PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	wu, Peixia; Cao, Wenzhu; Hu, Yan; Li, Huawei

VERSION 1 - REVIEW

REVIEWER	roberto teggi san raffaele scientific institute milano italy
REVIEW RETURNED	23-Oct-2018

GENERAL COMMENTS	In my opinion the study design can be implemented in some points - Comorbidities of patients should be considered (above all migraine and vascular disorders). Why to exclude overanxious people? - The duration of BPPV before repositioning maneuvers and the total number of maneuvers should be saved and considered in statistical analisis - Exclusion of previous vestibular disorders should be assessed through a bedside and possibly a video-HIT (specify the battery of performed tests) - Drug therapy could be performed for all the month rather than only 7 days? About outcomes: - the number of days with RD should be saved - A DHI test is suggested to measure dizziness of subjects after repositioning maneuvers Specific considerations page 6 line 6 vertigo instead of dizziness Page 6 Has superior canal been considered? Page 11 last line: why patients after 3 CRPs were excluded? Page 12: another weak point is that only few patients will perform MRI; the significance of MRI is to exclude cerebellar disorders rather than of the ponto cerebellar angle About timepoint: patients with RD will be enrolled at day 2 after successful repositioning maneuver. At inclusion another diagnostic test for BPPV will be performed? I suggest to include a intermediate control after 15 days, 4 months time seems too long for RD and in my opinion most patients already recovered from the disorder

REVIEWER	Andrés Soto-Varela Division of Neurotology Department of Otorhinolaryngology University of Santiago de Compostela - Complexo Hospitalario Universitario de Santigo Spain
REVIEW RETURNED	25-Nov-2018

GENERAL COMMENTS	The topic of this manuscript (to compare the effectiveness of vestibular rehabilitation vs betahistine vs vestibular rehabilitation plus betahistine) to improve residual dizziness after successful maneuvers in patients with benign positional paroxysmal vertigo is of interest. The paper is correctly written and presented; abstract and introduction are appropriate, and methodology is adequately described. References are appropriate too. However, before its acceptance, I recommend the authors clarify and / or discuss several points. Patients are included if they present residual dizziness two days after a successful maneuver. Two days is a very short time; residual dizziness can disappear spontaneously along the first week after the maneuver. It is possible that improvement attributed to the treatment may be actually spontaneous recovery. The groups of vestibular rehabilitation perform exercises five days per week (only one day at the clinic, home exercises the other four days). Why not seven days per week? Home exercises can be performed weekends too. The betahistine group are prescribed with betahistine for seven days. Why only one week, while vestibular rehabilitation is performed for four weeks? One of the secondary outcomes is the “Quality of life measured by DHI”. DHI is a very good tool to quantify the perceived handicap due to instability, but is not a questionnaire of quality of life.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

In my opinion the study design can be implemented in some points

- Comorbidities of patients should be considered (above all migraine and vascular disorders). Why to exclude overanxious people?

Author’s answer: Thank you for your comments. We will collect the demographic and clinical characteristics upon baseline checkup. These variables will be compared in statistical analysis to see if they are evenly distributed across three groups. We clarified this point in revised version as follows:

Demographic and clinical data collected will include: age, gender, education, employment, marital status, coexistent systemic diseases and medication intake, date of onset, duration of symptom from onset to treatment, involved ear side and canal, the number of CRP, DHI score after CRP.

For the second question, since we have observed that presence of anxiety or depression may be a barrier for achieving efficacy when performing VR. However, in light of your question, we were aware that excluding overanxious people would be inappropriate. So, we deleted this condition as an exclusion criterion in the revised version.

-The duration of BPPV before repositioning maneuvers and the total number of maneuvers should be saved and considered in statistical analysis.

Author's answer: Thanks for the reminder. We have added information about clinical feature data collection at baseline, as illustrated above.

- Exclusion of previous vestibular disorders should be assessed through a bedside and possibly a video-HIT (specify the battery of performed tests)

Author's answer: Routinely, we only perform V-Hit for those showing/presenting spontaneously nystagmus or whose vertigo is not head-motion-induced. In this study, V-Hit is not considered as a routine exam. We exclude previous vestibular disorders through comprehensive history taking and bedside examination, e.g., VNG and caloric test. The performed tests battery has been clarified in the revised draft as follows: After obtaining written consent form, the principal investigator 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.

- Drug therapy could be performed for all the month rather than only 7 days? Author's answer: We noted this weak point and did revise the drug therapy by prescribing betahistine for 4 weeks. We made this revision in abstract and methodology section as well.

About outcomes:

- the number of days with RD should be saved

Author's answer: Yes, the number of days with RD will be assessed as one of the secondary outcomes.

- A DHI test is suggested to measure dizziness of subjects after repositioning maneuvers

Author's answer: We will add the DHI test after repositioning maneuvers and have described this point in the procedure of method section.

After successful repositioning maneuver, patients are asked to complete a DHI test. Specific considerations

page 6 line 6 vertigo instead of dizziness Author's answer: Corrected.

Page 6 Has superior canal been considered?

Author's answer: To ensure homogeneity of participants in this study, superior canal will not be included in this study due to its rarity. Surely, we acknowledge that this type

BPPV warrants future studies.

Page 11 last line: why patients after 3 CRPs were excluded?

Author's answer: We observed that only small proportion of subjects who may need more than 3 CRPs, which is consistent with recent studies (listed below) that the majority of patients are adequately treated with 1 or 2 CRPs (79.4%-92.7%), 12.8% to 15.3% of patients require a second CRP, and 5.1% will be classified as treatment failures after 2 CRPs. See references:

Bruintjes TD, et al. A randomized sham-controlled trial to assess the long-term effect of the Epley manoeuvre for treatment of posterior canal benign paroxysmal positional vertigo. Clin Otolaryngol. 2014;39:39-44.

