




BMJ Open Epley manoeuvre for posterior semicircular canal benign paroxysmal positional vertigo in people with multiple sclerosis: protocol of a randomised controlled trial

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ABSTRACT

Introduction Vestibular disorders in multiple sclerosis (MS) could have central or peripheral origin. Although the central aetiology is the most expected in MS, peripheral damage is also significant in this disease. The most prevalent effect of vestibular peripheral damage is benign paroxysmal positional vertigo (BPPV). Impairments of the posterior semicircular canals represent 60%–90% of cases of BPPV. The standard gold treatment for this syndrome is the Epley manoeuvre (EM), the effectiveness of which has been poorly studied in patients with MS. Only one retrospective research study and a case study have reported encouraging results for EM with regard to resolution of posterior semicircular canal BPPV. The aim of this future randomised controlled trial (RCT) is to assess the effectiveness of EM for BPPV in participants with MS compared with a sham manoeuvre.

Methods and analysis The current protocol describes an RCT with two-arm, parallel-group design. Randomisation, concealed allocation and double-blinding will be conducted to reduce possible bias. Participants and evaluators will be blinded to group allocation. At least 80 participants who meet all eligibility criteria will be recruited. Participants will have the EM or sham manoeuvre performed within the experimental or control group, respectively. The primary outcome of the study is changes in the Dix Hallpike test. The secondary outcome will be changes in self-perceived scales: Dizziness Handicap Inventory and Vestibular Disorders Activities of Daily Living Scale. The sample will be evaluated at baseline, immediately after the intervention and 48 hours postintervention.

Ethics and dissemination The study was approved by the Andalusian Review Board and Ethics Committee of Virgen Macarena-Virgen del Rocio Hospitals (ID 0107-N-20, 23 July 2020). The results of the research will be disseminated by the investigators to peer-reviewed journals.

Trial registration number NCT04578262.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease characterised by demyelination, gliosis and neural loss.^{1 2} Disturbances in postural control and dizziness are among

Strengths and limitations of this study

- This randomised controlled trial will be the first to address knowledge gap on the effectiveness of the Epley manoeuvre in a multiple sclerosis population.
- Double-blind and concealed allocation will reduce the possibility of bias.
- Videonystagmography goggles will enable the primary outcome of the research to be measured more objectively.
- The Epley manoeuvre is an easy and quick vestibular treatment that results in significant changes in benign paroxysmal positional vertigo in a short period of time.
- Due to possible changes in drug treatment and manifestation of multiple sclerosis flares, it is difficult to perform a long-term evaluation of the sample.

the most recurrent symptoms in MS, with a direct repercussion on activities of daily living.^{3 4} This symptomatology could be caused by a vestibular system affection.^{5 6} In MS, vestibular affection could have peripheral or central origin.^{7 8} Central vestibulopathy impairments can appear in neuroanatomical locations such as in the eighth cranial nerve, vestibular nuclei, oculomotor tracts, medial longitudinal fasciculus and cerebellum.⁹ On the other hand, peripheral vestibulopathy is due to damages in the vestibular system, highlighting the semicircular canals.⁵ Within these canals, the most common affection is located in the altered information recorded by the posterior semicircular canal.^{10–12} In MS, although central demyelination is the most expected, vestibular peripheral aetiology is also quite common.^{9 13} In the study by Zeigelboim *et al*,¹³ it was determined that 86%

of cases of MS with vestibular problems had a peripheral origin.

