Intratympanic methylprednisolone versus gentamicin in patients with unilateral Ménière's disease: a randomised, double-blind, comparative effectiveness trial

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Summary

Background Ménière's disease is characterised by severe vertigo attacks and hearing loss. Intratympanic gentamicin, the standard treatment for refractory Ménière's disease, reduces vertigo, but damages vestibular function and can worsen hearing. We aimed to assess whether intratympanic administration of the corticosteroid methylprednisolone reduces vertigo compared with gentamicin.

Methods In this double-blind comparative effectiveness trial, patients aged 18–70 years with refractory unilateral Ménière's disease were enrolled at Charing Cross Hospital (London, UK) and Leicester Royal Infirmary (Leicester, UK). Patients were randomly assigned (1:1) by a block design to two intratympanic methylprednisolone (62·5 mg/mL) or gentamicin (40 mg/mL) injections given 2 weeks apart, and were followed up for 2 years. All investigators and patients were masked to treatment allocation. The primary outcome was vertigo frequency over the final 6 months (18–24 months after injection) compared with the 6 months before the first injection. Analyses were done in the intention-to-treat population, and then per protocol. This trial is registered with ClinicalTrials.gov, number NCT00802529.

Findings Between June 19, 2009, and April 15, 2013, 256 patients with Ménière's disease were screened, 60 of whom were enrolled and randomly assigned: 30 to gentamicin and 30 to methylprednisolone. In the intention-to-treat analysis (ie, all 60 patients), the mean number of vertigo attacks in the final 6 months compared with the 6 months before the first injection (primary outcome) decreased from 19·9 (SD 16·7) to 2·5 (5·8) in the gentamicin group (87% reduction) and from 16·4 (12·5) to 1·6 (3·4) in the methylprednisolone group (90% reduction; mean difference –0·9, 95% CI –3·4 to 1·6). Patients whose vertigo did not improve after injection (ie, non-responders) after being assessed by an unmasked clinician were eligible for additional injections given by a masked clinician (eight patients in the gentamicin group *vs* 15 in the methylprednisolone group). Two non-responders switched from methylprednisolone to gentamicin. Both drugs were well tolerated with no safety concerns. Six patients reported one adverse event each: three in the gentamicin group and three in the methylprednisolone group. The most common adverse event was minor ear infections, which was experienced by one patient in the gentamicin group and two in the methylprednisolone group.

Interpretation Methylprednisolone injections are a non-ablative, effective treatment for refractory Ménière's disease. The choice between methylprednisolone and gentamicin should be made based on clinical knowledge and patient circumstances.

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Introduction

Ménière's disease causes devastating vertigo attacks.[1] In the initial phases of the disease, no treatment decreases the frequency or intensity of the attacks.[2] However, in aggressive phases with frequent and severe vertigo episodes, intratympanic injections of gentamicin are effective.[3] This treatment is a minimally invasive outpatient procedure, but, since the therapeutic effects rely on the ototoxic properties of gentamicin, patients are left with a permanent vestibular deficit.[4] More worryingly, in up to 20% of cases, hearing function also deteriorates.[5,6]

Corticosteroids, which do not harm inner ear function, have also been used in Ménière's disease,[7] but, so far, no

double-blind, prospective, randomised controlled trial of steroids versus gentamicin has been done. In a double-blind study,[8] control of vertigo after intratympanic administration of the steroid dexamethasone was reported, but the control group received placebo, not gentamicin; study numbers were small (n=22); and a Cochrane review did not fully support its conclusions.[5] In a trial of gentamicin versus dexamethasone treatment,[9] dexamethasone was inferior at controlling vertigo, but the study was non-masked. As a result, opinions on the effectiveness of intratympanic steroid injections vary widely.[10–12]

We did a double-blind, randomised controlled trial of intratympanic gentamicin versus methylprednisolone for

Research in context

Evidence before this study
We searched PubMed and ClinicalTrials.gov between July, 2008, and April 21, 2016, for English-language studies with the terms "Ménière's disease", "gentamicin", "steroid", and "intratympanic". We identified no double-blind randomised controlled trial comparing intratympanic gentamicin with corticosteroids in unilateral refractory Ménière's disease. Findings from previous open-label trials showed a beneficial effect of intratympanic gentamicin versus placebo, but no definitive results were available for intratympanic corticosteroids. However, in the absence of evidence, many ear, nose, and throat surgeons use intratympanic steroids, but their efficacy is contested. Two recent Cochrane reviews highlighted the shortage of double-blind randomised controlled trials in Ménière's disease. This shortage is probably because of the difficulty recruiting patients and the long 2-year follow-up needed to meet the requirements for reporting results set out by the American Academy of Otolaryngology–Head and Neck Surgery.

Added value of this study
We present findings from, to our knowledge, the first double-blind, randomised controlled trial comparing

intratympanic gentamicin with methylprednisolone in unilateral Ménière's disease. Both gentamicin and methylprednisolone injections controlled vertigo attacks and vestibular-mediated disability in refractory unilateral Ménière's disease. Furthermore, the number of patients experiencing a clinically meaningful deterioration in speech perception was higher in those receiving gentamicin than in those receiving methylprednisolone.

