Intratympanic steroid for Menière’s disease: a systematic review

Abstract

Objectives To investigate the beneficial effects and safety of intratympanic steroid installation compared with placebo in patients with Menière's disease.

Methods We performed a systematic literature search in MEDLINE and EMBASE for existing systematic reviews and individual randomized controlled trials (RCTs). Studies were included if they investigated the usage intratympanic steroids in patients aged 18 and above, with definite or probable Menière's disease. The quality of the identified existing reviews was assessed using the AMSTAR tool. The risk of bias in RCTs were assessed using the Cochrane Risk of Bias Tool and overall quality of the individual outcomes were evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method.

Results The literature search provided four systematic reviews, from which one yielded a sufficient AMSTAR evaluation and subsequently provided three RCTs relevant for inclusion. Due to the lack of sufficient reporting of the data, quantitative synthesis was not applicable. In the qualitative synthesis for the primary outcome, the results from the RCTs showed that there was a slight indication of steroid treatment reducing the frequency of vertiginous attacks. No serious adverse events were reported. Based on the GRADE approach the quality for both findings is very low. No studies reported on the secondary outcomes.

Conclusion The effect of intratympanic steroid treatment in Menière’s disease is questionable. There is a great need for further research to sufficiently assess whether steroid treatment may be considered as a safe and effective treatment for patients with Menière’s disease.
Keywords: menieres, intratympanic steroid, corticosteroid, vertigo
Introduction

The diagnosis of Menière’s disease is based on characteristic episodic unilateral symptoms with spontaneous vertigo spells combined with fluctuating low frequency sensorineural hearing loss, tinnitus and aural fullness. The Barany Society published new diagnostic criteria for Menière's disease in 2015[1], but the diagnosis is still based on the clinical symptoms without a gold-standard test to confirm the diagnosis. Endolymphatic hydrops is considered a hallmark in Menière's disease[2] and it has often been proposed that Menière’s disease is an immune-mediated endolymphatic sac disorder[3]. This has prompted the use of steroids, in particular intratympanic steroid treatment. Intratympanic steroid is believed to pass the blood-labyrinth barrier and reach the perilymph primarily through the membrane of the round window, but also via the lacunar mesh surrounding the labyrinth and the oval window membrane[3]. The concentration of steroid within the perilymph has been estimated to be 260 times higher following intratympanic installation compared to oral administration[4].

Nevertheless, the true etiology of Menière's disease remains uncertain[5]. Consequently, physicians and patients face a broad variety of treatment options, e.g. lifestyle and dietary recommendations, medical treatment with betahistin or diuretics, intratympanic gentamicin, and surgery. Surgical treatment modalities include endolymphatic sac surgery, neurectomy of vestibular neurotomy or labyrinthectomy and are usually reserved as last resort treatments[6, 7]. However, regardless of the treatment, the auditory and vestibular deficits generally progress over time[8]. An international consensus paper on the treatment of Menière’s disease was published in 2018 from six experts on Menière’s disease, which recommended intratympanic steroid as a second step treatment modality[7]. This is also the case in the recent European position statement paper on diagnosis and treatment of Menière’s disease [6]. Treatment with intratympanic steroids has become very popular during the last two decades, as it is easy to administer even in an office setup [6]. This review aims
to systematically identify, summarize and critically appraise the current evidence concerning the
usage of intratympanic steroid in the treatment of patients (≥18 years of age) with definite or
probable Menière’s disease. Specifically, we sought to evaluate the effects of intratympanic steroid
treatment on frequency and duration of vertigo, serious adverse events, vestibular function as well
as quality of life, impact on daily life, tinnitus and hearing loss.

Methods

This work was performed in accordance with the guidelines of the Cochrane Collaboration and
PRISMA [9]. A PRISMA checklist can be found in the supplementary information figure 1. The
study protocol was registered in PROSPERO (CRD42018104113).

This review is a part of a larger guideline on Menière’s disease published by the Danish Health
Authority in 2018[10].

Literature search

We performed an electronic systematic literature search in two steps. First, a search for systematic
reviews was performed on December 19th 2017, with no restrictions to publication date, in order to
identify relevant primary studies to be included in the synthesis. Secondly, a search was performed
to identify individual randomized controlled trials (RCTs), where we limited the initiation date of
the search to the dates after the latest search in the systematic reviews. Thus, the search for RCTs
was performed on February 6th 2018 in EMBASE and MEDLINE databases. The search strategy
was developed using medical subject heading (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
on the search in regards to publication status, however the search was limited to literature written in
English, Danish, Norwegian and Swedish. Search protocols are provided in the supplementary information figure 2.

