

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a double blinded, randomised controlled trial to assess the effectiveness of endolymphatic duct blockage versus endolymphatic sac decompression in patients with intractable Ménière's disease
AUTHORS	Schenck, Annejet; Kruyt, Josephina; van Benthem, Peter Paul; Cannegieter, Suzanne; van den Hout, Wilbert; Böhringer, Stefan; Hammer, Sebastiaan; Hombergen, Susan; Blom, H.M.

VERSION 1 – REVIEW

REVIEWER	Nakashima, Tsutomu Nagoya University School of Medicine, Department of Otolaryngology
REVIEW RETURNED	28-Jun-2021

GENERAL COMMENTS	<p>This manuscript is a study protocol for a double-blinded, randomized controlled trial to assess the effectiveness of endolymphatic duct blockage versus endolymphatic sac decompression in patients with intractable Meniere's disease (MD).</p> <p>Endolymphatic sac decompression, shunting or drainage of the endolymphatic sac has 100 years of history since Portman performed the endolymphatic sac operation in the early 1920s to treat intractable MD. The endolymphatic sac operation has continued for one hundred years with improved methods, although many ENT doctors have doubted the true effect of controlling the vertigo attack. On the contrary, endolymphatic duct blockage surgery appeared relatively recently. Saliba et al. reported that endolymphatic duct blockage was more effective than endolymphatic duct decompression in controlling the vertigo attacks in intractable MD. (Endolymphatic duct blockage: a randomized controlled trial of a novel surgical technique for Meniere's disease treatment. Otolaryngol Head Neck Surg. 2015). The paper written by Saliba et al. was No. 32 in the reference list of this manuscript.</p> <p>Vertigo attacks in MD may be elicited by the abrupt movement of the longitudinal flow of the endolymph. If so, blockage of the endolymphatic duct is a direct method to prevent the longitudinal flow, and the decompression and shunting of the endolymphatic sac work for a damping effect.</p> <p>The protocol of this study was well-designed. The results may change surgical methods to treat intractable MD globally. Because the endolymphatic duct blockage method was already published, I expect to read the authors' paper with surgical results.</p>
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REVIEWER	van Esch, Babette Gelre Hospital Apeldoorn, Apeldoorn Dizziness Centre
REVIEW RETURNED	07-Jul-2021

GENERAL COMMENTS	<p>Dear authors,</p> <p>A well-designed randomized double-blind controlled trial to evaluate the effectiveness on endolymphatic duct clipping. Well chosen primary and secondary outcomes with the use of a daily questionnaire through the DizzyQuest app in order to get a clear picture on the evolvement of vertigo complaints. Moreover, the effort of including 12 centers to make sure that the sample size is reached is a real accomplishment.</p> <p>Some minor comments/clarifications:</p> <ul style="list-style-type: none"> - Based on previous research on ESD the effect of surgery is inconclusive (line 117) and could also be regarded as the placebo effect since patients in both the surgical intervention as well as the control group experience relief of complaints (line 155). The effect varied between 30 and 95% and could also be noted as the natural course of disease (line 150). How come it is concluded that a percentage of 70% was taken for the EDB group since based on the placebo controlled trails no difference in the placebo group and intervention group was found? - Since 12 centers will serve as inclusion site of subjects, adherence to the study protocol will take quite some effort and loss to follow-up is still at risk. It is mentioned that will occur in only a small percentage of cases, which percentage was used? Please explain how two sensitivity analyses will increase the sample size with n=10 per group. - Which reference were used for the basis to define the 'recent-onset MD participant' and the 'mature MD participants'? Previous research on duration of disease is also described up to 15 to 20 years. - What are the expected risk of surgery besides liquor leakage? For instance, damage to the posterior semicircular canal, superior semicircular canal, tegmen, need for ELD and prolonged hospital stay, meningitis, infection, bleeding, etc. Is the use of anti-coagulants a (relative) exclusion criteria? What if intraoperative no clear endolymphatic duct can be identified, for instance due to a sclerotic mastoid? Which anatomic variation are expected?
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VERSION 1 – AUTHOR RESPONSE

Reaction on the comments the reviewers

- Please include the trial registration details just after the abstract. Include the name of the registries and the registration ID numbers.