Implications of all the available evidence
Two effective treatments exist for refractory unilateral Ménière's disease: intratympanic gentamicin and steroids. Gentamicin is a vestibulotoxic (ie, ablative) treatment and the loss of vestibular function after injection is expected. If we add to this the small but not negligible risk to hearing posed by gentamicin injections, patients and doctors should weigh carefully individual circumstances and preferences when choosing a drug. Corticosteroids would be preferred by many patients because they have no side-effects and, unlike gentamicin, are suitable in bilateral disease.

unilateral Ménière's disease. Ménière's disease is a fluctuating disease with a strong placebo effect, and so we followed up patients for 2 years, as recommended by the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) guidelines.[13] These guidelines were issued in 1995, but no double-blind randomised controlled trial on intratympanic injections has fully adopted them.

Methods

Study design and participants
This double-blind comparative effectiveness trial was done at two centres in the UK: Charing Cross Hospital, London (primary site) and Leicester Royal Infirmary, Leicester (secondary site). Patients aged 18–70 years with definite unilateral Ménière's disease, defined according to the AAO-HNS, who had experienced at least two episodes of rotational vertigo lasting at least 20 min in the previous 6 months and who had shown no response to standard medical treatment were eligible for inclusion. Exclusion criteria were evidence of bilateral Ménière's disease, additional neuro-otological disorders (eg, vestibular migraine, vertebrobasilar transient ischaemic attack, or acoustic neuroma), concurrent middle ear disease, family history of unexplained deafness, known history of adverse effect to gentamicin or steroids, renal failure, severe disability (eg, neurological, orthopaedic, or cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up, or pregnancy.

All patients provided written informed consent before enrolment. This study was done in accordance with the Declaration of Helsinki and International Council for Harmonisation's Good Clinical Practice. All patients were individually discussed by MP, KA, and AMB and enrolled by MP and KA. The study was approved by the London-Fulham Research Ethics Committee, Imperial College Joint Research Compliance Office, and the Medicines and Healthcare products Regulatory Agency.

Randomisation and masking
Patients were randomly assigned (1:1) to methyl-prednisolone (62·5 mg/mL) or gentamicin (40 mg/mL). The double-blind randomisation sequence was generated by constructing 15 blocks of four possible combinations, containing two methylprednisolone and two gentamicin treatments to keep drug allocation roughly equal throughout recruitment; a technical engineer outside the trial team constructed this sequence. The randomisation sequence was allocated in numerical order, retained and concealed by the Charing Cross Hospital and Leicester Royal Infirmary pharmacy aseptic units who prepared each injection in unmarked 1 mL glass syringes and documented the drug history of each patient. The pharmacy units assigned participants to interventions, but did not reveal the drug sequence to any member of the trial team. All investigators and patients were masked to treatment allocation.

Procedures
Intratympanic injections were done in outpatient ear, nose, and throat clinics (appendix p 2). Two injections were given, the second 2 weeks after the first. We chose methylprednisolone rather than dexamethasone as the

See **Online** for appendix

steroid treatment because intratympanic perfusion in animals suggested higher endolymphatic concentrations of methylprednisolone than dexamethasone.[14] Methylprednisolone in human beings also produces high perilymph concentrations[15] and, if mineralocorticoid receptor binding is important in hearing recovery,[16] methylprednisolone has greater affinity for this than dexamethasone. From a practical viewpoint, high-dose dexamethasone (24 mg/mL) is not readily available in the UK and other countries, whereas methylprednisolone is readily available in most pharmacies at various concentrations.

Patients were advised not to change any previous oral drug or dietary treatments for Ménière's disease. Drug treatments for other illnesses were not restricted and patients saw their general practitioner as needed for general medical care.

Patients were assessed at baseline (0 months) and at 1, 2, 6, 12, 18, and 24 months (appendix p 3). An audiogram was obtained just before the second injection (2 weeks after the first), which was assessed by a masked clinician (MH) and findings reported to the pharmacy. For patients who had a 20 dB drop in hearing across any two consecutive frequencies, the pharmacy, without informing the trial team, switched gentamicin for saline. Since steroids do not disturb hearing, patients randomly assigned to methylprednisolone were given a second methylprednisolone injection.

If vertigo attacks returned at any time during the trial (ie, the patient was a non-responder) the unmasked clinician (BMS) prescribed a further course of intratympanic injections, but the patient and everybody else involved remained masked to treatment allocation. The clinician had the choice to prescribe the same drug or swap, basing this decision on the patient's response to previous injections.

Patients completed the Vertigo Symptom Scale short form (VSS; 0–60 scale,[17] comprising vertigo [VSS_V] and autonomic [VSS_A] subscales), the Dizziness Handicap Inventory (DHI; 0–100 scale),[18] the Functional Level Scale (FLS; a six-point scale to assess effects of vertigo on daily activities[13]), Tinnitus Handicap Inventory (THI; 0–100 scale),[19] and Aural Fullness Scale (AFS; 0–10 analogue scale[8]) at baseline and 2, 6, 12, 18, and 24 months.

Pure-tone audiometry (Interacoustics, Middelfart, Denmark) was assessed at baseline and 1, 2, 6, 12, 18, and 24 months. Pure-tone audiometry tests were contralesional and ipsilesional air conduction thresholds at 0·25, 0·5, 1, 2, 3, 4, 6, and 8 KHz and bone conduction at 0·5, 1, 2, and 4 KHz. In the analysis, we took the mean ipsilesional pure-tone low-frequency threshold across 0·5, 1, 2, and 3 KHz in line with the AAO-HNS recommendations for reporting hearing loss in Ménière's disease.[13] We used bone conduction thresholds in the speech audiometry assessment and for routine clinical assessment.

