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a systematic review

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Current state of evidence for endolymphatic sac surgery in Menière's disease: a systematic review

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Abstract

Background: Endolymphatic sac surgery is an invasive procedure recommended to patients with Menière's disease.

Aims/Objectives: To provide an overview and quality assessment of the existing evidence and to provide an updated assessment of the utility of endolymphatic sac surgery in Menière's disease.

Material and Methods: We performed a systematic literature search for systematic reviews and randomized controlled trials (RCTs). The AMSTAR tool was used to assess the quality of systematic reviews and the Cochrane risk of bias tool for RCTs. The overall certainty of effects for the individual outcomes was evaluated using the GRADE approach.

Results: One systematic review of high quality matched the inclusion criteria, and included three RCTs. An updated literature search from the last search date of the included review provided no further relevant RCTs. The identified RCTs individually reported a positive effect of both the placebo and active treatment groups following surgery, strongly indicative of a placebo effect. The overall certainty of the effect very low.

Conclusions and Significance: There is still a lack of high quality research suggesting that endolymphatic sac surgery provides a significant amount of symptomatic relief for Menière's patients.

Introduction

Menière's disease is characterized by spontaneous episodes of vertigo combined with tinnitus, aural fullness and fluctuating low frequency sensorineural hearing loss. It is a chronic inner ear disease where both hearing loss and vestibular deficits generally progress regardless of treatment. Even though the disease was first described more than 150 years ago, the etiology remains uncertain [1]. Endolymphatic hydrops due to endolymphatic malabsorption in the labyrinth's endolymphatic sac is considered a hallmark of Menière's disease [1]. Within recent years it has become possible to visualize endolymphatic hydrops with gadolinium magnetic resonance imaging (MRI). However, this has not been globally implemented and it is not a requirement in the newest set of diagnostic criteria from the Barany society [2]. As of now, there is no cure for Menière's disease. Wide ranges of different treatment modalities exist including dietary salt restriction as well as treatment with diuretics in an attempt to influence the endolymphatic pressure imbalance. Severely disabled patients with Menière disease, who have failed to respond to other available treatment modalities, may be offered endolymphatic sac surgery. Endolymphatic sac surgery is performed using different surgical procedures such as endolymphatic sac decompression and duct blockage. Both methods tend to regulate the endolymphatic flow using different approaches.

Endolymphatic sac surgery is an invasive procedure and therefore high-quality evidence is essential to evaluate its potential positive effects and associated risks, especially in relation to hearing loss. The objective of this review was to provide an overview and quality assessment of the existing evidence and, based on the identified literature, to provide an update on the usage of endolymphatic sac surgery in Menière's disease. The primary focus of this particular systematic review was patients (≥18 years of age) diagnosed with either definite or probable Meniére's disease undergoing endolymphatic sac surgery compared to no surgery/placebo surgery. Specifically, we sought to evaluate the effects of this treatment in regards to frequency, duration and severity of vertiginous

attacks, serious adverse events as well as quality of life, impact on daily life, tinnitus, patient reported operative effect, and hearing loss.

Methods

This work was performed in accordance with the guidelines of the Cochrane Collaboration and Preferred Reporting Items for Systematic review and Meta-analysis Protocols (PRISMA) [3,4]. The protocol is registered in PROSPERO. Registration number: CRD42018110118.

This review was a part of a larger guideline on Menière's disease which was published by the Danish Health Authorities in 2018.

Literature search

We performed a systematic literature search in two steps. Initially, we identified systematic reviews that, in accordance to our inclusion criteria, investigated the use of endolymphatic sac surgery in Menière's disease. The search for systematic reviews was performed on December 19th, 2017, with no restrictions regarding date of publication. Subsequently, we performed a search to identify individual randomized controlled trials (RCTs). The search for RCTs was performed February 2nd 2018, and was limited to the publication dates of the latest search in the identified systematic reviews (which in this case was November 2012). The search for individual RCTs was limited to the search date of the Cochrane review, as the search strategy and inclusion criteria of the Cochrane review was identical to that of the current manuscript. As such, the thorough and well-performed literature search performed in the Cochrane review served as a foundation, from which the authors of the current review performed an updated literature search All searches were performed in the databases EMBASE, MEDLINE, and PsycINFO via Ovid (Wolters Kluver, Aalphen aan der Rijn, the Netherands). The search strategy was developed using medical subject heading terms (MeSH)

and text words related to our eligibility criteria, i.e. Meniere, Menieres, Meniere disease/syndrome (English), Menieres sygdom/syndrome (Danish), menieres sykdom (Norwegian), Menieres sjukdom (Swedish). There were no restrictions in regard to publication status, however, the search was limited to literature written in English, Danish, Norwegian and Swedish. Search protocols are provided in the supplementary material section.