The main symptom observed when a vestibulopathy exists is vertigo, defined as an instability associated with a rotation sensation of oneself with respect to the environment. The problem is exacerbated by fast head movements and positional changes.^{14–16} Furthermore, the most common cause of vertigo without another associated neurological sign is benign paroxysmal positional vertigo (BPPV).^{9 14} BPPV is a syndrome defined as episodes of vertigo that last less than 60 s.^{17–19} The magnitude of BPPV in patients with MS has been shown in the research of Frohman *et al*,⁹ where 52% of the sample presented BPPV. Affection of the posterior semicircular canals is also apparent in 60%–90% of BPPV cases.^{20 21}

The Dix Hallpike manoeuvre is considered the gold standard in identifying posterior semicircular canal BPPV.^{22 23} If confirmed in this trial, the treatment of choice will be the Epley manoeuvre (EM),^{22 24–26} which has been reported effective in 80%–100% of patients with posterior canal BPPV.²⁷

Due to the central or peripheral origin of vertigo in the MS population, an exhaustive neuro-otological evaluation must be carried out for an accurate diagnosis.^{7 28} Nystagmus is one of the key symptoms to make a differential diagnosis. In vertigo of peripheral origin, nystagmus has a counterclockwise or clockwise movement sum to the horizontal direction.^{18 29 30} In vertigo of central origin, there are characteristic atypical movements with only one direction. Additionally, peripheral nystagmus is fatigable and fades with an inhibiting effect of ocular fixation.^{6 9 28} Finally, in patients with MS, if the vertigo is of peripheral origin, a specific vestibular rehabilitation programme can be indicated.^{7 9} This rehabilitation is based on canalith repositioning procedures aimed at removing the otolith debris inside the particular canal.^{13 22 27}

Notwithstanding the efficacy of EM for treatment of BPPV, this has been poorly studied in the MS population within the scientific literature. Only two previous research studies have investigated this manoeuvre as an intervention for BPPV in patients with MS. The first was a retrospective study conducted by Frohman *et al*²⁸ who reported that 100% of participants with MS with BPPV successfully recovered after receiving EM. The second was a case study conducted by Yoosefinejad and Siravani³¹ of a participant with relapsing-remitting MS who suffered from BPPV. Interventions applied in this research were the Epley and Semont manoeuvres and the BPPV remitted postintervention. In addition, the participant with MS declared more independence in activities of daily living.

As far as we know, the present study will be the first randomised controlled trial (RCT) to evaluate the application of EM in a population with MS diagnosed with BPPV. The purpose of this trial is to assess the effectiveness of EM in improving BPPV symptoms in participants with MS. We hypothesise a higher efficacy of the intervention for dizziness and activities of daily living improvement when compared with a sham manoeuvre.

METHODS AND ANALYSIS

Study design

This protocol describes a two-arm, parallel-group design and a double-blind, randomised clinical trial. A prospective study with randomised and concealed allocation will be performed to prevent possible bias. Participants and evaluators will be blinded to group allocation. The RCT will have three evaluations of the sample which will be carried out at baseline, immediately after the intervention and 48 hours later. The study design is described in figure 1.

This protocol meets the Standard Protocol Items: Recommendations for Interventional Trials.³² The RCT will be developed following instructions from the Consolidated Standards of Reporting Trials.³³ This study has been registered at ClinicalTrials.gov.

Study setting

The trial will be conducted at the Physical Therapy Department of the University of Sevilla (Spain). The Vithas Nisa Hospital will be the main healthcare institution involved in this research. Inclusion of other healthcare centres in the area is expected.

Participants and recruitment

Recruitment of participants is expected to start in February 2021 and is estimated to be completed in June 2022. It will be carried out in the healthcare institutions of the participants. To recruit the study sample, the research team will first contact the Multiple Sclerosis Unit of Seville Vithas Nisa Hospital (Spain). Next, patients with MS who meet the eligibility criteria will be phoned and given an explanation regarding the development and conditions of the RCT. After providing oral and written information, the subjects will be free to decide if they wish to participate. After the invitation, participants who desire to be part of the study will sign the written informed consent (see online supplemental material 1 for the informed consent form).

Inclusion criteria

- ▶ Adults of both genders aged 18–65 years old.
- ▶ Clinically diagnosed of any MS subtype (relapsing-remitting, primary progressive and secondary progressive).
- ▶ Expanded Disability Status Scale score ranging from 1 to 5 points.
- ▶ Diagnosed with posterior semicircular canal BPPV by an otolaryngologist and a physical therapist expert in vestibular rehabilitation.