Assessment of speech discrimination was done at baseline and 1, 2, 6, 12, and 24 months by ipsilesional suprathreshold word recognition. Arthur Boothroyd's isophonemic word lists (Guymark, Southampton) comprising sets of ten words were played into the ipsilesional ear at the low-frequency pure-tone threshold of 0·5, 1, and 2 kHz +30 dB with masking sound in the contralesional ear as appropriate. The formula for masking level was low-frequency pure-tone threshold in the ipsilesional ear minus bone conduction mean threshold (0·5, 1, and 2 KHz) in the contralesional ear minus 40 dB. Speech loudness and masking were rounded to the nearest 5 dB. Step increments and decrements of 10 dB for speech loudness and masking were used to attain the maximum speech discrimination score.

We did vestibular function tests to assess the vestibular response to the drugs, in particular the ototoxic effect of gentamicin, at baseline and 1, 2, 12, and 24 months, including caloric tests, cervical vestibular evoked myogenic potentials, and utricular centrifugation (appendix p 3).

Outcomes

The primary outcome was relief from vertigo,[13] assessed as the number of vertigo attacks in the final 6 months (18–24 months after the first injection) compared with the 6 months before the first injection.[13] The number of vertigo attacks was assessed during a face-to-face appointment before treatment and at 24 months of follow-up.

Secondary outcomes were the number of vertigo attacks in the final 1 month compared with the month before the first injection, questionnaire measures of audio-vestibular symptoms (VSS, DHI, FLS, THI, and AFS), and hearing levels measured with audiometry and speech discrimination. Primary and secondary outcomes, presented according to the reporting recommendations of the AAO-HNS[13] are described in the appendix (p 3).

Statistical analysis

At the time of planning of our study, there were few published data on intratympanic gentamicin versus steroid treatment for Ménière's disease. Hearing loss can be a substantial side-effect of gentamicin treatment for Ménière's disease because it is an ablative drug, whereas steroids are not likely to cause this side-effect. We used the hearing loss data in the study by Sennaroglu and colleagues[20] to make an estimate of hearing loss for the two types of treatment. In Sennaroglu and colleagues' study,[20] several patients were classified as having total hearing loss, which occurred only in the gentamicin group. We assigned a value of –70 dB for total hearing loss. From these data, we calculated that the dexamethasone group had a mean hearing loss of –2 dB and the gentamicin group had a mean hearing loss of –11 dB. We estimated the effect size as the difference in hearing loss between the two treatments of 9 dB divided by the SD of 11 dB, giving an estimate of effect size for the difference between the two treatments in terms of hearing loss as

$d=0·8$. Using the package G*Power,[21] we calculated that with the effect size set to $0·8$, a two-tailed p value of $0·05$, and 80% power, we would need 26 patients per group. To allow for 10% dropout, and taking into account four-patient block randomisation, 30 patients per group were needed.

Baseline characteristics were compared between groups with independent-samples t tests. We did repeated-measures general linear model ANOVA to investigate drug differences (gentamicin vs methyl-prednisolone), the difference between before and after treatment across all measured timepoints (ie, time), and interactions. For the number of vertigo attacks during the final 6 months (primary outcome) and during the final month, time refers to two intervals only (baseline vs final), but for all other outcomes it includes all tested intervals. Drug actions were deemed to be not significantly different if there was no significant drug or drug×time interaction effect for the variable under consideration in the ANOVA.

Analyses were done in the intention-to-treat population, and then per protocol (ie, removing treatment failures). We did χ^2 and independent-samples t tests where appropriate, and calculated standardised effect sizes with Cohen's d. In addition to the main statistical analysis, we processed the results according to the categories recommended by the AAO-HNS (appendix p 3). Only findings that differed between the main ANOVA analysis and the AAO-HNS-recommended reporting procedure are presented in the Results; all other findings are presented in the appendix.

For patients who were unable to complete an audiometry or vestibular test, a mean value was fitted for data. All analyses were done in SPSS, version 22.

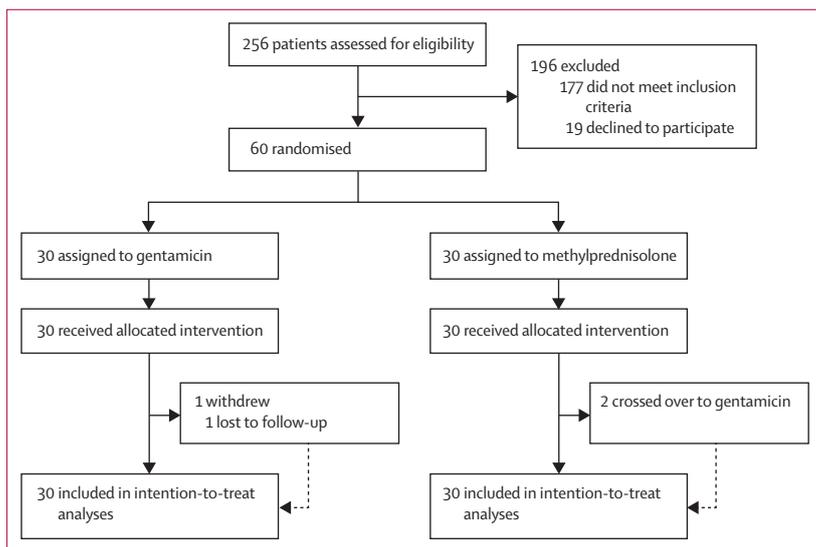This study is registered with ClinicalTrials.gov, number NCT00802529.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between June 19, 2009, and April 15, 2013, 256 patients with Ménière's disease (according to the AAO-HNS)[13] were screened, of whom 19 declined to participate and 177 did not fulfil inclusion criteria (figure 1). We recruited 60 patients with definite unilateral Ménière's disease:[13] 55 at the primary site and five at the secondary site. 30 patients were assigned to the gentamicin group (15 women, 12 right-sided) and 30 to the methylprednisolone group (ten women, 13 right-sided). Mean age was $52·5$ years (SD $10·5$) and mean disease duration was $4·5$ years (SD $4·5$; table 1).