Amor-Dorado JC, et al. Particle repositioning maneuver versus Brandt-Daroff exercise for treatment of unilateral idiopathic BPPV of the posterior semicircular canal: a randomized prospective clinical trial with short- and long-term outcome. Otol Neurotol. 2012;33:1401-1407.

Badawy WM, et al. Effect of a hybrid maneuver in treating posterior canal benign paroxysmal positional vertigo. J Am Acad Audiol. 2015;26:138-144.

Balikci HH, et al. Effects of postural restriction after modified Epley maneuver on recurrence of benign paroxysmal positional vertigo. Auris Nasus Larynx. 2014;41:428-431.

Since this study primarily aims to find treatment for RD after successful CRP, we are prone to set a rigid criterion for “successful CRP” in terms of both negativity of positional test and the number of repetitions of CRP. Therefore, we won’t include patients who need more than 3 CRPs and we are currently running another trial specifically looking at those treatment-resistant cases.

Page 12: another weak point is that only few patients will perform MRI; the significance of MRI is to exclude cerebellar disorders rather than of the ponto cerebellar angle

Author’s answer: Routinely, we don’t prescribe CT or MRI for BPPV patients. Only for those atypical cases or whose diagnosis is unclear, we would ask them to undergo such examination.

The purpose of MRI was not accurately described in our submitted manuscript and we have corrected this mistake according to your comments. Below is the revised description.

Whenever necessary, imaging exam such as CT scan or MRI is supplemented to exclude cerebellar disorders.

About timepoint: patients with RD will be enrolled at day 2 after successful repositioning maneuver. At inclusion another diagnostic test for BPPV will be performed? I suggest to include an intermediate control after 15 days, 4 months time seems too long for RD and in my opinion most patients already recovered from the disorder

Author’s answer: Yes, we will perform another diagnostic test at inclusion to make sure the findings are negative. We added this in the revised draft.

You raised a very valuable point that spontaneous recovery will be expected. We will comply with your suggestion of adding an intermediate checkpoint at 2-week and deleting the 12th week follow-up. We have included this correction in the revised manuscript (in abstract, main text, table 2 and figure 1, wherever indicating follow-up timepoint).

Reviewer: 2

Reviewer Name: Andrés Soto-Varela

Institution and Country: Division of Neurotology

Department of Otorhinolaryngology

University of Santiago de Compostela - Complexo Hospitalario Universitario de Santigo Spain

The topic of this manuscript (to compare the effectiveness of vestibular rehabilitation vs betahistine vs vestibular rehabilitation plus betahistine) to improve residual dizziness after successful maneuvers in patients with benign positional paroxysmal vertigo is of interest. The paper is correctly written and

presented; abstract and introduction are appropriate, and methodology is adequately described. References are appropriate too.

Author's answer: Thank you for the encouraging comments.

However, before its acceptance, I recommend the authors clarify and / or discuss several points.

Patients are included if they present residual dizziness two days after a successful maneuver. Two days is a very short time; residual dizziness can disappear spontaneously along the first week after the maneuver. It is possible that improvement attributed to the treatment may be actually spontaneous recovery.

Author's answer: Thank you for this insightful comment. Surely, we totally agree with you that spontaneous recovery exists. However, we still choose to commence the treatment at day 2 anticipating that the first week will be the most suffering period of residual dizziness in our patients. We are planning a future study in which a nontreatment control group will be set to verify natural recovery of this disorder. The groups of vestibular rehabilitation perform exercises five days per week (only one day at the clinic, home exercises the other four days). Why not seven days per week?

Home exercises can be performed weekends too.

Author's answer: We have modified the rehabilitation plan from five days to seven days per week in the revised version.

The betahistine group are prescribed with betahistine for seven days. Why only one week, while vestibular rehabilitation is performed for four weeks?

Author's answer: We noted this weak point and did revise the drug therapy by prescribing betahistine for 4 weeks. We made this revision in abstract and methodology section as well.

One of the secondary outcomes is the "Quality of life measured by DHI". DHI is a very good tool to quantify the perceived handicap due to instability, but is not a questionnaire of quality of life.

Author's answer: We made inaccurate description of DHI. Dizziness-related handicap instead of quality of life is used in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Roberto Teggi San Raffaele Scientific Institute - Milano - Italy
REVIEW RETURNED	21-Jan-2019

GENERAL COMMENTS	In the paper outcomes have been clarified. I still think that the number in days of RD should be considered the main outcome

REVIEWER	Andrés Soto-Varela, PhD Division of Neurotology Department of Otolaryngology Complexo Universitario Hospitalario Universidade de Santiago de Compostela Spain
REVIEW RETURNED	09-Jan-2019

GENERAL COMMENTS	All the questions have been satisfactorily clarified. Good luck!

VERSION 2 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

In the paper outcomes have been clarified. I still think that the number in days of RD should be considered the main outcome

Author's answer: Thanks for giving us so much insightful comments. Surely, we agree that the duration of RD is a very important outcome in current study. However, based on our observation and previous studies, the number in days of RD may not be significantly different in patients who received various treatment, probably due to its quite objective nature. Thus, we tend to focus more on the aspect of patients' activity and participation as well as balance outcome.

Reviewer: 2

All the questions have been satisfactorily clarified. Good luck!

Author's answer: Thank you so much for your encouragement.