The selection of studies was based on the Population, Intervention, Comparison and Outcome (PICO) framework[11], with the following structure: **Population:** Inclusion criteria consisted of studies including patients aged 18 or above, with definite or probably Menière's disease as defined by Bárány Society 2015[1] or the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria from 1995[12]. **Exclusion** criteria were studies including patients with a vertigo diagnosis other than Menière's disease and studies not applying diagnostic criteria that matched the above-mentioned diagnostic criteria. **Intervention and Comparison:** We included randomized controlled trials (RCT) investigating the usage of intratympanic steroid treatment compared to patients receiving placebo. **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, tinnitus reduction, quality of life, impact on daily life, vestibular function, frequency of vertigo, and length of vertigo attack(s). The effect on tinnitus and duration of the vertigo attack was assessed three months following the initial treatment. The remaining secondary outcomes were assessed at the longest follow-up time (minimum one year after initial treatment). Frequency of vertigo and duration of attacks at the longest follow-up time (minimum one year following the initial treatment) was also included as a secondary outcome measure.

**Study selection**

The results of the literature search were imported to RefWorks, (Review Manager Software, version 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) [13] duplicate references were removed, and the remaining records were imported into Covidence
software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) [14] for the screening process and data management. Title and abstract of potential studies were screened by one reviewer (LD) in order to assess if they meet the inclusion criteria as described above. The initial selection of studies was assessed by an additional reviewer (HEC). Subsequently, the full texts on potential studies were screened by two review authors (LD and BD) for eligibility. Disagreement was resolved through discussion or by consultation of a third reviewer (HEC).

Neither of the review authors were blinded to the journal titles, study authors/institutions or year of publication. A flow chart was created and used to document the number of studies identified, selected and excluded.

Quality assessment and critical appraisal of the evidence

The quality of the included systematic reviews was assessed using the AMSTAR tool [15], to ensure methodological rigidity of the reviews that we based our subsequent search upon.

For the critical appraisal of the individual RCTS, the Cochrane risk of bias tool[16] was applied including 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.

Quality assessments of the individual outcomes of interest were subsequently evaluated using GRADE method [17], with the four possible ratings of the quality: high, moderate, low and very low. Downgrading was done, by investigating the following domains; risk of bias; inconsistency; indirectness; imprecision and publication bias. The overall quality of evidence was based on the lowest quality of the primary outcome.

Data extraction
Two review authors (LD and HEC) independently extracted data and assessed risk of bias for the included RCTs in Covidence. Data extraction of the studies included the population demographics and baseline characteristics, details on intervention and control conditions, study design, outcome and time of measurement, as well as risk estimates. Discrepancies was identified and resolved through discussion. Following data extraction, all demographic data was exported to Review Manager [13].

Statistical analysis and summary of findings

It was not possible to perform the intended statistical analysis and summary of findings as described in our protocol, due to heterogenic reporting style and lack of data in the individual studies included in this review. Thus, the effect on individual outcomes and overall quality assessment were solely narratively described. Only the data that was available in the respective studies was used. Authors of the included studies were not contacted for further information.

Results

In the search for systematic reviews, we identified 122 records. Following a check for duplicates and none-relevant references, we identified seven systematic reviews that were obtained in full length and read thoroughly. Of these, four systematic reviews [3, 18-20] matched our clinical question, including a high quality Cochrane review containing one relevant RCT[21]. The remaining three reviews of low to high quality did not contribute with any further studies. The AMSTAR assessment of the four systematic reviews can be found in the supplementary information figure 3. A search for primary studies based on the search date from the Cochrane review (which in this case was the 13th of January 2011) [3], identified 194 references that after the screening and selection process were reduced to two RCT matching the inclusion criteria[22, 23].
Subsequently the total amount of evidence in this review is based on three RCT with a total of 220 patients[21-23]. A flowchart with reasons for exclusion can be seen in figure 1.

The population in the included studies consisted of patients aged 18-84 years, all with unilateral definite Meniere disease in accordance to the diagnoses criteria of AAO-HNS 1995. In all the studies, the intervention was treatment with intratympanic dexamethasone compared to placebo. In the studies of Lambert 2012[23] and Lambert 2016[22], the intervention investigated was OTO-104, which consists of a heat sensitive gel that solidified once reaching body temperature (dosage ranging from 3 mg/ml to 60 mg/ml). A further description of the included studies can be found in the supplementary information figure 4.

