss or tinnitus, double vision, fainting with experience of unconsciousness or blacking out. Adverse events will be reported to Institute of Review board of Eye & ENT Hospital of Fudan University within 48 hours.

The tolerability judgments for betahistine were reported as good.[34] Major possible side effects include gastrointestinal system disturbances and headache.[35] In current study, participants are encouraged to report spontaneously of any event after betahistine intake. The investigator will routinely contact the participant once a week and ask if there are any unexpected symptoms coming up. Any adverse events likely caused by betahistine during the trial will be recorded and reported to the Adverse Drug Reaction (ADR) administration of Eye & ENT Hospital of Fudan University within 48 hours.

Withdrawal/ retention of participants

Participation is voluntary in this study and the participants have the right to withdraw at any time. However, we will use approaches as recommended by Dziura et al.[36] to improve adherence to the intervention protocols and minimize attrition rates. These include data collection not requiring clinical appointments, a reimbursement mechanism for extra auxiliary examination fees that encourages study completion, and the provision of weekly phone-call contact during the trial. Any concerns, such as unexpected symptoms, as well as logistic issues such as travelling to clinic or parking issue will be evaluated during each telephone consultation. In rare cases, participants may be withdrawn owing to unforeseen circumstances. Every reason for withdrawal will be recorded.

Outcome measures

Evaluating therapy success in patients suffering from vestibular disorder is often difficult due to the complexity of this condition and the lack of specific apparatus-based parameters. Various measurements have been utilized; however, no consensus was reached as to what aspects should be addressed. An international group of investigators and health care providers developed a core set, based on the International Classification of Functioning, Disability and Health (ICF)

framework, illustrating key aspects of functioning that should be measured when assessing patients with vertigo, dizziness, and imbalance.[37] Of which, two main domains are included: (1) body function and structure; (2) activity and participation. Recently published evidence-based clinical practice guideline made recommendations for specific rehabilitation outcome assessment by using recommended measures across the ICF domains.[26] In current study, both ICF-based activity and participation aspect and apparatus-based measures will be included to capture the whole picture of effectiveness of VR on managing RD after successful repositioning in BPPV patients.

Primary outcomes

Primary outcomes are focused on patients' daily functional aspects and balance ability, which include:

1. Participant's activity and participation, quantified by Vestibular Activities and Participation (VAP) measure. The VAP is a 34-item self-report questionnaire based on ICF framework to evaluate the effect of dizziness and/or balance problem on the ability to perform activity and participation tasks.[38] The difficulty of each task is rated without assistance of other persons. Each item of the VAP is set as a five-point scale indicating the level of difficulty; 0 refers to none difficulty and 4 represents unable to do. Total score is obtained by calculating the average item scores after excluding the "not applicable" responses. Previous study established cross-cultural validity of VAP.[39] We recently have completed the translation and validation work of Chinese version of VAP.

2. Balance function, measured by computerized dynamic posturography (CDP, Equitest, NeuroCom International, Inc.). The Sensory Organization Test (SOT) of CDP evaluates the ability

of subjects to utilize vision, vestibular and somatosensory for maintaining their balance.[40] Six increasingly challenging conditions (from SOT 1 through SOT6) that disrupt portions of balance sensory input or visual surrounding are carried out to fulfill balance evaluation. An Equilibrium Score (ES) for each condition is calculated by comparing the angular difference between the subject's calculated maximum and minimum sagittal plane body sway to a theoretical maximum displacement (12.5°). In terms of overall performance, a Composite Score (CS) is given as an estimate of postural stability, a CS score near 100% indicates little sway, while scores approaching 0% indicate evidenced instability or fall. Both ES in each test condition from SOT 1 to SOT 6 and the CS will be used for analysis in this study. The values are considered as abnormal when the score is lower than the age-specific norm data.

Secondary outcomes

Secondary outcomes include dizziness-related handicap, recovery of otolith dysfunction, and duration of symptoms.

1. Dizziness-related handicap measured by DHI. DHI has been widely used as a reliable tool for evaluating the self-perceived handicap effects imposed by vestibular system disease and has been translated and standardized for the Chinese by Ding et al. [41] The DHI consists of 25 self-assessment items which can be broken down into three subscales: physical, emotional, and functional. Total scores of DHI range from 0 to 100 with increasing scores indicating greater perception of handicap because of dizziness. It has been widely used as a reliable and valid tool for assessing the harmful effects of dizziness on QoL of patients including BPPV.[42]

2. Otolith function, analyzed by Vestibular Evoked Myogenic Potentials (VEMPs). VEMPs is now established as clinical test of otolith function. Cervical VEMP (cVEMP) is used to assess

inferior nerve otolith function (test mainly saccular function) and ocular VEMP (oVEMP) is believed to exam superior nerve otolith function (test mainly utricular function). Previous studies[43, 44]identified that, in patients with BPPV underwent successful CRP, the occurrence of residual symptoms was correlated to the abnormalities of oVEMP, suggesting that utricular dysfunction is responsible for RD presence. Controversially, another study found that BPPV patients with saccular dysfunction were more than those with utricular dysfunction.[42] Therefore, in present study, both cVEMP and oVEMP will be recorded by using Bio-Logic Naviator Pro 9.0 (Natus Medical Inc., San Carlos, USA) system. The procedure will be performed in a sound-proof room. The methodology is reported in detail elsewhere.[45] Otolith dysfunction in our patients is defined as the lack of unilateral responses in cVEMP or oVEMP.

3. Duration of symptoms reported by patients. During the trial period, a researcher contacts the participants once a week to probe how many days do they experience symptoms in the previous week. By the end of the study, the reported symptoms' day of each week will be added together representing the whole duration of symptoms.

Timepoint of outcome measures

Outcome measures are applied at baseline and at three follow-ups. Baseline assessments occur on the second day following successful CRP. Demographic and clinical data collected will include: age, gender, education, employment, marital status, coexistent systemic diseases, date of onset, duration of symptom from onset to treatment, involved ear side and canal, the number of CRP. Participants are required to return to clinic at 2-week, 4-week and 8-week post allocation. They will fill out the same questionnaires (VAP and DHI) upon each follow-up, while the CDP and VEMPs will only be repeated when the previous exam shows abnormality. Schedule of

enrollment, interventions and outcome assessments are presented in table2.