The intention-to-treat population comprised all 60 patients. Baseline characteristics (table 1) did not differ between groups. One patient in the gentamicin group was withdrawn at 12 months owing to loss of contact. This patient had a successful reduction in vertigo attacks at last

Figure 1: Trial profile

	Gentamicin (n=30)	Methylprednisolone (n=30)
Age (years)	53·3 (10·8)	51·6 (10·2)
Sex		
Male	15 (50%)	20 (67%)
Female	15 (50%)	10 (33%)
Disease duration (years)	4·9 (5·6)	4·1 (3·2)
Number of attacks in the past 6 months	19·9 (16·7)	16·4 (12·5)
Number of attacks in the past 1 month	6·9 (7·3)	5·5 (6·5)
Vertigo Symptom Scale score (0–60)	24·7 (12·6)	21·8 (10·5)
Dizziness Handicap Inventory score (0–100)	59·3 (20·6)	51·0 (20·5)
Functional Level Scale score (0–6)	4·0 (0·9)	3·5 (0·9)
Tinnitus Handicap Inventory score (0–100)	45·7 (30·3)	39·4 (25·4)
Aural Fullness Scale score (0–10)	6·6 (3·1)	5·3 (3·0)
Pure-tone average (dB)	51·5 (11·3)	53·3 (21·2)
Speech discrimination (%)	71·1 (21·7)	65·0 (29·3)
Caloric asymmetry (%)	35·3 (20·1)	44·9 (25·1)
Caloric directional preponderance (%)	–7·7 (17·1)	–6·9 (30·8)
Vestibular evoked myogenic potential asymmetry (%)	31·1 (26·0)	29·9 (30·6)
Utricular centrifugation weakness (%)	14·3 (84·6)	41·4 (60·4)

Data are mean (SD) or number (%).

Table 1: Demographics and baseline characteristics

contact and was included in all analyses. Two patients allocated to the methylprednisolone group crossed over to gentamicin during follow-up at 7 months and 18 months. Both patients were judged to be treatment failures and were removed from the per-protocol analyses (appendix p 5), which also showed no difference at baseline between groups. Unless otherwise specified, data for the intention-to-treat population are presented here.

20 (67%) patients in the methylprednisolone group and 19 (63%) in the gentamicin group had no attacks of vertigo between 18 months and 24 months after the first injection. Thus, ten (33%) patients in the methyl-prednisolone group and 11 (37%) in the gentamicin group had vertigo attacks. No difference between drugs was noted for the odds of having a vertigo attack in the final 6 months (odds ratio 1·2, 95% CI 0·4–3·3; χ^2 p=0·79). The mean number of vertigo attacks decreased from 19·9 (SD 16·7) in the 6 months before the first injection to 2·5 (5·8) in the final 6 months in the gentamicin group (87% reduction) and from 16·4 (12·5) to 1·6 (3·4) in the methylprednisolone group (90% reduction; p<0·0001; table 2; figure 2). We noted no significant difference between groups for the number of vertigo attacks in the final 6 months compared with the 6 months before the first injection (drug p=0·27; drug×time interaction p=0·51).

The mean number of vertigo attacks in the final 1 month compared with the month before the first injection did not differ between groups (drug p=0·33; drug×time interaction p=0·47; table 2; figure 3). Both drugs reduced the number of attacks (p<0·0001), gentamicin by 90% and methylprednisolone by 91%.

There was no significant difference between drugs for VSS score (drug p=0·07; drug×time interaction p=0·74), DHI score (drug p=0·07; drug×time interaction p=0·99), FLS score (drug p=0·06; no drug×time interaction p=0·98), THI score (drug p=0·14; drug×time interaction p=0·57), and AFS score (drug p=0·07; drug×time interaction p=0·50; table 2; figure 4). Scores for the VSS_A and VSS_V subscales also did not differ between groups (appendix p 5). Total scores decreased significantly over time for VSS (change from baseline to 24 months 67% for gentamicin and 76% for methylprednisolone; p<0·0001), DHI (59% and 68%; p<0·0001, FLS (45% and 46%; p<0·0001), THI (43% and 54%; p<0·0001), and AFS (47% and 45%; p<0·0001).