Primary outcome

The effect on the frequency of vertigo attack(s) was mentioned in two of the identified studies. In Lambert et 2012[23], 44 patients received a single injection of intratympanic OTO-104 at two different dosages (3mg/ml (n=14), 12mg/ml (n= 16)) or placebo (n= 14). The patients were observed for three months, and the frequency of vertigo was assessed as the fraction of days per month with definite vertigo. At three months, the 12 mg of OTO-104 led to the largest reduction in the frequency of vertigo (mean -0.211 ± SD 0.153), as compared to placebo (mean -0.124 ± SD 0.153). This finding was not significant (p=0.086). In addition, there was no effect of 3mg OTO-104 (mean -0.147 ± SD 0.166) on vertigo frequency as compared to placebo (p= 0.493). These findings are similar to the study of Lambert et al 2016[22], who found no effect on the rate of vertigo, three months following treatment with 60mg/ml OTO-104 as compared to placebo (mean change -0.052 (95% CI -0.108 - 0.004), p= 0.067). There were no serious adverse events observed in either of the two studies. The study of Anaya et al. [21] investigated the effect of 4mg/L
Dexamethasone on vertigo frequency and severity during a study period of two years. The authors report a decrease in the number of vertiginous spells during the course of the study (no analysis provided in the study). Furthermore, the authors found a significant reduction in vertigo severity in the group receiving dexamethasone as compared to placebo (90% versus 42%, p<0.001) measured by the Functional Level Scale from AAO-HNS 1995. Anaya et al did not report on serious adverse events.

Secondary outcome:

Lambert et al 2012 assessed the effect on tinnitus via the tinnitus handicap inventory (THI) (total score), and found a reduction at three months (Mean change -12.2, -15.0 and -4.0 following 3mg, 12, mg and placebo, respectively (no statistical analysis was provided in the study)). Quality of life was measured by the Menière’s disease Patient oriented Symptom-severity Index (MDPOSI), from which no effect was found (no data provided in the study). In addition, there were no clinically meaningful changes in hearing at all frequencies (no data provided in the study). Lambert et al 2016 reports that the THI as well as frequency of tinnitus remained stable throughout the study period (no data provided in the study). Quality of life was measured through the SF-16 (16-item short-form health survey). Here, OTO-104 did not have an effect on the highest domain of the SF-16 as compared to placebo (mean 2.78 versus 1.20 (no statistical analysis provided in the study)), yet there was a significant effect at three months on certain subscales in the group receiving OTO-104 as compared to placebo. These subscales included bodily pain (mean 3.01 versus 0.29, p= 0.039), vitality (mean 2.53 versus -0.35, p= 0.045) and social functioning (mean 3.52 versus 0.16, p= 0.025).

Anaya et al. investigated pure tone average hearing, and found no significant change at a two-year follow-up, as the dexamethasone group had a mean hearing threshold of 53.4 dBHL, and the
placebo group a mean hearing threshold of 56 dBHL (no statistical analysis provided in the study).

In addition, the impact on daily life was assessed through the dizziness handicap inventory (DHI), on which dexamethasone had statistical effect two years following the initiation of treatment as compared to placebo (mean 8.3 versus 23.7, p<0.008).

There were no studies assessing the effect on the duration of vertigo attacks three months following initial treatment. In addition, neither vestibular function nor quality of life was reported at the longest follow-up (minimum one year after initiating treatment).

**Quality assessment and critical appraisal of the evidence**

Overall, the critical appraisal as assessed using the Cochrane risk of bias tool revealed that the random sequence generation and allocation concealment was unclear across all three studies, due to inadequate description. There was low risk of bias for the remaining risk of bias domains. An overview of the risk of bias assessment can be seen in figure 2.

In accordance to the GRADE approach, this serious risk of bias due unclear sequence generation and allocation concealment combined with serious imprecision due to few patients in single studies, led to the overall quality of the individual outcome being very low.

**Discussion**

Based on the evidence from the evidence included in this review, there is still a lack of solid confirmation that intratympanic corticosteroid treatment has a positive effect in Menière’s disease.

According to GRADE, the quality of evidence was very low for the individual outcomes investigating the effect of intratympanic corticosteroid in patients aged 18 and above, with definite or probably Menière's disease. The results were based on very few patients, which diminished the
precision and power of the estimates. In addition, there was risk of bias and inadequate reporting of
outcome data.

