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Intratympanic steroid for Menière's disease

a systematic review

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Title:

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

1 **Introduction**

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

14 Nevertheless, the true etiology of Menières disease remains uncertain[5]. Consequently, physicians
15 and patients face a broad variety of treatment options, e.g. lifestyle and dietary recommendations,
16 medical treatment with betahistin or diuretics, intratympanic gentamicin, and surgery. Surgical
17 treatment modalities include endolymphatic sac surgery, neurectomy of vestibular neurotomy or
18 labyrinthectomy and are usually reserved as last resort treatments[6, 7]. However, regardless of the
19 treatment, the auditory and vestibular deficits generally progress over time[8]. An international
20 consensus paper on the treatment of Menières disease was published in 2018 from six experts on
21 Menières disease, which recommended intratympanic steroid as a second step treatment
22 modality[7]. This is also the case in the recent European position statement paper on diagnosis and
23 treatment of Menière's disease [6]. Treatment with intratympanic steroids has become very popular
24 during the last two decades, as it is easy to administer even in an office setup [6]. This review aims

25 to systematically identify, summarize and critically appraise the current evidence concerning the
26 usage of intratympanic steroid in the treatment of patients (≥ 18 years of age) with definite or
27 probable Menière's disease. Specifically, we sought to evaluate the effects of intratympanic steroid
28 treatment on frequency and duration of vertigo, serious adverse events, vestibular function as well
29 as quality of life, impact on daily life, tinnitus and hearing loss.

30

31 **Methods**

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

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

37

38 Literature search

39 We performed an electronic systematic literature search in two steps. First, a search for systematic
40 reviews was performed on December 19th 2017, with no restrictions to publication date, in order to
41 identify relevant primary studies to be included in the synthesis. Secondly, a search was performed
42 to identify individual randomized controlled trials (RCTs), where we limited the initiation date of
43 the search to the dates after the latest search in the systematic reviews. Thus, the search for RCTs
44 was performed on February 6th 2018 in EMBASE and MEDLINE databases. The search strategy
45 was developed using medical subject heading (MeSH) and text words related to our eligibility
46 criteria, i.e. Meniere, Menieres, Meniere disease/syndrome (English), Menieres sygdom/syndrome
47 (Danish), Menieres sykdom (Norwegian), Menieres sjukdom (Swedish). There were no restrictions
48 on the search in regards to publication status, however the search was limited to literature written in

49 English, Danish, Norwegian and Swedish. Search protocols are provided in the supplementary
50 information figure 2.

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

68

69 Study selection

70 The results of the literature search were imported to RefWorks, (Review Manager Software, version
71 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) [13]
72 duplicate references were removed, and the remaining records were imported into Covidence

73 software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia)
74 [14] for the screening process and data management. Title and abstract of potential studies were
75 screened by one reviewer (LD) in order to assess if they meet the inclusion criteria as described
76 above. The initial selection of studies was assessed by an additional reviewer (HEC). Subsequently,
77 the full texts on potential studies were screened by two review authors (LD and BD) for eligibility.
78 Disagreement was resolved through discussion or by consultation of a third reviewer (HEC).
79 Neither of the review authors were blinded to the journal titles, study authors/institutions or year of
80 publication. A flow chart was created and used to document the number of studies identified,
81 selected and excluded.

82

83 Quality assessment and critical appraisal of the evidence

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

86 For the critical appraisal of the individual RCTS, the Cochrane risk of bias tool[16] was applied
87 including the following characteristics: randomization sequence generation; treatment allocation
88 concealment; blinding of patients and personnel; blinding of outcome assessors; completeness of
89 outcome data; selective outcome reporting; other sources of bias.

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

95

96 Data extraction

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

103

104 Statistical analysis and summary of findings

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

110

111 **Results**

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

121 Subsequently the total amount of evidence in this review is based on three RCT with a total of
122 number of 220 patients[21-23]. A flowchart with reasons for exclusion can be seen in figure 1.