Table 2 Schedule of enrollment, interventions and outcome assessments

	Study period				
	Screening and eligibility /Allocation	**Post allocation**			**Close-out**
Timepoint	T0	T1	T2	T3	
(D=day, W=week)	D2	W2	W4	W8	
Eligibility screening	✓				
Medical history reviewing	✓				
Physical and VNG examination	✓				
Informed consent	✓				
Demographical and clinical characteristics	✓				
Allocation	✓				
Interventions					
VR (group A)	←	—	→		
Betahistine (group B)	←	—	→		
VR plus Betahistine (group C)	←	—	→		
Assessments of outcome variables					
VAP	✓	✓	✓	✓	
CDP	✓		✓/#	✓/#	
DHI	✓	✓	✓	✓	
oVEMP	✓		✓/#	✓/#	
cVEMP	✓		✓/#	✓/#	
Symptom duration		✓	✓	✓	

VNG, videonystagmography; VR, vestibular rehabilitation; VAP, the Vestibular Activities and Participation measure; CDP, computerized dynamic posturography; DHI, Dizziness Handicap

Inventory; VEMP, Vestibular Evoked Myogenic Potential; # indicates test only be repeated when the previous one shows abnormality.

Statistical analysis

Sample size calculation

The study sample size was based on one of the primary outcomes--- VAP measure, which is a useful clinical tool to assess a patient's limitation in activities and participation due to vertigo, dizziness, and unsteadiness. The validation study of VAP in patients who complained about dizziness or imbalance showed the minimum detectable change (MDC) for the VAP was 0.58, with a standard error of 0.21[39]. In this study, a 0.6 difference of VAP score is considered clinically meaningful. Thus, to detect an MDC of 0.6 for the VAP with 80% power (alpha level of 0.05, two-sided test), 55 per group will be required. Although there are three groups in this study, controlling for type 1 error rate is not needed because our hypotheses are: (1) VR will be better than betahistine (Group A versus Group B) and (2) VR will be non-inferior to VR plus betahistine (Group A versus Group C); therefore, only two comparisons will be executed. Allowing a 20% loss to follow-up, a total sample of 183 (61 per group) will be required for the current study.

Data Analysis

Statistical analyses will be completed using IBM SPSS Statistics for Windows (SPSS V.22.0) and the level of significance will be set at $p<0.05$. Firstly, descriptive analysis will be conducted to determine outliers and distributions of the data. Then, the intervention group and control group will be analyzed for baseline comparability with respect to the baseline variables. Analysis of the outcome measures will be based on the conservative intention-to-treat (ITT) approach; moreover, as a secondary analysis, a per protocol analysis will also be performed. Drop-out / attrition is anticipated. We will examine the structure and pattern of missing data and, if appropriate, multiple imputation methods will be used in both ITT and the per-protocol analyses.

The main analysis of change in the primary outcomes (VAP score and SOT composite) will use mixed-model with repeated measures (MMRM) models, with fixed effects for group and time and a random effect for subject. Mathematical transformation or categorization of raw scores will be undertaken to meet distributional assumptions that required in MMRM models. Models will adjust for age, gender and other baseline potential confounders. Secondary outcomes include both continuous data (DHI score, duration of symptoms) and dichotomous data (otolith function, defined as normal or abnormal). Analysis of secondary outcomes will be conducted using mixed model with repeated measures for continuous outcomes or logistic regression for dichotomous data, again controlling for baseline potential confounders. Statistical analysis will be carried out by a statistician from Fudan University Medical School, who is blinded to group allocation and study hypothesis. To achieve that blinding, all participants are anonymized and study arms are coded as A, B, C.

Trail status and recruitment

Protocol V.2.0, 10 August, 2018. Planned date of first enrolment is September 1, 2018. The estimated time required for recruitment is 15 months. The total duration of this study is expected to be 23 months, including statistical analysis and study results drafting.

Data management

Data Safety and Monitoring Board (DSMD) has already been set up. DSMD will monitor day-to-day running of the trial, review the accumulation data, check database integrity, and be responsible for carry out interim analyses. DSMD consists of five persons: a chair, a statistician, a methodologist experienced in research with BPPV, a clinical expert, and a patient representative. All members are independent from the study sponsor and report no competing interest. The

DSMD meets approximately every month from the start of the trial. Trial sponsor compensate DSMD members for their time and effort, similar to the compensation provided to other trial support personnel.

For data collection, an electronic case report form (CRF) has been designed to record all the data from the baseline and the three follow-ups during the trial. Electronic data are stored on a public platform at www.medresman.org sponsored by China clinical trial registry center. The database uses standard techniques to provide security. Access to database is controlled by user names and encrypted passwords. Individual participant data (IPD) will be made public in 6 months after the completion of the study through the IPD sharing platform.

Patient and public involvement

Patients and the public were not involved in the design of this study. However, we have consulted with a patient representative about his views on how best to involve patients throughout the proposed project. His views have been incorporated in our revised protocol. Patients and the public will be informed of the study results via peer-reviewed journals or academic conference.

Dissemination of the study findings

We plan to publish the study findings in peer-reviewed academic journals. We also intend to deliver presentation of this study at local, national and international conferences where possible. Furthermore, we will draft a summary of the study results on website of Eye & ENT hospital that can be accessed by all trial participants as well as relevant interest groups.

Competing interests

No competing interests exist.

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Ethics approval

Institute Review Board of Eye & ENT Hospital of Fudan University (reference number.2017046).

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Figure 1 Study flow chart.

Figure 2 Screenshot of head movement exercises in the training video.

Figure 3 Screenshot of gait exercise in the training video.