The chosen primary outcome was frequency of vertigo. Garduno-Anaya et al. [21] displayed the
results on frequency of vertigo in a box-plot figure. However, there is no additional data or
information on whether or not there is a statistically significant difference between the treatment
and placebo group. Garduno-Anaya et al. reported a statistically significant reduction in the severity
of vertigo measured with functional level scale and class A (complete control of vertigo) 24 months
following initial treatment in the treatment group compared to the placebo group. The two
remaining studies from Lambert et al 2012 and Lambert et al 2016 [22, 23] originate from the same
research group. In contrast to Garduno-Anaya et al. they used OTO-104, a suspension of
dexamethasone in a buffered gelatin in order to achieve a sustained release of dexamethasone.

However, neither of these two studies was able to demonstrate a statistically significant effect of
OTO-104 compared to placebo on the primary outcome frequency of vertigo. Nevertheless, they did
report a positive effect in favor of intratympanic treatment with OTO-104 in some of the subscales
(bodily pain, vitality and social functioning) in the quality of life questionnaire. None of the studies
reported of any serious adverse advents. In the light of these findings, it should be noted that the use
of steroid treatment in Meniere’s disease and in particular the usage of OTO-104 is still in the
investigational stage. In accordance, the Food and Drug Administration (FDA) in the United States
approve neither OTO-104 nor any other intratympanic steroid treatments for Menière’s disease. It is
off-label use in many counties.

We identified four reviews [3, 18-20] in our systematic literature search. However, none of them
included the same three studies as we did. The Cochrane review[3] only included Gurduno-Anaya
et al.[21] Lagvigne et al. [19] included prospective randomized trials, but did not restrict it to trials
that had included a placebo group. The natural history with fluctuations in symptoms over time
makes these study designs less favorable. Nevertheless, they included six studies in total but
concluded that only one study [21] demonstrated a reduction in severity of vertigo from
intratympanic steroid treatment. The review of Patel et al [24] included non-randomized studies and
reported a beneficial effect of intratympanic steroid treatment on vertigo control in these study
designs [24]. Non-randomized trials are not included in the current review due to the high risk of
bias in these study designs, yet the discrepancy between this current review and Patel et al [24]
indicates that more research is needed on the usage of intratympanic steroid in Menière’s disease.
Furthermore, reviews that also includes both randomized and non-randomized trials followed by a
direct comparison of effects as a consequence of study designs should be conducted.

Research in effective treatment modalities for Menière’s disease has been challenged not only by
the absence of known etiology but also by lack of consensus on the diagnostic criteria and on how
to report outcome data. The inconsistency in reporting outcome data hinders the possibility to
perform high quality meta-analysis. There is also a lack of consensus on the treatment protocol for
applying intratympanic steroids that results in inhomogeneity in the treatment protocols in the
published studies [6]. In order to facilitate collaboration and improve the quality of clinical studies,
Bárány Society published new consensus diagnostic criteria in 2015 [1]. The standardization of the
diagnostic criteria may in the future increase the amount of comparable research, which currently is
lacking within this field. However, as it is demonstrated in this review it is also essential to reach an
international consensus on how to report outcome data.

Strengths and limitations related to this systematic review

Our systematic review were performed using transparent methods and a priori defined criteria in
accordance with the guidelines of the Cochrane Collaboration and PRISMA, including protocol
registration, comprehensive search and duplicate study selection, data extraction and quality
assessment. Limitations included a restricted search in language and study design, as this particular review was restricted to randomised controlled trials. Furthermore, two of included studies investigate the usage of a novel treatment method for the application of steroid treatment that is investigational and therefore not widely used. The authors of the included studies were not contacted for further information and thus the results are solely based on the published data.

**Conclusion**

There is still a need for high quality research to determine the effectiveness of intratympanic steroids in the treatment of Menière’s disease. Based on current evidence from RCT-studies, the effect of intratympanic steroid treatment in Menière’s disease is questionable. However, other study types beyond RCT designs have indicated an effect of intratympanic steroids in patients with Menière’s disease. Thus, it is not possible to rule out that there might be a beneficial effect linked to this treatment modality.


Figure legends

Figure 1: Flowchart showing the process of selecting a) systematic reviews and b) primary studies. Number of included studies and reason for exclusion is provided.

Figure 2: 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.