Exclusion criteria

- ▶ Changes in MS pharmacotherapy within the last 3 months.
- ▶ BPPV treatments such as vestibular sedatives, corticosteroids, morphine and antihistamines, at least 72 hours before the intervention.
- ▶ Alcohol consumption in the last 72 hours.
- ▶ Severe visual impairments.

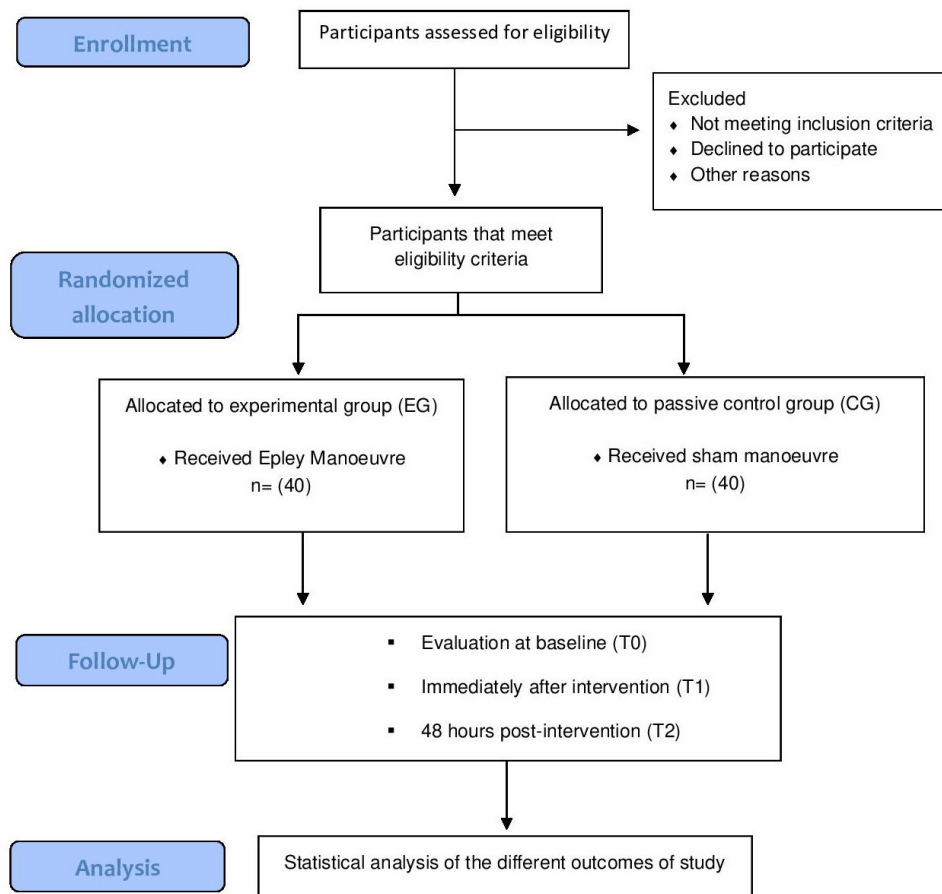


Figure 1 CONSORT flow diagram of participants' recruitment and progress through the phases of the trial. CONSORT, Consolidated Standards of Reporting Trials; CG, control group; EC, experimental group.

- ▶ Received vestibular rehabilitation within the last 3 months.
- ▶ Existence of any other neurological disease.

Randomisation, concealment allocation and blinding

Once the informed consent is signed by all participants, a baseline evaluation will be carried out. Randomisation will then be performed by an independent researcher in a computer-generated random sequence. We will consider a 1:1 distribution ratio. The allocation group will be concealed, and it will be sent in an opaque envelope to the physical therapist who will execute the EM. Evaluators and participants will be blinded to group allocation. Double-blinding will reduce the risk of bias.