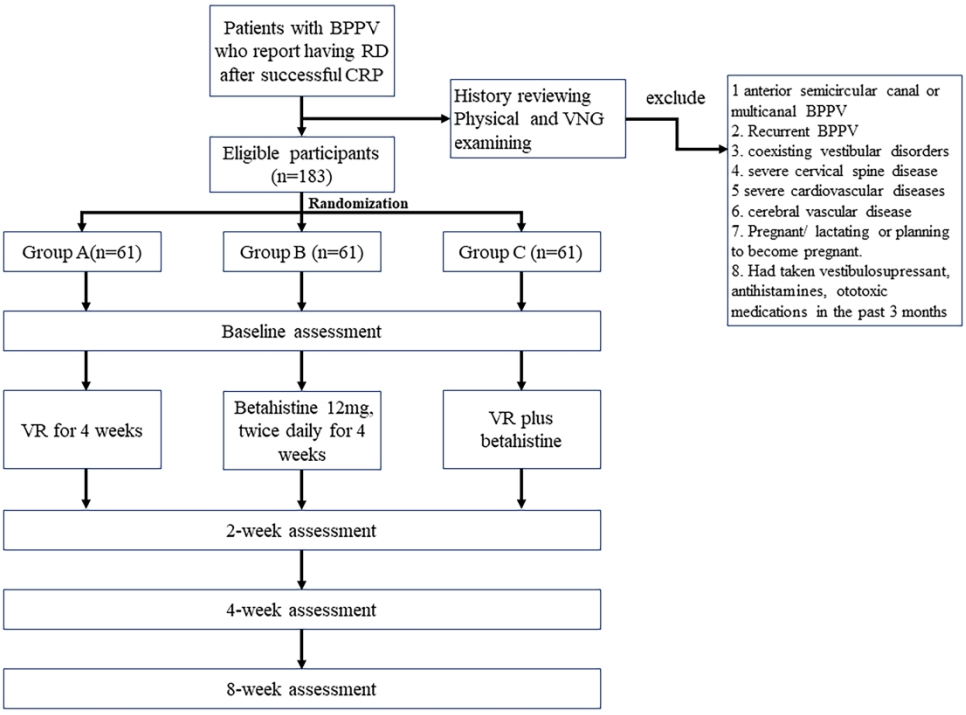

Figure 1 Study flow chart

254x190mm (300 x 300 DPI)

Figure 2 Screenshot of head movement exercises in the training video

285x160mm (300 x 300 DPI)

Figure 3 Screenshot of gait exercises in the training video

528x297mm (96 x 96 DPI)

BMJ Open

The effects of vestibular rehabilitation, with or without betahistine, on managing residual dizziness after successful repositioning manoeuvres in patients with benign paroxysmal positional vertigo : a protocol for a randomized controlled trial

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The effects of vestibular rehabilitation, with or without betahistine, on managing residual dizziness after successful repositioning manoeuvres in patients with benign paroxysmal positional vertigo：a protocol for a randomized controlled trial

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ABSTRACT

Introduction

Benign paroxysmal positional vertigo (BPPV) is recognised as the leading cause of peripheral vertigo in adults. The canalith repositioning procedure (CRP) can be used for effective treatment of BPPV. However, some patients experience residual dizziness (RD) even after successful CRP, resulting in a significant negative impact on their daily function and quality of life. Exercise-based vestibular rehabilitation (VR) has been proven as an effective method for managing dizziness and has been applied in patients with various vestibular disorders. However, the efficacy of VR to specifically target RD post-BPPV is unknown. This study aims to investigate the efficacy of VR, compared to betahistine or VR plus betahistine treatment, in the treatment of patients experiencing RD after successful CRP.

Methods and analysis

A randomised single-blinded controlled trial will be carried out to determine the efficacy of VR compared to betahistine or VR plus betahistine treatment in mitigating RD and improving balance function. Patients with BPPV who experience RD after successful CRP will be recruited. Participants will be randomised into one of three groups to receive VR, betahistine, or VR plus betahistine. There will be 61 participants in each group. The primary outcomes will be changes in the patient's daily function as measured by the Vestibular Activities and Participation questionnaire and balance ability assessed by computerised dynamic posturography. The secondary outcomes will be dizziness-related handicap, otolith function, and duration of RD symptoms.

Outcome measures will be noted at baseline and at 2, 4, and 8 weeks post-randomisation. This study has the potential to reduce unnecessary anti-vertigo drug prescriptions and may lead to a

general consensus regarding the use of VR as a first-line treatment for RD in patients with BPPV.

Ethics and dissemination

This trial received ethical approval from the Institutional Review Board of Eye & ENT Hospital of Fudan University (reference number.2017046). The study results will be disseminated via peer-reviewed journals and conferences.

ClinicalTrials.gov identifier: NCT03624283

Strengths and limitations of this study

►To the best of our knowledge, this is the first randomised controlled trial to evaluate the effects of vestibular rehabilitation (VR), compared to betahistine or VR in addition to betahistine, on managing residual dizziness after successful canalith repositioning procedure in patients with benign paroxysmal positional vertigo.

► Both subjective and objective outcome measures will be comprehensively assessed with a reasonably long follow-up period. In particular, patients' activities and participation aspect based on the International Classification of Functioning, Disability and Health framework will be evaluated. Such a trial will be able to fully reflect the efficacy of the proposed intervention.

► For practical reasons, there will be no control group with sham, placebo, or no treatment in this study; therefore, the study will not be useful to determine whether participants improve spontaneously or to determine the mechanisms by which the three interventions may function to alter outcomes.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the leading cause of peripheral vertigo, with a prevalence of 10.7-64 per 100,000 people and a lifetime prevalence of 2.4%.[1] The time at onset is most commonly between the fifth and seventh decade of life, but BPPV can occur at any age.[2] Two hypotheses, involving cupulolithiasis[3] and canalithiasis,[4] are among the most widely accepted hypotheses that elucidate the pathophysiology of BPPV. The hypothesis involving canalithiasis has gained wider acceptance in the scientific field because it offers a better explanation of the symptoms.[5] According to the canalithiasis hypothesis, BPPV is caused by free otoconia dislodging from the utricular macula and entering the semicircular canal, which promotes inappropriate flow of endolymph whenever the head is rotated in the plane of the affected canal.[4] Although any of the three semicircular canals can be affected, the posterior semicircular canal is the most common, followed by the horizontal canal. Treatment for BPPV consists of the canalith repositioning procedure (CRP) with the aim of repositioning the displaced particles from the affected canal to their original location.[6] The CRP has long been a mainstay therapy and is now well established as the gold treatment for BPPV.[7] Posterior canal BPPV can be treated by performing Epley's manoeuvre or Semont's liberatory manoeuvre. For horizontal canal BPPV, barbecue rotation or the Gufoni manoeuvre have been demonstrated to be effective.