Study selection:

The results of the search for systematic reviews and individual RCTs were imported to RefWorks (Proquest, Ann Arbor Michigan, USA). Subsequently, duplicate references were removed and the remaining records were imported into Covidence software (Covidence, Melbourne Australia) for literature screening and data management. Titles and abstracts of potential studies was screened by one reviewer (LD) to assess if the inclusion criteria were met. The initial selection of studies was assessed by an additional reviewer (HEC). Subsequently, the full text of potential studies was screened independently by two review authors (LD and JHS) for eligibility. Disagreement was resolved through discussion or by consultation of a third reviewer (HEC). Neither of the review authors were blinded in regard to journal titles, study authors/institutions or year of publication. A PRISMA flow chart [5] was created and used to document the number of studies identified.

The selection of studies was based on the Population, Intervention, Comparison and Outcome (PICO) framework [6] with the following structure: **Population:** *Inclusion* criteria were age 18 or above, and a diagnosis of definite or probably Menière's disease as defined by Bárány Society 2015 [2] or the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria from 1995 [7]. Bárány Society diagnostic criteria for definite Menière's disease include: A) Two or more spontaneous episodes with dizziness, each lasting between 20 minutes and 12 hours. B) At least one hearing test showing low to medium frequency sensorineural hearing loss on the affected

ear before, during or after a dizziness episode. C) Fluctuating symptoms of the affected ear in the form of tinnitus, hearing loss or increased volume / pressure. D) Symptoms cannot be explained better by another diagnosis. Partially, the diagnostic criteria for probable Menière's disease include the same criteria (A, C, D), but no evidence of a continuing or fluctuating sensorineural hearing loss is required. *Exclusion* criteria were patients with a diagnosis of vertigo other than Menière's disease and patients with Ménière's syndrome that did not fulfill the appropriate criteria as described above. **Intervention and Comparison:** We included randomized controlled studies investigating the usage of endolymphatic sac surgery compared to patients that did not receive endolymphatic sac surgery. **Outcome:** The primary outcomes included the frequency of vertigo attack(s) and serious adverse events as assessed at a minimum of three month following initial treatment. Secondary outcomes included; hearing loss, reduction of tinnitus, quality of life, impact on daily life, vestibular function, frequency and length of vertiginous attacks, severity of the attacks and patient-reported operative effect. Tinnitus and duration of the vertiginous attacks were investigated three months after initiating of the intervention. The remaining secondary outcomes were evaluated at the longest follow-up (minimum one year after the intervention). Frequency and duration of vertiginous attacks at longest follow-up (minimum one year after the intervention) were included as a secondary outcome measure.

Quality assessment and data extraction

The quality of the included systematic review was assessed using the AMSTAR tool [8]. The AMSTAR evaluation was performed to ensure methodological rigidity of the review, from which the second literature search for individual RCTs was based upon. The quality of individual RCTs was evaluated using the Cochrane risk of bias tool which included the following characteristics: Randomization sequence generation; Treatment allocation concealment; Blinding of patients and

personnel; Blinding of outcome assessors; Completeness of outcome data; Selective outcome reporting; Other sources of bias. Following a combined assessment of the results reported in the included studies, the certainty of effect on the individual outcomes was evaluated using the GRADE approach [9]. Results from RCT studies are by default considered to be of high quality, yet the quality may be downgraded to either moderate, low or very low based upon the following domains: overall risk of bias; inconsistency; indirectness; imprecision and publication bias. The overall quality of evidence was subsequently based upon the lowest quality of the primary outcome in accordance to the GRADE approach.

Two review authors (LD and HEC) independently performed the quality assessment and subsequent data extraction. Data extraction included population demographics, baseline characteristics, details on intervention and control conditions, study design, outcome, and time of measurement.
All data was exported to Review Manager (version 5.2) (Informer Technologies Inc) and any potential discrepancies were resolved through discussion.

Statistical analysis

Due to a heterogenic reporting style and inconsistent reporting of primary data in the identified studies, it was not possible to perform any data-analysis or summary of findings. As such, the effect estimates for the individual outcome and overall quality of the evidence were solely narratively described. Authors of the included studies were not contacted for further information.

Results

In the search for systematic reviews, we identified 87 references. Following removal of duplicates and none-relevant references, we identified seven systematic reviews [10-16] that we obtained in full text and read thoroughly. Of these, one systematic Cochrane review [15], which included three relevant RCTs, matched our clinical question,. A search for further RCTs based on the search date from the Cochrane review (which was November 2012) [15] identified 57 references. Following the screening and selection process, there were no RCTs published after the search date from the Cochrane review, that matched the inclusion criteria. The total amount of evidence in this review is based on three RCT with a total of number of 59 patients [17-19]. A flowchart can be seen in figure 1.