Mean hearing level did not differ between groups (drug p=0·96; drug × time interaction p=0·18; table 2; figure 5). Hearing levels did not significantly change from baseline over time (p=0·07), with a 4% increase for gentamicin and 12% for methylprednisolone at 24 months. There was

	Mean (SD) score at baseline		Mean (SD) score at 24 months		Change from baseline (%)		Mean difference between drugs at 24 months (95% CIs)	Effect size between drugs at 24 months (d)	p value*
	Gentamicin	Methylprednisolone	Gentamicin	Methylprednisolone	Gentamicin	Methylprednisolone			
Primary endpoint									
Number of vertigo attacks in previous 6 months	19·9 (16·7)	16·4 (12·5)	2·5 (5·8)	1·6 (3·4)	87%	90%	–0·9 (–3·4 to 1·6)	0·19	0·51
Secondary endpoints									
Number of vertigo attacks in previous 1 month	6·9 (7·3)	5·5 (6·5)	0·7 (2·8)	0·5 (1·4)	90%	91%	–0·2 (–1·4 to 0·9)	0·09	0·47
Vertigo Symptom Scale score (0–60)	24·7 (12·6)	21·8 (10·5)	8·2 (11·4)	5·3 (6·3)	67%	76%	–2·9 (–7·6 to 1·7)	0·31	0·74
Dizziness Handicap Scale score (0–100)	59·3 (20·6)	51·0 (20·5)	24·5 (26·7)	16·3 (16·7)	59%	68%	–8·2 (19·7 to 3·3)	0·37	0·99
Functional Level Scale score (0–6)	4·0 (0·9)	3·5 (0·9)	2·2 (1·3)	1·9 (0·9)	45%	46%	–0·3 (–0·9 to 0·2)	0·27	0·98
Tinnitus Handicap Inventory score (0–100)	45·7 (30·3)	39·4 (25·4)	25·9 (29·5)	18·1 (20·8)	43%	54%	–7·8 (–21·3 to 5·6)	0·31	0·57
Aural Fullness Scale score (0–10)	6·6 (3·1)	5·3 (3·0)	3·5 (2·8)	2·9 (2·6)	47%	45%	–0·6 (–2·0 to 0·8)	0·22	0·50
Pure-tone average (dB)	51·5 (11·3)	53·3 (21·2)	49·4 (18·1)	46·9 (24·0)	4%	12%	–2·45 (–13·4 to 8·5)	0·12	0·18
Speech discrimination (%)	71·1% (21·7)	65·0% (29·3)	65·0% (30·1)	76·3% (29·4)	9%†	15%	11·3 (–4·1 to 26·7)	–0·38	0·13

*For drug×time interaction from general linear model analysis. †Notes a worsening of speech discrimination in the gentamicin arm at 24 months compared with baseline.
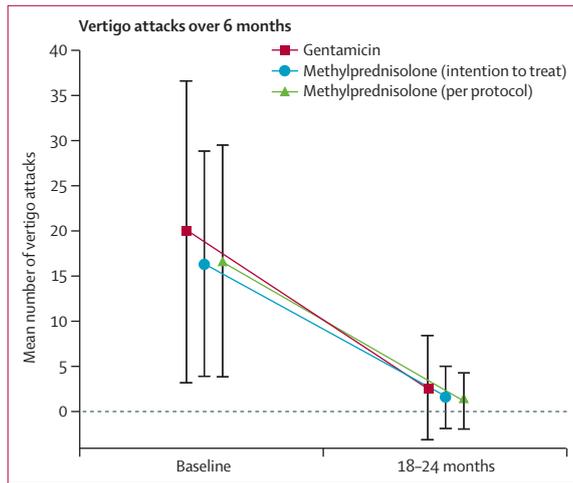
Table 2: Primary and secondary outcomes

Figure 2: Mean number of attacks of vertigo 6 months before treatment and in the final 6 months
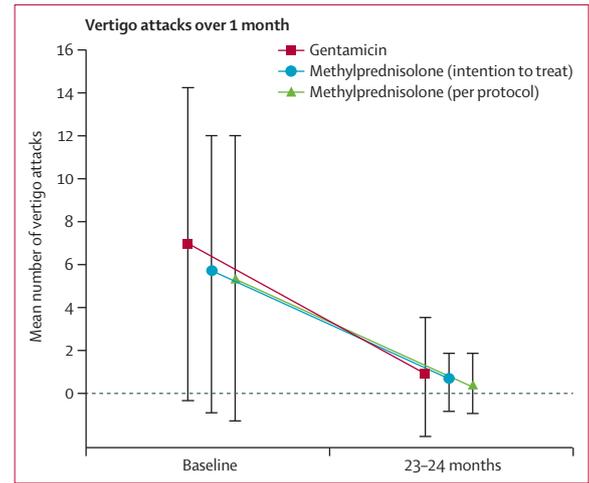Bars are SDs.

Figure 3: Mean number of attacks of vertigo in the 1 month before treatment and in the final 1 month
Bars are SDs.

also no significant difference between drugs for speech discrimination (drug p=0·79; drug×time interaction p=0·13; figure 5; table 2), although there were significant fluctuations over the 24-month follow-up (p=0·03). Between baseline and 24 months, speech discrimination decreased in the gentamicin group (9%) and increased in the methylprednisolone group (15%).

AAO-HNS outcomes[13] are presented in the appendix (pp 7–8). There were no differences between the intention-to-treat analysis reported here and the AAO-HNS outcomes, except for speech discrimination. Eight of 30 patients in the methylprednisolone group compared with three of 30 in the gentamicin group experienced a clinically meaningful improvement in speech discrimination (odds ratio 0·31, 95% CI 0·1–1·3), and three of 30 patients in the methylprednisolone group compared with nine of 30 in the gentamicin group experienced clinically meaningful worsening (3·9, 0·9–16·0). The number of patients with improvement versus worsening of speech discrimination per group was compared statistically and showed a significant advantage for methylprednisolone over gentamicin (χ² p=0·02; followed up with a Fisher's exact test p=0·039). Results were similar when analysed per protocol (χ² p=0·01; appendix pp 7–8).