Despite the fact that the CRP can provide rapid relief of vertigo in patients with BPPV, residual symptoms may remain even after the disappearance of typical vertigo and nystagmus following a successful CRP. These residual symptoms, also referred to as residual dizziness (RD), imply a non-specific sensation of unsteadiness, lightheadedness, disorientation, fogginess, or drowsiness.[8] The reported incidence of RD ranges from 29.6% to 76.9%, and the duration of RD

can range from a few days to several months.[8-12] Several authors have reported that RD symptoms may persist for >3 months,[13,14] resulting in adverse physical and psychological consequences.

Different pathophysiological mechanisms have been proposed to explain the presence of RD, but the cause remains unknown. Previous studies have suggested the following possible explanations: (1) the persistence of debris in the canal is insufficient to provoke detectable positional nystagmus or vertigo;[11] (2) otolith dysfunction;[15,16] (3) coexisting vestibular disease that leads to incomplete central adaptation; (4) potential autonomic dysfunction such as orthostatic hypotension;[17] and (5) persistent postural-perceptual dizziness.[18]

Dizziness increases the risk of falls or fear of falling, disturbs daily life, and results in restriction of social activities. As a result, many patients with BPPV tend to avoid certain activities, limit their movement, and avoid specific circumstances due to fear of provoking dizziness and unanticipated unsteadiness attacks.[19] It is not surprising that increased postural instability has been documented in patients who experience RD.[20, 21] Given the high prevalence of RD after successful repositioning and its negative impact on patient recovery, this impairment should be managed properly.

To date, there is no consensus regarding how to effectively manage RD after successful CRP in patients with BPPV. Betahistine is the most widely used medication to ameliorate dizziness due to its effects of increasing labyrinthine microcirculation as well as suppressing the increased neuronal activity in vestibular receptor cells, afferent neurons, and vestibular nuclei.[11,22] However, conflicting data exist regarding the efficacy of betahistine for preventing or treating RD. Guneri et al.[23] evaluated the efficacy of betahistine in reducing symptoms after Epley's

manoeuvre for posterior canal BPPV; they found that 48 mg of daily betahistine was more effective than Epley's manoeuvre alone or combined with a placebo in improving symptoms as assessed by four different vertigo symptoms scales. In contrast, Acar et al.[24] carried out a randomised controlled clinical trial to investigate the efficacy of betahistine (compared to a no medication group) for the treatment of RD after successful CRP. After 3 and 5 days of treatment, the mean Dizziness Handicap Inventory (DHI) scores of the groups receiving medication did not differ from the mean DHI score of the control group, indicating that betahistine did not produce greater alleviation of RD than did no treatment. However, both studies have unclear randomisation sequence generation and allocation concealment and only included subjective outcomes. These results suggest that clinical trials with more rigorous methodology and that include comprehensive outcome assessments are warranted.

Recently, non-pharmacological interventions such as vestibular rehabilitation (VR) have been recommended as the first line treatment for chronic vertigo.[22] VR, which has been available since the 1940s, is an exercise-based treatment consisting of varied eye, head, and body movements designed to stimulate the vestibular system and optimise vestibular compensation.[25] The current VR approach typically includes a combination of three different exercise components to address the impairments or functional limitations identified during evaluation: (1) gaze stability exercises; (2) habituation exercises, including optokinetic exercises; and (3) balance and gait training in different conditions.[26] The aim of VR is to improve the visual-vestibular interaction and increase balance ability. It is also proven to improve daily function and reduce the symptoms of dizziness.[26] The mechanism underlying its efficacy is thought to rely on the following three aspects: (1) compensation/habituation, a central process referring to the concept that repeated

exposure to a provocative stimulus will result in a reduction in the symptomatic response to that treatment;[27] (2) adaptation, which is the recovery of dynamic vestibulo-ocular responses due to the ability of the vestibular system to make long-term changes in the neuronal response to input; and (3) substitution, which is the use of other strategies to replace the lost function.[28]

The updated evidence-based clinical guideline of the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) indicates that the clinician should offer VR as treatment for BPPV, stating that although movement/ habituation-based VR should not be a first-line treatment modality for BPPV, it is indicated for patients who experience persistent disability following CRP.[29] VR is particularly indicated in subjects with additional impairments, such as nonspecific dizziness and heightened fall risk.[7] A Cochrane review[30] was conducted to assess the efficacy of VR in patients with symptomatic unilateral peripheral vestibular dysfunction; this included eight studies investigating VR in BPPV specifically. This review supports the contention that the primary intervention for BPPV should be CRP that directly treat the condition, but movement/habituation-based VR will further aid and benefit long-term functional recovery. A more recent review by Bressi et al.[31] proposed that a hierarchy of interventions should be offered to patients with BPPV, starting with CRP and followed by post-treatment exercises. The findings also indicated that CRP and VR seem to have a synergic effect in patients with BPPV.[31]

While previous studies have shed light on the benefits of VR in BPPV patients, to date, no randomised clinical trial has been conducted to specifically investigate VR, with or without betahistine, in treating RD following CRP in patients with BPPV. This study has been designed with the broad aim of verifying the efficacy of VR as a first-line treatment option for RD. It

conforms to the current recommendations for best clinical practice with respect to the implementation of VR for persons with impairments and functional limitations related to vestibular deficit.[26] We hypothesise that participants in the VR group will exhibit fewer activity and participation restrictions and less balance dysfunction than participants in the betahistine group. Moreover, we expect that participants in the VR group will experience shorter durations of RD, reduced dizziness-related handicaps, and enhanced recovery of otolith dysfunction. We also hypothesise that the effects of VR alone will be non-inferior to a combination of VR and betahistine in terms of the outcome measurements mentioned above.