Answer: Registration details are added at page 4, directly after de abstract.

- Please check the paper for typographical errors. Page 3: “minimalize bias”. Do you mean “minimize bias”?

Answer: The whole document was thoroughly checked and corrected if needed.

- We note that the introduction section includes the results of an unpublished pilot study. Please do not reference unpublished data. If you would like to present the results and findings of your pilot study here then you would need to deposit your pilot study article as a preprint and you can then cite the preprint.

Answer: The data that was referred to is now published. Therefore, a reference is added.

- The methods section includes an ‘ethics’ sub-section. Please move this information to the ‘Ethics and Dissemination’ section.

Answer: The information was replaced to the appropriate section. We apologize for the inconvenience.

- Please include an ‘Ethics and dissemination’ section after the methods and analysis, as per journal requirements for study protocols (see: <http://bmjopen.bmj.com/site/about/guidelines.xhtml#studyprotocols>) Please state the names of all ethics committees that have approved this study along with the approval reference numbers. You can include this as a supplementary file and cite this file in this section, if necessary.

Answer: This information too was added and can be found on page 17 and 18.

- There appears to be some redundant information at the end of the paper. For example, you do not need to include the contact details of all authors again, as this is already on the title page. Can the authors’ contributions section merge with the roles and responsibilities section?

Answer: The redundant information was removed, we do apologize. There is a section stating the authors’ contributions at place 20.

- Please ensure all items from the SPIRIT checklist have been accurately completed and included in your submission. For example, please include a model consent form as a supplementary file and refer to this in the methods section when you mention consent. This is requested in item 32. It’s not clear why this (and some other items) are completed as not applicable. For help and guidance completing the checklist see: <http://www.bmj.com/content/346/bmj.e7586>

Answer: An updated SPIRIT checklist is attached, and some additional information has been added to the manuscript.

- Please remove the full protocol. The full protocol only needs to be provided for research articles reporting the results of the clinical trial.

Answer: The full protocol is removed from the submitted documents. We apologize for the inconvenience.

Reviewer Reports:

Reviewer: 1

Prof. Tsutomu Nakashima, Nagoya University School of Medicine

Comments to the Author:

This manuscript is a study protocol for a double-blinded, randomized controlled trial to assess the effectiveness of endolymphatic duct blockage versus endolymphatic sac decompression in patients with intractable Meniere's disease (MD).

Endolymphatic sac decompression, shunting or drainage of the endolymphatic sac has 100 years of history since Portman performed the endolymphatic sac operation in the early 1920s to treat intractable MD. The endolymphatic sac operation has continued for one hundred years with improved methods, although many ENT doctors have doubted the true effect of controlling the vertigo attack. On the contrary, endolymphatic duct blockage surgery appeared relatively recently. Saliba et al. reported that endolymphatic duct blockage was more effective than endolymphatic duct decompression in controlling the vertigo attacks in intractable MD. (Endolymphatic duct blockage: a randomized controlled trial of a novel surgical technique for Meniere's disease treatment. *Otolaryngol Head Neck Surg.* 2015). The paper written by Saliba et al. was No. 32 in the reference list of this manuscript.

Vertigo attacks in MD may be elicited by the abrupt movement of the longitudinal flow of the endolymph. If so, blockage of the endolymphatic duct is a direct method to prevent the longitudinal flow, and the decompression and shunting of the endolymphatic sac work for a damping effect.

The protocol of this study was well-designed. The results may change surgical methods to treat intractable MD globally. Because the endolymphatic duct blockage method was already published, I expect to read the authors' paper with surgical results.

Answer: We thanks the reviewer for the comments.