Further injections were needed for eight (27%) non-responders in the gentamicin group and 15 (50%) in the methylprednisolone group (odds ratio 0·36, 95% CI 0·1–1·1). The two patients in the methylprednisolone group who crossed over and were deemed treatment failures also needed further courses of gentamicin. There was no significant difference between the number of non-responders in the gentamicin group and the methylprednisolone group (χ² p=0·06). In a post-hoc analysis, the time before further injections were needed was 12·0 months (SD 3·6) in the gentamicin group and 9·4 months (4·3) in the methylprednisolone

group. An independent samples *t* test showed no significant difference between groups (mean difference −2·6, 95% CI −5·9 to 0·7; p=0·17).

The total number of injections per patient was 2·7 (SD 1·7) in the gentamicin group, and 3·7 (2·5) in the methylprednisolone group in the intention-to-treat analysis and 3·2 (1·6) in the per-protocol analysis. Independent samples *t* tests showed no significant difference between drugs for the total number of injections needed in the intention-to-treat (mean difference 1·0, 95% CI −0·1 to 2·1; p=0·09) or per-protocol analyses (0·5, −0·4 to 1·3; p=0·32).

There were no suspected unexpected serious adverse reactions, serious adverse reactions, or serious adverse events. Six patients reported one adverse event each: three in the gentamicin group and three in the methyl-prednisolone group. The most common adverse event was minor ear infections, which was experienced by three patients: one in the gentamicin group and two in the methylprednisolone group. One patient in each group refused further injections after the first for pain. Tympanoplasty was not needed for any patient, nor was there any evidence of persistent perforations. This finding was verified by tympanometry before caloric testing at 1, 2, 12, and 24 months of follow-up.

At each injection, we asked patients to score pain from 0 to 10 (0=no pain, 10=unbearable). In a post-hoc analysis, mean pain score for the first injection was 4·6 (SD 3·0) with gentamicin and 6·0 (2·7) with methylprednisolone. In an independent samples *t* test the mean difference between groups for pain from the first injection was −1·4 (95% CI −2·9 to 0·0; p=0·053). For the second injection, mean pain score was 4·6 (SD 3·4) with gentamicin and 5·0 (2·9) with methylprednisolone and an independent samples *t* test showed no significant difference between drugs for pain (95% CI −2·1 to 1·2; p=0·61).
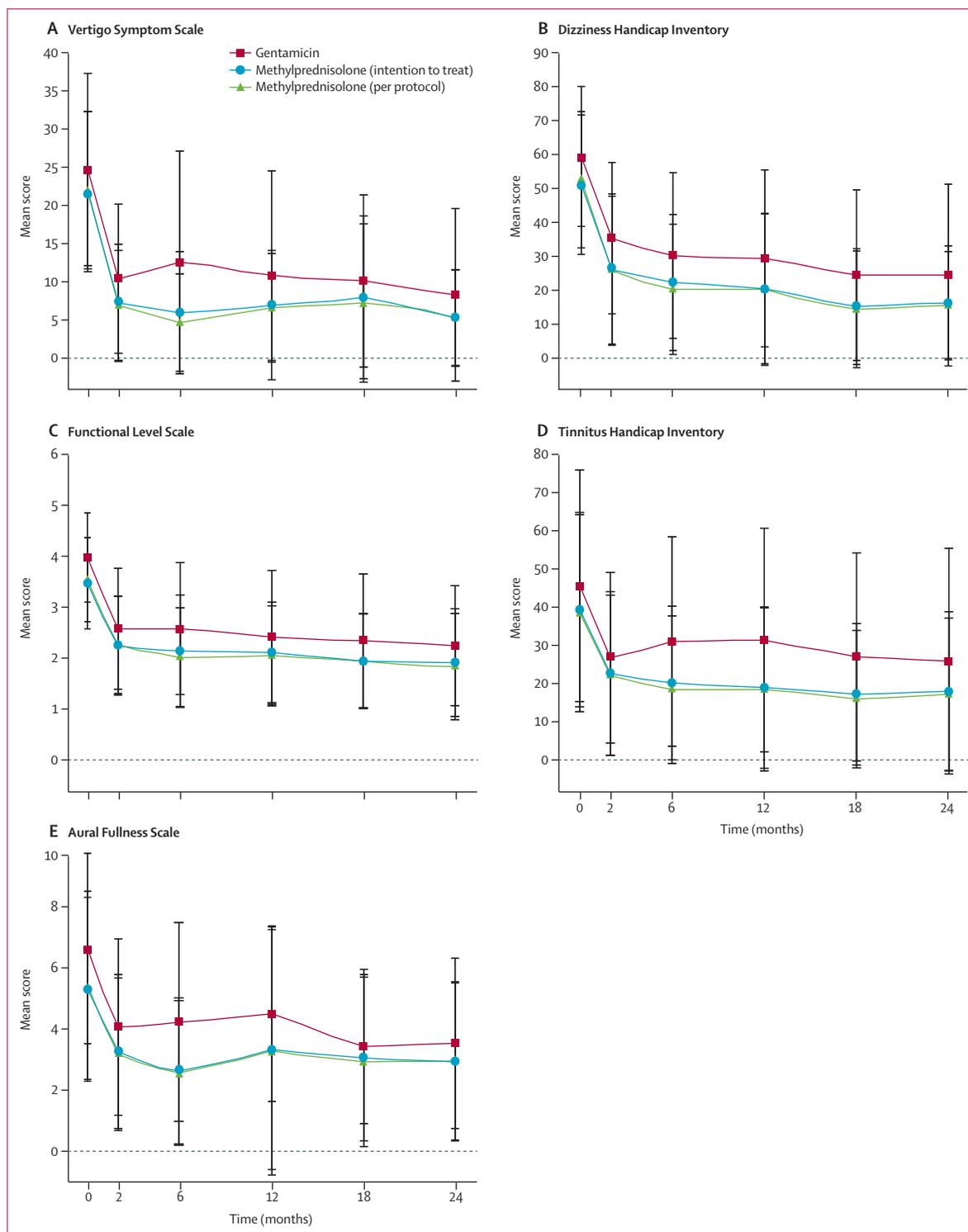
Figure 4: Mean scores for (A) Vertigo Symptom Scale, (B) Dizziness Handicap Inventory, (C) Functional Level Scale, (D) Tinnitus Handicap Inventory, and (E) Aural Fullness Scale at each timepoint
Bars are SDs.