METHODS AND ANALYSIS

Study design, setting, and participants

This study was designed as a randomised controlled prospective single-blinded study. Outcome assessment will be conducted by two researchers who are blinded to group allocations.

The study setting is the largest ear, nose, and throat (ENT)-specialised hospital in China. The hospital serves a population of ~23 million persons in Shanghai. It also serves as a referral centre accepting patients from all over the country.

The eligibility criteria are as follows: (1) diagnosis of unilateral BPPV (unilateral posterior semicircular canal BPPV or horizontal semicircular canal BPPV) according to the clinical practice guideline by AAO-HNSF in 2017,[29] (2) age 18-80 years, and (3) residual symptoms after successful repositioning manoeuvres. Participants will be excluded if they (1) are confirmed to have anterior semicircular canal BPPV or multi-canal BPPV; (2) are confirmed to have recurrent BPPV; (3) are diagnosed with coexisting vestibular disorders, including Meniere disease, vestibular neuritis, labyrinthitis, and peripheral vestibular loss; (4) are diagnosed with severe

cervical spine disease; (5) are diagnosed with severe cardiovascular disease; (6) are diagnosed with known cerebral vascular disease such as carotid stenosis; (7) are pregnant/ lactating or planning to become pregnant during the study period; or (8) have taken vestibulosuppressants, antihistamines, and/or ototoxic medications in the previous 3 months.

Procedure

The study protocol was reviewed and approved by the Institutional Review Board of the Eye & ENT Hospital of Fudan University (Reference Number: 2017046). Patients who are suspected of having BPPV and visit an ENT specialist are potentially eligible for this study. They will undergo a Dix-Hallpike test, a roll test, and an anterior canal provoking test to confirm whether they are experiencing solely unilateral posterior canal or horizontal canal BPPV. After diagnosis by an ENT specialist, posterior canal BPPV will be treated using Epley's manoeuvre or Semont's liberatory manoeuvre, while horizontal canal BPPV will be treated with barbecue rotation manoeuvres. The same physiotherapist will apply both the testing procedure and the CRP manoeuvre. The CRP is repeated up to three times over the course of 1 day. After a successful repositioning manoeuvre, patients will be asked to complete a DHI test. Patients who fail to respond when up to three CRPs have been performed will not be included in this study.

On the second day following successful CRP, a lead investigator will contact the patient by either telephone or Webchat. Patients will be asked whether they are experiencing residual symptoms. If yes, they will be initially screened via telephone interview, and those who meet the inclusion criteria will be invited to participate in the study. A face-to-face interview will be arranged for patients who express an interest in the trial, written informed consent will be obtained from candidates who agree to participate. After obtaining written consent, the principal

investigator (Li HW) will fully review the participant's medical history and perform a physical examination and videonystagmography (VNG) including a caloric test to exclude any central nervous system pathologies or other vestibular diseases. The diagnostic test for BPPV will be repeated to confirm that the exclusionary characters are negative. Pure-tone audiometry and tympanometry will be checked. Gait and balance will also be assessed (Romberg, sharpened Romberg). Whenever necessary, an imaging exam such as a computed tomography scan or magnetic resonance imaging will be used to exclude cerebellar disorders. The purpose of the above-mentioned examination is to confirm the diagnosis and validate the homogeneity of all participants who take part in the study. After eligibility screenings, participants will be randomly allocated to one of three groups: Group A patients will perform VR exercises; Group B patients will be prescribed betahistine; and Group C patients will be offered both VR and betahistine. Outcome measurements will be noted at baseline and at 2, 4, and 8 weeks post-randomisation. Outcome measurements will be executed by two independent researchers; one will be responsible for apparatus-based measures and another for subjective data collecting. Both researchers will be unaware of the treatment assignment until the end of the study. A study flow chart is provided in Figure 1.

Randomisation and blinding

Participants will be randomly assigned to three groups of 61 persons each. The randomisation process will be carried out by an internet-based randomisation tool provided by the China clinical trial registration centre. The website is accessible to the public via http://www.medresman.org/login.aspx. The randomisation sequence will be generated automatically when the administrator logs into the website and requests the allocation number

(once an eligible patient is recruited). Participants will be randomly allocated at a ratio of 1:1:1 and stratified by sex and age (≤60 years, >60 years). As the randomisation is on-line and automatic, neither the researchers nor the patients can manipulate which treatment the patients will receive; this ensures that group allocations are randomly assigned.

Since VR is an operational intervention, it is not possible for either the patients or the physiotherapists and physicians to be blinded to allocation. However, two independent researchers will contact the patients to collect both subjective and apparatus-based data. The statistician of our trial team will remain blinded until the statistical analyses are complete.

Interventions

Participants in Group A (VR group) will perform VR exercises twice a day, 7 days per week, over a period of 4 weeks. The exercise protocol was developed based on clinical experience and adapted from previous studies[32,33] in which vestibular stimulation exercise was demonstrated to improve balance ability and functional performance among BPPV patients who had undergone CRP. A dedicated physiotherapist (Wu PX) drafted the initial protocol. The content was reviewed by three experts with experience in caring for patients with chronic dizziness and was then piloted with two female and two male patients who have experienced RD post-BPPV. Participants reported no difficulties in practicing these exercises. The protocol primarily consists of three categories: oculomotor exercises, head movement exercises, and gait and balance training (Table 1).