Patient and public involvement

Patients or the public are not involved in designing the trial, but a number of public organisations are contacted for patient recruitment (eg, Hospital Virgen Macarena, Ilustre Colegio Profesional de Fisioterapeutas de Andalucía). Once the results are published, participants will be informed by email in an understandable writing. Furthermore, the researchers will perform meetings in each public organisation engaged in the recruitment.

Intervention

Experimental group

Participants allocated to the experimental group will receive the EM, a canalith repositioning procedure. This manoeuvre was developed by Dr John Epley and enables the free-floating otolith debris of the posterior semicircular canal to return to the vestibule.^{26 34 35} The subject will undergo only one EM, which will be performed by a physiotherapist expert in vestibular rehabilitation. Before the experimental intervention, all participants will be instructed to keep their eyes open throughout the process. The aim is to detect the appearance of nystagmus in different positions. Moreover, to record and provide quantitative assessment, videonystagmography (VNG) goggles will be worn by participants at the same time as EM is carried out.³⁶ The aim of this tool is to record nystagmus along with the EM and to confirm the repositioning of the otoliths after the intervention.^{37–39} VNG is an infrared camera which detects the black of the pupil, allowing measurement of eye movement speed.³⁸ Additionally, thanks to the opaqueness of the VNG, evaluation of nystagmus will not be disturbed by the mechanism of ocular fixation.³⁷

EM is a five-step procedure. In the first step, with the patient in supine posture, the head will be positioned

at 45° turned towards the unaffected ear, with the head slightly overhanging the edge of the couch. In the second step, maintaining the previous position of the head, the physiotherapist will turn the head 45° towards the affected ear. In the third step, the whole body will be turned until it is 135° from the baseline supine position. In the fourth step, while the head is kept turned to the affected ear, the patient will be incorporated until he is sitting. In the fifth step, while the patient is seated with the head in neutral position, the chin will be bent 20°. Each procedure will be held for 30 s or 2 min as the dizziness or the nystagmus disappears. After the intervention, the physiotherapist will provide instructions that the participant must follow. The instructions are to not move the head abruptly, to sleep propped up and to not lie down on the affected side in the 48 hours postintervention.³⁵ The participant will be re-evaluated 48 hours after the intervention.

Control group

Participants allocated to the control group will receive a sham manoeuvre. The sham intervention is based on the Semont diagnostic manoeuvre, as described in a study by Bruinjtes *et al.*³⁵ The intervention will also be carried out by an expert physiotherapist. The sham manoeuvre will start with the participant in a neutral seated position. To sum up, the head is rotated 45° towards the unaffected vestibule, after which the participant will be guided by the physiotherapist to a lateral decubitus position towards the affected side on which his nose will be pointing above. To conclude, the participant will return to a seated position without rotating the head. Each position of the sham manoeuvre will be maintained for 1 min. During the process, the VNG goggles will be worn by the participant and they will be instructed to not close their eyes during the intervention. This group will also be evaluated 48 hours after execution of the manoeuvre.

Once postintervention data are recorded in both groups, EM will be administered to the control group. The same postintervention instructions given to the other group will be followed.

Outcomes and measurements

The primary outcome of this research will be change from a positive to a negative Dix Hallpike test. The secondary outcome will be self-perceived changes in dizziness symptoms and impact on activities of daily living postintervention.