Reviewer: 2

Prof. Babette van Esch, Gelre Hospital Apeldoorn

Comments to the Author:

Dear authors,

A well-designed randomized double-blind controlled trial to evaluate the effectiveness on endolymphatic duct clipping. Well chosen primary and secondary outcomes with the use of a daily questionnaire through the DizzyQuest app in order to get a clear picture on the evolvement of vertigo complaints. Moreover, the effort of including 12 centers to make sure that the sample size is reached is a real accomplishment.

Some minor comments/clarifications:

- Based on previous research on ESD the effect of surgery is inconclusive (line 117) and could also be regarded as the placebo effect since patients in both the surgical intervention as well as the control group experience relief of complaints (line 155). The effect varied between 30 and 95% and could also be noted as the natural course of disease (line 150). How come it is concluded that a percentage of 70% was taken for the EDB group since based on the placebo controlled trails no difference in the placebo group and intervention group was found? Answer: In the feedback, the

reviewer mentions a percentage of 70% in the EDB group, but we assume that the ESD was supposed to be mentioned.

We thank the reviewer for his insightful question. The success rate of 70% was extracted from various articles, including Brinson (2007) and Convert (2006). We agree there is a broad range of success rates in literature, which is also mentioned in the protocol, but we had to choose a cut-off point. In a consensus meeting, 70% was chosen as the cut-off value, as most of the articles report success rates similar to this number.

We agree with the reviewer that it cannot be determined if this is (at least in part) the placebo effect. However, both patients in both study arms will benefit from the same 'amount' of placebo effect as they all undergo surgery. Therefore, we do not expect the differences between EDB and ESD in our study to be distorted by the placebo effect.

- Since 12 centers will serve as inclusion site of subjects, adherence to the study protocol will take quite some effort and loss to follow-up is still at risk. It is mentioned that will occur in only a small percentage of cases, which percentage was used? Please explain how two sensitivity analyses will increase the sample size with $n=10$ per group.

Answer: Two sensitivity analyses will be conducted as well, where missing outcomes will be treated as failures or success, respectively (line 331-332). To account for variation in baseline risk, smaller than anticipated effect size and drop out, 42 patients will be recruited per group. The main reason is to make the study robust against deviations from assumptions but, in principle, this increase can account for up to 31% of dropout. We expect a dropout rate of 25%. The sensitivity analyses will therefore flip the outcome for up to 21 [= $0.25 \cdot 84$] patients as compared to the true outcome allowing to judge robustness of findings. These analyses will use the full sample size of 84.

- Which reference were used for the basis to define the 'recent-onset MD participant' and the 'mature MD participants'? Previous research on duration of disease is also described up to 15 to 20 years.

Answer: This cut off is based on the references mentioned in line 91. After a 2 year period, the majority of patients with Ménière's disease are free of vertigo attacks. Therefore, the authors reasoned that Ménière's disease with attacks for longer than 2 years can be considered 'mature'.

However, we agree with the reviewer that there is a great variation in duration of disease, but to avoid (the possibility of) bias because of duration of disease, it was decided to stratify randomization for this factor.

- What are the expected risk of surgery besides liquor leakage? For instance, damage to the posterior semicircular canal, superior semicircular canal, tegmen, need for ELD and prolonged hospital stay, meningitis, infection, bleeding, etc. Is the use of anti-coagulants a (relative) exclusion criteria? What if intraoperative no clear endolymphatic duct can be identified, for instance due to a sclerotic mastoid? Which anatomic variation are expected?

Answer: We agree with the reviewer that this information was lacking. A section containing this information was added on page 11 (line 275-286).

VERSION 2 – REVIEW

REVIEWER	van Esch, Babette Gelre Hospital Apeldoorn, Apeldoorn Dizziness Centre
REVIEW RETURNED	14-Jul-2021
GENERAL COMMENTS	Great improvement of the previous version of the manuscript, specifically with now more detailed information on the risks of surgery.