Table 1. Overview of the VR program

Components	**Movements**	**Rationale**
Oculomotor	VOR × 1	Improve gaze stability and

exercises	VOR × 2 Smooth pursuits Saccades	VOR gain adaptation
Head movement exercises	Shaking the head right and left, nodding the head up and down, and circumducting the head clockwise and counter clockwise while maintaining focus on a visual target	Habituate vestibular responses and relieve symptoms
Gait and balance training	Static standing on varied base of support (feet apart, feet together, semi-tandem, tandem) Static standing with different arm positions (arms away from body, arms close to body, arms reaching forward, arms tossing a ball) Sitting to upright Sitting upright then bending down to pick up objects Walking with yaw head movement Walking with pitch head movement Tossing a ball above the eye level while walking Tandem walking on a level surface Tandem walking on a foam surface	Facilitate the vestibulospinal response, improve postural stability, and regain balance and physical function

VOR, vestibulo-ocular reflex.

The difficulties of the tasks in each session are set according to each participant's balance performance (as measured by computerised dynamic posturography [CDP]) or tolerance to vestibular stimulation. We intend to make the tasks progressively challenging. The approaches used to increase the level of difficulty will be as follows: (1) increasing the velocity of exercise performance; (2) changing target distance (near to far) while performing VOR × 1; (3) placing the target in a distracting visual pattern; (4) performing the exercises with eyes open, then with eyes closed; (5) altering the surface from solid to foam; and (6) performing dual tasks such as doing math or talking on a cell phone while walking.

The VR protocol involves one office-based session per week conducted by a skilled physiotherapist (Wu PX) at the clinic and home-based exercises for the remaining 6 days of the week. Compliance will be assessed during home exercise; an exercise diary outlining the time and duration of each exercise is required to be filled out every week. A video and booklet have been developed illustrating the program and will be used as guides when participants carry out exercise at home. Figures 2 and 3 present the screenshots of the training video; written consent from the person in the video has been obtained. During the first clinical visit, the physiotherapist will provide adequate supervised VR for the patients to help them understand the goals of the program and methods to manage their own progress independently. Patients will be instructed not to start any new physical activity during the study period.

Participants in Group B (betahistine group) will be prescribed betahistine 12 mg (manufactured by Wei Cai China Pharmaceutical Co., Ltd.) (two tablets taken twice daily for 4 weeks). Participants will be asked not to take any other types of antivertiginous medicine during

the course of the study; in such a case, the patient should inform his/her ENT specialist. The pharmacy department of the study hospital will be responsible for dispensing betahistine to each participant. There are 30 tablets in one prescription package. Four packages will be prescribed at the commencement of treatment. During the first two follow-up visits (2 and 4 weeks post-randomisation), participants will be asked to bring their drug packages and the specialist will count the remaining tablets; if the participant fully adheres to the protocol, eight tablets should be left at the 4th week follow-up visit.

Participants allocated to Group C (VR plus betahistine group) will receive a combination of the VR and betahistine protocols as described above.

Adverse events

Adverse events are rare while performing VR. However, patients will be instructed to report any complaints or symptoms occurring during or after the exercises. The following symptoms are considered as signs to stop or modify the VR protocol: vomiting, nausea, or muscle soreness; a sharp or prolonged pain sensation in the neck, arms, or legs; a sensation of ear fullness, hearing loss, or tinnitus; double vision; or fainting.

The tolerability for betahistine is reported to be good.[34] Major possible side effects include gastrointestinal system disturbances and headache.[35] In this study, participants will be encouraged to report any adverse events after betahistine intake. The investigator will routinely contact the participant once per week and ask if any unexpected symptoms have appeared. Any adverse events likely caused by betahistine during the trial will be recorded and reported to the Adverse Drug Reaction administration of the Eye & ENT Hospital of Fudan University within 48 h.

Withdrawal/retention of participants

Participation in this study is voluntary and participants have the right to withdraw at any time. However, we will use the approaches recommended by Dziura et al.[36] to improve adherence to the intervention protocols and minimise attrition rates. These include data collection that does not require clinical appointments, a reimbursement mechanism for extra auxiliary examination fees to encourage study completion, and the provision of weekly phone-call contact during the trial. Any concerns, such as unexpected symptoms, as well as logistic issues such as travelling to the clinic or parking issues will be evaluated during each telephone consultation. In rare cases, participants may withdraw owing to unforeseen circumstances. Every reason for withdrawal will be recorded.

Outcome measures

Evaluating therapeutic success in patients experiencing vestibular disorder is often difficult due to the complexity of this condition and the lack of specific apparatus-based parameters. Various measurements have been utilised; however, no consensus has been reached as to which aspects should be addressed. An international group of investigators and health care providers developed a core set based on the International Classification of Functioning, Disability and Health (ICF) framework that illustrates key aspects of functioning that should be measured when assessing patients with vertigo, dizziness, and imbalance.[37] Of these, two main domains are included: (1) body function and structure and (2) activity and participation. A recently published evidence-based clinical practice guideline has made recommendations for specific rehabilitation outcome assessment by using recommended measures from across the ICF domains.[26] In the current study, ICF-based activity and participation aspect and apparatus-based measures will be

included to provide a full overview of the efficacy of VR on managing RD after successful repositioning in BPPV patients.

Primary outcomes

The primary outcomes will focus on patients' daily functional aspects and balance ability, which include:

1. The participant's activity and participation as quantified by the Vestibular Activities and Participation (VAP) scale. The VAP is a 34-item self-reporting questionnaire based on the ICF framework to evaluate the effect of dizziness and/or balance problems on the ability to perform activity and participation tasks.[38] The difficulty of each task (without assistance from other persons) is rated. Each item of the VAP is scored on a five-point scale indicating the level of difficulty; 0 refers to no difficulty and 4 indicates inability to complete the task. A total score is obtained by calculating the average item scores after excluding the "not applicable" responses. Previous studies have established the cross-cultural validity of the VAP.[39] We recently completed the translation and validation of a Chinese version of the VAP.