Change from a positive to a negative Dix Hallpike test

The Dix Hallpike manoeuvre is targeted to diagnose posterior semicircular canal BPPV.^{40–42} With regard to symptoms, it is necessary to focus on the nystagmus to detect the presence of paroxysmal nystagmus and vertigo.^{18 29} In BPPV, nystagmus is defined by fatigability with a duration of under 60 s and a torsional upbeat direction.⁴³ The performance of Dix Hallpike test consists of a subject sitting on a table with the head being turned 45° towards the side being tested. Once this position is

established, the evaluator is going to lay back the patient in a quick movement to produce a neck extension of 20° while his affected ear down.^{9 23} Throughout the process, the subject will be instructed to keep their eyes open so that nystagmus can be detected. If torsional nystagmus or vertigo appears while the head is down, it is indicative of posterior canal BPPV.^{18 44} In the current protocol, the Dix Hallpike test will be supported by VNG. This tool provides objective information on the Dix Hallpike test, thanks to the pupil tracking software which assesses eye movement and speed.³⁷ Testing with VNG provides several advantages, such as evaluation of the eyes by the clinician in real time, recording of video for documentation and later review, and recognition of torsional eye movement. Also, nystagmus will not be disturbed by environment illumination and mechanisms of ocular fixation.^{38 43}

Dizziness

Dizziness will be assessed using the Dizziness Handicap Inventory (DHI). The aim of this inventory is to assess the impact of dizziness on the quality of life. In addition, it evaluates the perception of balance in activities of daily living. The DHI is a 25-item self-assessment questionnaire with a total score of 100. The score is calculated by summing the responses to ordinal scales. A higher score means a higher level of disability and handicap, composed of physical, emotional and functional subscales. Scores for physical and emotional subscales range from 0 to 36 points, and for functional subscale from 0 to 28 points.^{43 45 46}

Activities of daily living

The Vestibular Disorders Activities of Daily Living Scale (VADL) is a self-reported questionnaire that measures independence in activities of daily living of people with vestibular disorders.⁴⁷ This scale is composed of 28 items divided into 3 subcategories: 12 questions on functional skills, 9 questions on ambulation skills and 7 questions on instrumental skills. Each item is rated on a 10-point scale, where a higher score means less independence in activities of daily living. The total score is the median of each subscale.^{48 49}

Evaluation of the sample will be performed at baseline (T0), immediately after the intervention only for the Dix Hallpike manoeuvre (T1) and 48 hours postintervention (T2). VADL will be again evaluated 1 week postintervention (table 1).

Sample size calculation

The sample size was calculated using the G*Power software (V.3.1.7; Kiel University, Kiel, Germany).⁵⁰ The sample size has been calculated as 80 participants for a one-tailed hypothesis, with an α error of 0.05, size effect of $d=0.8$, statistical power of 80% and an estimated dropout rate of 15%.^{51 52}

Statistical analysis

Normal distribution of variables will be assessed by Shapiro-Wilk test, and the Levene test will be carried out for variance homogeneity. Regarding the

Table 1 Data collection

Data and outcomes of the study		Screening and recruitment	Baseline (T0)	After intervention (T1)	Follow-up at 48 hours postintervention (T2)
Eligibility assessment		X			
Demographic variables		X			
Change from positive to negative Dix Hallpike test	Dix Hallpike manoeuvre		X	X	X
Dizziness	DHI		X		X
Activities of daily living	VADL		X		X*

*Follow-up at 1-week postintervention.

DHI, Dizziness Handicap Inventory; VADL, Vestibular Disorders Activities of Daily Living Scale.

description of quantitative variables, it will be drawn on central tendency measures and dispersion as mean and SD when they follow normal distribution. On the other hand, when variables do not follow this distribution, median, minimum and maximum intervals, and percentiles will be shown. Additionally, the results for the qualitative variables will be shown as absolute and relative frequencies.

For normal distribution, Student's t-test will be implemented to compare the means of independent samples. On the other hand, similar non-parametric tests will be applied in case of non-normal distribution. Cohen's criteria will be followed to assess the effect size of the studied variables. A 95% CI will be considered. Intention-to-treat principles will be considered for all analyses. Graphical and numerical analyses of data will be conducted using SPSS V.25.0 and GraphPad Prism (GraphPad, San Diego, California, USA).