The included studies:

The populations in the included studies were described as classical Menière's disease patients without specification of the diagnostic criteria applied. Thomsen et al., (1981) [19] compared endolymphatic shunt surgery with mastoidectomy in 30 patients refractory to medical treatment. All patients filled out a dizziness related questionnaire (frequency, duration, and severity of attacks) as well as a registration of their self-perceived symptoms of vertigo, tinnitus, and hearing impairment on a scale ranging from zero to three (higher scores indicative of more severe symptoms). These measurements were performed three months prior to and 12 months following surgery. At the end of the trial, patients were asked about their subjective evaluation of the effect and a pure tone audiometry (PTA) was performed. The study by Bretlau et al., (1989) [17] consisted of a nine-year follow-up of the study by Thomsen et al., (1981) [19] In this follow-up study, 23 patients from Thomsen et al., (1981) [19] participated. Patients were once again asked about their subjective evaluation of the surgical effect and a PTA was performed. The study from Thomsen et al., (1998)

[18] compared endolymphatic shunt surgery with insertion of ventilation tubes in 29 patients refractory to medical treatment. On a daily basis, the patients registered frequency and severity of vertiginous attacks six months pre-surgery and 12 months following surgery. Patients were interviewed about their subjective symptoms and a PTA audiogram was performed.

Frequency of vertigo attacks

In the study by Thomsen et al., (1998) [18] there was a general improvement in patient-reported vertigo scores following surgery both in the active group and in the control group when compared to preoperative conditions ($p<0.01$, no primary data provided). When treatment groups were compared, patients in the placebo group had a slightly worse vertigo score following surgery compared to the active group ($p<0.05$, no primary data provided). In the nine-year follow-up by Bretlau et at., (1989) [17] only one patient in the active group continued to have periodic attacks, whereas no patients in the placebo group had any recurrent attacks. There continued to be no difference between the two treatment groups (no data or statistical analysis provided). In another study by Thomsen et al., (1998) [17], there was a reduction in the number of dizzy spells in both groups following endolymphatic shunt surgery and insertion of ventilation tube, with approximately 30 percent of patients in both groups having no attacks following surgery. There were no significant differences between the two treatment groups (no primary data provided).

Reduction in tinnitus

In the study by Thomsen et al., (1981) [19], an improvement in patient-reported tinnitus was observed in the active group following surgery when comparing to preoperative conditions. There was no difference between the active group and the placebo group (no primary data or statistical

analysis provided). In Thomsen et al., (1998) [17], there was no significant effect on tinnitus in neither the placebo group nor the shunt surgery group (no primary data provided, $p>0.05$).

Impact on daily life

Following surgery, in terms of functionality, Thomsen et al., (1981) [19] reported a significant reduction in disease severity in both groups when assessed by investigators' global score (no primary data provided, $p<0.005$). There was, however, no differences in disease severity between the placebo group and the active groups (no primary data or statistical analysis provided). In correlation, Thomsen et al. 1998 [18] reported an improved level of functionality in both groups following surgery (no primary data provided, $p<0.05$), with no difference between the two groups (no primary data provided).

Hearing loss

At the end of the trial, Thomsen et al., (1981) [19] found no significant differences between the placebo group and the active group in regard to average mean values of 250, 500 and 1000 Hz, as measured by pure tone audiometry (PTA) (no primary data or statistical analysis provided). In the nine-year follow-up from Bretlau et al. (1989) [17], there continued to be non-significant inter-group difference between mean values measured by PTA (no primary data or statistical analysis provided). In the study by Thomsen et al., (1998) [18], there was no significant differences in PTA between groups, neither before surgery (sac shunt: 55dB (23-86); ventilation tube: 54db (8-71), median (range)) nor 12 months following surgery (sac shunt: 55 (26-anacusis); ventilation tube 48 (5-79), median range) ($p>0.05$).

Patient-reported operative effect

In Thomsen et al. (1981) [19], both groups reported positive operative effect as compared to pre-surgery (73% active group; 67% placebo group), with no significant differences between the two groups (no analysis provided). In the nine-year follow-up study by Bretlau et al., (1989), 70 % of the patients in both groups continued to consider their surgery successful (no analysis provided). In Thomsen et al., (1998), 86% of patients receiving ventilation tube and 60% receiving endolymphatic shunt surgery, reported a favorable effect of the intervention. There were no significant differences between the two groups ($p>0.05$).

None of the studies reported on serious adverse events, quality of life, length of vertigo attack or vestibular function.

Quality of evidence

The AMSTAR evaluation of the included systematic review showed that this review had an adequate description of all necessary domains, and thus was considered of high quality.
The assessment of the individual RCTs by the Cochrane Risk of bias tool, showed that in all three studies the random sequence generation and allocation concealment was unclear and there was a high risk of other biases due to inadequate reporting of primary data and statistical analysis. Subsequent rating of the overall certainty of effect was very low for all outcomes due to serious imprecision and serious risk of bias. An overview of the AMSTAR evaluation and the Cochrane risk of bias can be found in the figures 2 and 3.