2. Balance function, as measured by CDP (Equitest, NeuroCom International, Inc.). The Sensory Organization Test (SOT) of CDP evaluates the ability of subjects to utilise vision (vestibular and somatosensory) to maintain their balance.[40] Six increasingly challenging conditions (from SOT1 to SOT6) that disrupt portions of balance sensory input or visual surroundings are provided to evaluate balance. An Equilibrium Score (ES) for each condition is calculated by comparing the angular difference between the subject's calculated maximum and minimum sagittal plane body sway to a theoretical maximum displacement (12.5°). In terms of overall performance, a Composite Score (CS) is given as an estimate of postural stability: a CS

score near 100% indicates little sway, while scores approaching 0% confirm instability or a fall. The ES for each test condition from SOT1 to SOT6 and the CS will be used for analysis in this study. The values are considered abnormal when the score is lower than the age-specific norm data.

Secondary outcomes

The secondary outcomes will include dizziness-related handicap, recovery of otolith dysfunction, and duration of symptoms.

1. Dizziness-related handicap as measured by the DHI. The DHI has been widely used as a reliable tool for evaluating the self-perceived handicap effects imposed by vestibular system disease and has been translated to Chinese and standardised by Ding et al.[41] The DHI consists of 25 self-assessment items that can be broken down into three subscales: physical, emotional, and functional. Total scores of the DHI range from 0 to 100 with increasing scores indicating greater perception of handicap due to dizziness. It has been widely used as a reliable and valid tool for assessing the harmful effects of dizziness on quality of life for patients including those with BPPV.[42]

2. Recovery of otolith function as analysed by Vestibular Evoked Myogenic Potentials (VEMPs). VEMPs are now established as a clinical test of otolith function. The cervical VEMP (cVEMP) is used to assess inferior nerve otolith function (testing mainly saccular function), while the ocular VEMP (oVEMP) is believed to examine superior nerve otolith function (testing mainly utricular function). Previous studies[43,44] identified that, in patients with BPPV who underwent successful CRP, the occurrence of residual symptoms was correlated with oVEMP abnormalities; this suggests that utricular dysfunction is responsible for RD presence. In contrast, another study

found that BPPV patients with saccular dysfunction experienced more significant effects than did those with utricular dysfunction.[42] Therefore, in this study, both cVEMP and oVEMP will be recorded using the Bio-Logic Navigator Pro 9.0 (Natus Medical Inc., San Carlos, USA) system. The procedure will be performed in a sound-proof room. The methodology is reported in detail elsewhere.[45] Otolith dysfunction in our patients will be defined as a lack of unilateral responses in cVEMPs or oVEMPs.

3. Duration of symptoms as reported by patients. During the trial period, a researcher will contact the participants once per week to ask how many days they experienced symptoms in the previous week. By the end of the study, the number of days per week with reported symptoms will be summed to represent the duration of symptoms.

Time-points of outcome measurements

Outcome measurements will be performed at baseline and at three follow-up visits. Baseline assessments will be performed on the second day following successful CRP. Demographic and clinical data collected will include: age, sex, education, employment, marital status, coexisting systemic diseases, date of onset, duration of symptoms from onset to treatment, affected ear and canal, and the number of CRPs performed. Participants are required to return to the clinic at 2, 4, and 8 weeks post-allocation. They will fill out the same questionnaires (VAP and DHI) at each follow-up, while the CDP and VEMPs will only be repeated when the previous exam indicates abnormality. The schedule of enrolment, interventions, and outcome assessments are presented in Table 2.

Table 2. Schedule of enrolment, interventions, and outcome assessments

	Study period				
	Screening and eligibility /allocation	**Post-allocation**			**Close-out**
Time-point	T0	T1	T2	T3	
(D=day, W=week)	D2	W2	W4	W8	
Eligibility screening	✓				
Medical history review	✓				
Physical and VNG examination	✓				
Informed consent	✓				
Demographic and clinical characteristics	✓				
Allocation	✓				
Interventions					
VR (Group A)	←	—	→		
Betahistine (Group B)	←	—	→		
VR plus betahistine (Group C)	←	—	→		
Assessments of outcome variables					
VAP	✓	✓	✓	✓	
CDP	✓		✓/#	✓/#	
DHI	✓	✓	✓	✓	
oVEMP	✓		✓/#	✓/#	
cVEMP	✓		✓/#	✓/#	
Symptom duration		✓	✓	✓	

VNG, videonystagmography; VR, vestibular rehabilitation; VAP, Vestibular Activities and Participation; CDP, computerised dynamic posturography; DHI, Dizziness Handicap Inventory;

oVEMP, ocular Vestibular Evoked Myogenic Potential; cVEMP, cervical Vestibular Evoked Myogenic Potential. # Test is only repeated when the previous exam indicates abnormality.

Sample size calculation

The study sample size was based on the VAP measure (one of the primary outcomes), which is a useful clinical tool for assessing a patient's limitations in activities and participation due to vertigo, dizziness, and unsteadiness. The validation of VAP in patients who complained of dizziness or imbalance showed the minimum detectable change (MDC) for the VAP was 0.58, with a standard error of 0.21.[39] In this study, a VAP difference of 0.6 will be considered clinically meaningful. Thus, to detect an MDC of 0.6 for the VAP with 80% power (alpha level of 0.05, two-tailed test), 55 subjects per group will be required. Although there are three groups in this study, controlling for the type I error rate is not needed because our hypotheses are: (1) VR will be superior to betahistine (Group A versus Group B) and (2) VR will be non-inferior to VR plus betahistine (Group A versus Group C); therefore, only two comparisons will be executed. Allowing for a 20% loss during the follow-up period, a total sample of 183 (61 per group) will be required for the current study.

Data analysis

Statistical analyses will be completed using IBM SPSS Statistics for Windows (SPSS V.22.0) and the level of significance will be set at $p<0.05$. First, a descriptive analysis will be conducted to determine outliers and the distributions of the data. The three groups will then be analysed with respect to baseline values. Analysis of the outcome measures will be based on the conservative intention-to-treat (ITT) approach; moreover, as a secondary analysis, a per protocol analysis will also be performed. Drop-out/attrition is anticipated. We will examine the structure and pattern of missing data and, if appropriate, multiple imputation methods will be used in both the ITT and the per-protocol analyses.