123

124 The population in the included studies consisted of patients aged 18-84 years, all with unilateral
125 definite Meniere disease in accordance to the diagnoses criteria of AAO-HNS 1995. In all the
126 studies, the intervention was treatment with intratympanic dexamethasone compared to placebo. In
127 the studies of Lambert 2012[23] and Lambert 2016[22], the intervention investigated was OTO-
128 104, which consists of a heat sensitive gel that solidified once reaching body temperature (dosage
129 ranging from 3 mg/ml to 60 mg/ml). A further description of the included studies can be found in
130 the supplementary information figure 4.

131

132 Primary outcome

133 The effect on the frequency of vertigo attack(s) was mentioned in two of the identified studies. In
134 Lambert et 2012[23], 44 patients received a single injection of intratympanic OTO-104 at two
135 different dosages (3mg/ml (n=14), 12mg/ml (n= 16)) or placebo (n= 14). The patients were
136 observed for three months, and the frequency of vertigo was assessed as the fraction of days per
137 month with definite vertigo. At three months, the 12 mg of OTO-104 led to the largest reduction in
138 the frequency of vertigo (mean $-0.211 \pm SD 0.153$), as compared to placebo (mean $-0.124 \pm SD$
139 0.153). This finding was not significant ($p=0.086$). In addition, there was no effect of 3mg OTO-
140 104 (mean $-0.147 \pm SD 0.166$) on vertigo frequency as compared to placebo ($p= 0.493$). These
141 findings are similar to the study of Lambert et al 2016[22], who found no effect on the rate of
142 vertigo, three months following treatment with 60mg/ml OTO-104 as compared to placebo (mean
143 change -0.052 (95% CI $-0.108 - 0.004$), $p= 0.067$). There were no serious adverse events observed
144 in either of the two studies. The study of Anaya et al. [21] investigated the effect of 4mg/L

145 Dexamethasone on vertigo frequency and severity during a study period of two years. The authors
146 report a decrease in the number of vertiginous spells during the course of the study (no analysis
147 provided in the study). Furthermore, the authors found a significant reduction in vertigo severity in
148 the group receiving dexamethasone as compared to placebo (90% versus 42%, $p < 0.001$) measured
149 by the Functional Level Scale from AAO-HNS 1995. Anaya et al did not report on serious adverse
150 events.

151

152 Secondary outcome:

153 Lambert et al 2012 assessed the effect on tinnitus via the tinnitus handicap inventory (THI) (total
154 score), and found a reduction at three months (Mean change -12.2, -15.0 and -4.0 following 3mg,
155 12, mg and placebo, respectively (no statistical analysis was provided in the study)). Quality of life
156 was measured by the Menière's disease Patient oriented Symptom-severity Index (MDPOSI), from
157 which no effect was found (no data provided in the study). In addition, there were no clinically
158 meaningful changes in hearing at all frequencies (no data provided in the study). Lambert et al 2016
159 reports that the THI as well as frequency of tinnitus remained stable throughout the study period (no
160 data provided in the study). Quality of life was measured through the SF-16 (16-item short-form
161 health survey). Here, OTO-104 did not have an effect on the highest domain of the SF-16 as
162 compared to placebo (mean 2.78 versus 1.20 (no statistical analysis provided in the study)), yet
163 there was a significant effect at three months on certain subscales in the group receiving OTO-104
164 as compared to placebo. These subscales included bodily pain (mean 3.01 versus 0.29, $p = 0.039$),
165 vitality (mean 2.53 versus -0.35, $p = 0.045$) and social functioning (mean 3.52 versus 0.16, $p =$
166 0.025).

167 Anaya et al. investigated pure tone average hearing, and found no significant change at a two-year
168 follow-up, as the dexamethasone group had a mean hearing threshold of 53.4 dBHL, and the

169 placebo group a mean hearing threshold of 56 dBHL (no statistical analysis provided in the study).
170 In addition, the impact on daily life was assessed through the dizziness handicap inventory (DHI),
171 on which dexamethasone had statistical effect two years following the initiation of treatment as
172 compared to placebo (mean 8.3 versus 23.7, $p < 0.008$).
173 There were no studies assessing the effect on the duration of vertigo attacks three months following
174 initial treatment. In addition, neither vestibular function nor quality of life was reported at the
175 longest follow-up (minimum one year after initiating treatment).