A double-blind hearing test was done before the second injection to screen for hearing loss. 14 of 60 patients had substantial hearing loss: nine (30%) after gentamicin treatment and five (17%) after methylprednisolone treatment (odds ratio 2·1, 95% CI 0·6 to 7·4; p=0·22).
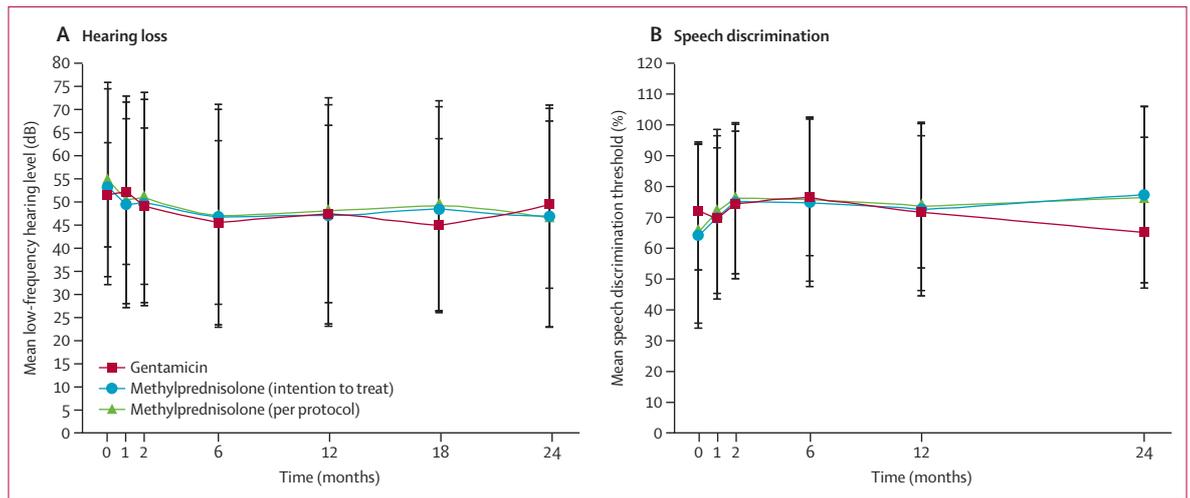
Figure 5: **Mean (A) low-frequency pure tone audiometry level and (B) speech discrimination threshold over the 24-month follow-up**
Bars are SDs.

In a post-hoc analysis, severe vertigo and vomiting 3–7 days after injection developed in eight (27%) patients after gentamicin and one (3%) after methylprednisolone treatment (odds ratio 10·5, 95% CI 1·2–90·7; p=0·01).

Vestibular tests showed ablation of vestibular function after gentamicin but not methylprednisolone injections (appendix p 8). Accordingly, vestibular function was significantly different between gentamicin and methyl-prednisolone groups, as described in the appendix (p 8) for all tests (caloric canal paresis, vestibular evoked myogenic potentials, and utricular centrifugation).

Discussion

In this double-blind, randomised controlled trial, we found no significant difference between gentamicin and methylprednisolone at controlling vertigo. The overall reduction in vertigo attacks in the final 6 months of follow-up compared with the 6 months before treatment was 90% for methylprednisolone injections and 87% for gentamicin, far higher than expected for spontaneous remission.[22] The number of vertigo attacks was similar between groups for the final 1 month, in the final 1 month compared with the 1 month before treatment, and in per-protocol analyses over both 6 months and 1 month.