Discussion

The objective was to provide an overview and quality assessment of the current evidence regarding the use of endolymphatic sac surgery in patients with definite and probable Menière's disease. Our

findings showed that, despite surgery being applied to treat Meniere disease since 1927, the amount of well-performed RCTs on the matter continues to be scarce. Of the identified literature, only three RCTs were found compatible with the inclusion criteria of this particular review. All studies investigated the use of endolymphatic sac surgery, but one of the RCT studies was a nine-year follow-up on the patients from one of the other RCTs. The included RCTs were identified in one high quality Cochrane review as assessed by the AMSTAR tool. An updated literature search showed that no further relevant RCTs have been published since the search applied in the systematic review. As assessed by the Cochrane risk of bias tool, the quality of the included RCTs was poor, with inadequate reporting of primary data and underlying statistical analysis, in addition to the inclusion of few patients and other substantial methodological flaws. In accordance, the overall certainty of the effect on the predefined outcomes, as assessed by the GRADE approach, was very low. Due to a severe lack in the reporting of primary data in all three studies, it was not possible to perform any combined analysis and thus to identify any common effects of this intervention. All three studies, however, individually reported of an improvement in symptoms in both groups after surgery when compared with preoperative conditions. This included an improvement in vertigo, impact on daily life and in patient-reported operative effect. When the placebo and active groups were compared, there were no significant differences in treatment effects for these above-mentioned outcomes. In accordance to the findings within the included studies, these findings may indicate a substantial placebo effect following surgery for Menière's disease, yet it may also to some extend reflect the natural disease progression found in Menières disease.

It is important to include a suspected non-effective placebo treatment in studies on surgical procedures in Menières disease. A recent study by Saliba et al. 2015 [20] compared endolymphatic sac decompression with endolymphatic duct blockage in a randomized non-blinded design. . This study compared two procedures related to the endolymphatic sac and was therefore not included in

the present study. The study has an important risk of bias due to non-blinded design towards the patients and the observers, which might have biased the conclusions even though endolymphatic duct blockage was proven to be superior in vertigo control compared to endolymphatic sac decompression. Thus, it is important that the new surgical procedure of endolymphatic duct blockage is compared to a suspected non-effective placebo sham surgery in blinded design towards patients and observers conducting the clinical examinations.

The well-known placebo effect in Menière's disease, as well as the natural progression of this disease, serve as potentially serious confounders when seeking to evaluate treatment effects, and thus there is a need for large, well-performed RCT studies. We chose not to include non-randomized trials in this review, because these types of studies would not sufficiently directly address our research question, in addition to the high risk of bias in these types of study designs. That being said, a review by Lim et al., (2015) [12], who included observational studies, also failed to substantiate the efficacy of this treatment in Menière's disease and subsequently pointed towards the need for better research.

As such, based on the current evidence, it is not possible to conclude whether endolymphatic surgery in Menière's disease yields any positive results aside from a potential placebo effect. This is in line with the conclusions of other systematic reviews previously published on this matter [12,15]. Nevertheless, based on expert opinions, this treatment is still, in some cases, considered a good treatment option for Menière's disease [11]. Given the fact that this is an invasive treatment, there is a high demand for well-performed studies that indeed show that the potential benefits following surgery exceeds the potential side effects.

Strength and limitations of the current study

This systematic review was performed using a transparent method and a priori defined criteria. This included a protocol registration, a systematic literature search, duplicate study selection, quality assessment, and data extraction. Limitations include a restricted search in study design and language. The results mentioned in this review are solely based upon the published data, as authors of the included studies were not contacted for further information.

Disclosure of interest

The authors report no conflict of interest.

Conclusion

Given that endolymphatic sac surgery is an invasive procedure, there should be a demand for good evidence evaluating its potential beneficial effects and associated risks. However, until now there is still a lack of high quality research underlining the fact that endolymphatic sac surgery may provide significant and adequate symptomatic relief for patients diagnosed with Menière's disease.

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Figure legends

Figure 1:

Flowcharts showing the inclusion and exclusion of systematic reviews and primary studies

Figure 2:

Assessment of the methodological quality of the included systematic reviews (AMSTAR). The different domains are presented in the top row. The individual studies are shown in the left column.

Figure 3:

Risk of bias assessment as assessed by the Cochrane risk of bias tool. A plus (+) indicates low risk of bias; a question mark (?) indicates unclear risk of bias and a minus (-) indicates high risk of bias. The specific type of bias is presented in the top column, and the individual studies in the left row.