176

177 Quality assessment and critical appraisal of the evidence

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

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

185

186 **Discussion**

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

189 According to GRADE, the quality of evidence was very low for the individual outcomes
190 investigating the effect of intratympanic corticosteroid in patients aged 18 and above, with definite
191 or probably Menière's disease. The results were based on very few patients, which diminished the

192 precision and power of the estimates. In addition, there was risk of bias and inadequate reporting of
193 outcome data.

194 The chosen primary outcome was frequency of vertigo. Garduno-Anaya et al. [21] displayed the
195 results on frequency of vertigo in a box-plot figure. However, there is no additional data or
196 information on whether or not there is a statistically significant difference between the treatment
197 and placebo group. Garduno-Anaya et al. reported a statistically significant reduction in the severity
198 of vertigo measured with functional level scale and class A (complete control of vertigo) 24 months
199 following initial treatment in the treatment group compared to the placebo group. The two
200 remaining studies from Lambert et al 2012 and Lambert et al 2016 [22, 23] originate from the same
201 research group. In contrast to Garduno-Anaya et al. they used OTO-104, a suspension of
202 dexamethasone in a buffered gelatin in order to achieve a sustained release of dexamethasone.
203 However, neither of these two studies was able to demonstrate a statistically significant effect of
204 OTO-104 compared to placebo on the primary outcome frequency of vertigo. Nevertheless, they did
205 report a positive effect in favor of intratympanic treatment with OTO-104 in some of the subscales
206 (bodily pain, vitality and social functioning) in the quality of life questionnaire. None of the studies
207 reported of any serious adverse events. In the light of these findings, it should be noted that the use
208 of steroid treatment in Menieres disease and in particular the usage of OTO-104 is still in the
209 investigational stage. In accordance, the Food and Drug Administration (FDA) in the United States
210 approve neither OTO-104 nor any other intratympanic steroid treatments for Menière's disease. It is
211 off-label use in many countries.

212 We identified four reviews [3, 18-20] in our systematic literature search. However, none of them
213 included the same three studies as we did. The Cochrane review[3] only included Garduno-Anaya
214 et al.[21] Lagvigne et al. [19] included prospective randomized trials, but did not restrict it to trials
215 that had included a placebo group. The natural history with fluctuations in symptoms over time

216 makes these study designs less favorable. Nevertheless, they included six studies in total but
217 concluded that only one study [21] demonstrated a reduction in severity of vertigo from
218 intratympanic steroid treatment. The review of Patel et al [24] included non-randomized studies and
219 reported a beneficial effect of intratympanic steroid treatment on vertigo control in these study
220 designs [24]. Non-randomized trials are not included in the current review due to the high risk of
221 bias in these study designs, yet the discrepancy between this current review and Patel et al [24]
222 indicates that more research is needed on the usage of intratympanic steroid in Menière's disease.
223 Furthermore, reviews that also includes both randomized and non-randomized trials followed by a
224 direct comparison of effects as a consequence of study designs should be conducted.

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

235

236 *Strengths and limitations related to this systematic review*

237 Our systematic review were performed using transparent methods and a priori defined criteria in
238 accordance with the guidelines of the Cochrane Collaboration and PRISMA, including protocol
239 registration, comprehensive search and duplicate study selection, data extraction and quality

240 assessment. Limitations included a restricted search in language and study design, as this particular
241 review was restricted to randomised controlled trials. Furthermore, two of included studies
242 investigate the usage of a novel treatment method for the application of steroid treatment that is
243 investigational and therefore not widely used. The authors of the included studies were not
244 contacted for further information and thus the results are solely based on the published data.

245

246 **Conclusion**

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

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304

305

306 **Figure legends**

307 **Figure 1:** Flowchart showing the process of selecting a) systematic reviews and b) primary studies.

308 Number of included studies and reason for exclusion is provided.

309 **Figure 2:** Risk of bias assessment as assessed by the Cochrane risk of bias tool. A plus (+) indicates
310 low risk of bias; a question mark (?) indicates unclear risk of bias and a minus (-) indicates high risk
311 of bias. The specific type of bias is presented in the top column, and the individual studies in the left
312 row.

313

314