Ethics and dissemination

The study was approved by the Andalusian Review Board and Ethics Committee of Virgen Macarena-Virgen del Rocio Hospitals (ID 0107-N-20, 23 July 2020). All participants will undergo and accept informed consent before data compilation. The investigators will disseminate the study results via publication in peer-reviewed scientific journals.

DISCUSSION

The aim of this future RCT is to assess the effectiveness of a vestibular rehabilitation intervention based on EM in participants with MS with posterior semicircular canal BPPV.

Vestibular dysfunction in MS can be caused by a central demyelination of the vestibular tracts and a peripheral vestibular damage, or both at the same time. These affections may induce an incorrect vestibular ocular or vestibulospinal reflex response, resulting

in ocular and balance disorders.^{7 13 28 53} Imbalance and vertigo are symptoms used to be misdiagnosed by healthcare professionals especially in people with MS.⁵⁴ This is due to the myriad of aetiologies of vestibular impairments in MS.¹³ In most cases, central vestibulopathy in MS is taken as the main cause of vertigo even without accurate neuro-otological examination.^{7 9} However, peripheral vestibular disorders are quite recurrent in the MS population, with BPPV being the most common.⁷ Although the posterior semicircular canal is mainly affected in BPPV, we should also remember that this canal could be damaged by several causes that also result in vertigo. Because of this, an accurate diagnosis of posterior semicircular canal impairment is necessary. One of the possible affections of the inner ear is the posterior semicircular canal dehiscence, caused by a defect in the bony roof of the temporal bone. Thus, Thabet *et al*⁵⁵ state that contralateral oVemps (extraocular vestibular-evoked myogenic potential) response and multidetector CT scanner (MDCTS) are essential to rule out inner ear defects and to reach a correct diagnosis. Reaching a correct vestibular diagnosis in MS is difficult, which is why diagnostic tools such as VNG, electronystagmography, cervical or ocular Vemps, magnetic resonance, MDCTS and specific vestibular manoeuvres, along with clinical manifestations, could play a fundamental role in the neuro-otological examination.^{9 55-60}

Due to misdiagnosis, people with MS who suffer from acute BPPV are improperly treated because they receive pharmacological treatment instead of choice therapy. An elective treatment prevents patients with MS from unnecessary ingestion of drugs, including vestibular sedatives, corticosteroids, morphine and antihistamines.^{14 28} The proper approach in BPPV is the EM.^{16 17 26 34} In this future RCT, to avoid misdiagnosis and to recruit subjects with MS with BPPV, an extensive neuro-otological evaluation will be carried out.^{58 61}



EM for resolution of posterior semicircular canal BPPV has been studied in depth in patients having only this syndrome.^{21 27 34} The success of EM has also been proven against other canalith repositioning procedures by Brandt-Daroff.⁶² Furthermore, Bruintjes *et al*³⁵ revealed that EM has long-term effects after the intervention. The impact of dizziness on activities of daily living was also assessed. In this case, significant changes were recorded for DHI after an intervention based on EM.³⁵ The results of the study by Gupta *et al*²⁵ showed that canalith repositioning procedures of EM are suitable in improving the quality of life of people who suffer from BPPV.

Even though research has investigated patients with BPPV only, the effectivity of EM in MS has not been studied sufficiently. The previously mentioned studies conducted by Frohman *et al*²⁸ and Yoosefinejad and Siravani³¹ are the only ones that performed EM as an intervention. Several studies have shown that the MS population with BPPV would benefit from specific rehabilitation programmes based on EM. They also exposed the need for scientific papers to fill the knowledge gap on this topic in this patient population.^{27 28} Therefore, to improve the strength of evidence, the current protocol describes a prospective double-blind RCT that will carry out EM in patients with MS with BPPV. If the intervention proves to be effective, its outcome could reduce unnecessary pharmacological treatments and therefore healthcare expenditure. Furthermore, if dizziness is reduced in MS, a lower self-perceived disease impact on activities of daily living could be achieved.

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