The main analysis of change in the primary outcomes (VAP score and SOT composite) will use mixed-model with repeated measures (MMRM) analyses of variance (ANOVAs), with group and time as fixed effects and subject as a random effect. Mathematical transformation or categorisation of raw scores will be undertaken to meet the distributional assumptions that are required in MMRM models. Models will adjust for age, sex and other baseline potential confounders. Secondary outcomes include both continuous data (DHI score, duration of symptoms) and dichotomous data (otolith function, defined as normal or abnormal). Analysis of secondary outcomes will be conducted using MMRM ANOVAs for continuous outcomes or logistic regression for dichotomous data, again controlling for baseline potential confounders. Statistical analysis will be carried out by a statistician from Fudan University Medical School, who will be blinded to group allocations and the study hypotheses. To achieve blinding, all participants will be anonymised and study groups will be coded as A, B, C.

Study status and recruitment

This is protocol V.3.0, updated 20 February 2019. The planned date of first enrolment is 1 April 2019. The estimated time required for recruitment is 15 months. The total duration of this study is expected to be 23 months, including statistical analysis and drafting of the study results.

Data management

The Data Safety and Monitoring Board (DSMD) has been organised. The DSMD will monitor the day-to-day running of the trial, review the accumulation data, check the database integrity, and be responsible for carrying out interim analyses. The DSMD consists of five persons: a chair, a statistician, a methodologist experienced in research with BPPV, a clinical expert, and a patient representative. All members are independent of the study sponsor and report

no competing interests. The DSMD will meet approximately once per month from the start of the trial. The trial sponsor will compensate DSMD members for their time and effort, similar to the compensation provided to other trial support personnel.

For data collection, an electronic case report form has been designed to record all of the data at baseline and the three follow-up visits during the trial. Electronic data will be stored on a public platform at www.medresman.org, which is sponsored by the China Clinical Trial Registry. The database uses standard techniques to provide security. Access to the database is controlled by usernames and encrypted passwords. Individual participant data (IPD) will be made public at 6 months after the completion of the study via the IPD sharing platform.

Patient and public involvement

Patients and the public were not involved in the design of this study. However, we have consulted with a patient representative about his views on how best to involve patients throughout the proposed project. His views have been incorporated into our revised protocol. Patients and the public will be informed of the study results via peer-reviewed journals or academic conferences.

ETHICS AND DISSEMINATION

This study has received ethical approval from the Institutional Review Board of Eye & ENT Hospital of Fudan University (reference number.2017046).

We plan to publish the study findings in peer-reviewed academic journals. We also intend to present this study at local, national, and international conferences where possible. Furthermore, we will draft a summary of the study results to be posted on the website of Eye & ENT hospital that can be accessed by all trial participants as well as relevant interest groups.

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Contributors All authors have made an intellectual contribution to this protocol. Li Huawei was the principal investigator of the trial, with full responsibility for the project. Wu PX, Cao WZ and Hu Yan conceived the design, developed the protocol, and wrote the first draft of this manuscript. Li Huawei and Hu Yan revised and approved the final version of the study protocol and the final manuscript. Li Huawei and Hu Yan are co-corresponding authors whom contributed this paper equally.

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Competing interests No competing interests exist.

Patients consent for publication Not required.

Ethics approval This study was approved by the Institute Review Board of Eye & ENT Hospital of Fudan University (reference number.2017046).

Figure 1 Study flow chart.

Figure 2 Screenshot of head movement exercises in the training video.

Figure 3 Screenshot of gait exercise in the training video.

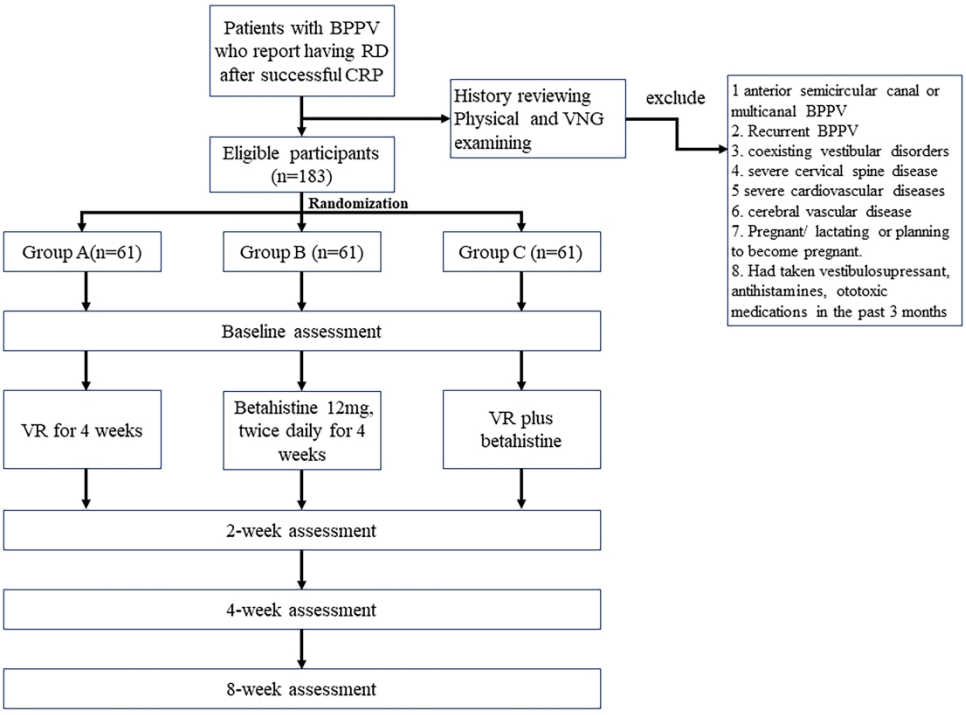

Figure 1 Study flow chart

254x190mm (300 x 300 DPI)

Figure 2 Screenshot of head movement exercises in the training video

285x160mm (300 x 300 DPI)

Figure 3 Screenshot of gait exercises in the training video

528x297mm (96 x 96 DPI)