For the secondary outcomes, scores were significantly reduced with both drugs for all validated vestibular questionnaires used (VSS, DHI, and FLS). In addition to long-duration vertigo attacks, these questionnaires incorporate several additional factors, including short-duration attacks (VSS_V) as well as function-based, psychological, and autonomic components (FLS, VSS_A, and DHI), which all add to the aggregate disability of these patients. Most of the reduction in symptoms occurred sharply at the first follow-up 2 months after the injections and, from then on, levels remained constant up to trial conclusion at 24 months. Pure-tone audiometry

and speech discrimination also did not differ between the two drugs, although some evidence of better discrimination was suggested for methylprednisolone over gentamicin; according to AAO-HNS trial-reporting recommendations,[13] more patients experienced a clinically meaningful improvement and fewer patients experienced a clinically meaningful drop in speech discrimination after methylprednisolone compared with gentamicin, a difference previously noted in an unmasked study.[9]

In view of the disabling nature of the vertigo attacks in Ménière's disease, we felt that depriving patients who did not respond to the initial programmed two injections from further treatment would be unethical. Therefore, patients experiencing two or more vertigo episodes lasting more than 20 min (ie, non-responders) received one to ten new injections, but we found no significant difference between drugs for the mean number of injections per patient or number of non-responders over the 2-year follow-up period, both for the intention-to-treat and per-protocol analyses.

Unpredictable attacks of vertigo are the main cause of disability in Ménière's disease;[1] accordingly, the primary outcome in this study was reduction in the number of vertigo attacks. Although non-invasive treatments for Ménière's disease are ineffective,[23,24] delaying semi-invasive treatments such as intratympanic injections for months or years is customary. This approach is reasonable for several reasons. First, Ménière's disease is notorious for spontaneous fluctuations and remissions.[22,25] Second, intratympanic gentamicin exerts its effects through its well known ototoxic properties.[26] Accordingly, patients and doctors are cautious before starting such treatment because acute iatrogenic vertigo, a permanent reduction in vestibular function, and hearing loss are possible after gentamicin injection.[3,27] Hearing loss was present in 25% of cases in a Cochrane review,[6] but was uncommon in

other meta-analyses.[28,29] Third, up to 50% of cases progress to bilateral Ménière's disease in the long term[30] and, therefore, inducing an audiovestibular deficit on one side with gentamicin is problematic if the other side might need similar treatment. For these reasons, intratympanic steroids have become a popular alternative because no permanent cochlea-vestibular damage is expected. However, neither a double-blind randomised controlled trial of the drugs nor consensus documents are available. Unsurprisingly, many otologists are sceptical about their value.[10,31]

Tests of vestibular function were not a trial outcome measure because they are generally poorly associated with clinical disability and symptom load.[32,33] However, they were an essential part of the study as an objective way of monitoring vestibulotoxic effects of the drugs or progression of the underlying disease, or both. In the case of gentamicin, findings from vestibular tests showed that the injected drug reached the inner ear and acted in the expectedly ablative manner. Conversely, as expected, methylprednisolone preserved vestibular function.

The action of gentamicin in the inner ear has been investigated extensively. Gentamicin accumulates predominantly in type 1 vestibular hair cells and causes subsequent atrophy of these cells as well as the whole of the neuroepithelium.[26] The action of steroids on the inner ear remains speculative.[34] Both glucocorticoid and mineralocorticoid receptors are present in the vestibular and cochlear systems. Steroids seem to have an effect on ion homoeostasis functions as well as immune modulation[35] via both types of receptor. They also have an effect on aquaporins,[35] a family of small transmembrane water transporters, and they play a part in regulating homoeostasis in the inner ear fluids. Furthermore, steroids have an effect on absorption and osmotically coupled water flux.[16,36]

A main strength of this trial is the long-term follow-up of patients (2 years) in an attempt to minimise the effect of the natural fluctuations in this disorder, in line with current recommendations.[13] Most studies comparing these drugs have several limitations, including a retrospective approach, unbalanced patient numbers, underpowered, poor follow-up, and absence of randomisation and masking.[5,6] Notwithstanding these drawbacks, some studies have reported good results using intratympanic steroids[8,37] and some evidence of better hearing outcome with steroids,[8] as we found in this study. The impression that gentamicin, in contrast to steroids, is a definitive treatment is not supported by our results; additional injections were needed in eight of 30 patients who received gentamicin and this could reflect variable rates of diffusion through the round window or different susceptibility of the labyrinthine epithelium in different patients.[38,39]

The absence of a placebo control group and the retrospective collection of pre-treatment phase symptoms are potential limitations of this study. However, to be left untreated for 2 years or 6 months, respectively, would

have been unethical and not acceptable to patients in severely symptomatic stages of the disease. Another possible limitation is the potential for loss of masking because methylprednisolone injections are more painful than gentamicin whereas gentamicin is more likely to induce a prolonged vertigo episode. However, at the time of the injection all patients were told that "it might sting" and that if they experienced vertigo they should "continue doing the rehabilitation exercises and it will all settle with time" (appendix p 2). No patient identified which drug they received on the basis of their side-effects. Similarly, no masked researcher was confident about which drug a particular patient received and the matter was never discussed between patients and researchers. Finally, in view of the fluctuations associated with the disease, a longer duration of follow-up would be desirable, but here we have complied with the minimum recommendations of the AAO-HNS for trial reporting in Ménière's disease.

In summary, steroid injections are a non-ablative, safe, and effective treatment for refractory Ménière's disease. Patients and clinicians have a choice of two effective treatments, but, on the basis of clinical knowledge and patterns in our data, either drug might be favoured in different circumstances. For instance, for a patient with no geographical access to repeat injections, who is not afraid of a gentamicin-induced vertigo attack, and who does not rely professionally on hearing (eg, a non-musician), gentamicin might be appropriate. For a patient with easy access to further injections who is concerned about any further hearing loss and who does not wish to experience a vertigo episode after gentamicin injection, intratympanic methylprednisolone seems more appropriate.

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