Structured Abstract

Objectives:

1) To determine whether long term (>48 months) symptomatic vertigo control is sustained in patients with Menière's disease from a previous comparative trial of intratympanic methylprednisolone versus gentamicin, and 2) if the two treatments remain non significantly different at long-term follow-up.

Study Design:

Mail survey recording vertigo frequency in the previous one and six months, further intratympanic treatment received, and validated symptom questionnaires.

Setting:

Outpatient hospital clinic setting.

Patients:

Adult patients with definite unilateral refractory Menière's disease, who previously received intratympanic treatment in a comparative trial.

Intervention:

A survey of trial participants who received intratympanic gentamicin (40mg/mL) or methylprednisolone (62.5mg/mL).

Outcome measures:

Primary: number of vertigo attacks in the 6 months prior to receiving this survey compared with the 6 months before the first trial injection.

Secondary: number of vertigo attacks over the previous 1 month; validated symptom questionnaire scores of tinnitus, dizziness, vertigo, aural fullness and functional disability.

Results:

Average follow-up was 70.8 months (standard deviation 17.0) from first treatment injection. Vertigo attacks in the 6 months prior to receiving the current survey reduced by 95% compared to baseline in both drug groups (intention-to-treat analysis, both $p<0.001$). No significant difference between drugs was found for the primary and secondary outcomes. Eight participants (methylprednisolone =5 and gentamicin=3) required further injections for relapse after completing the original trial.

Conclusion:

Intratympanic methylprednisolone treatment provides effective long-lasting relief of vertigo, without the known inner-ear toxicity associated with gentamicin. There are no significant differences between the two treatments at long term follow up.

Introduction

Menière's disease is a chronic relapsing-remitting labyrinthine disease which significantly impacts patients' quality of life, causing unpredictable attacks of vertigo, tinnitus, aural fullness and hearing loss. [1]

Randomized controlled trials have not demonstrated high-level evidence for non-invasive medical treatments (e.g. lifestyle counselling, low-salt diet, betahistine, diuretics, pressure pulse treatments), despite these being the first-line management commonly recommended by clinicians. [2-6] The evidence against prophylactic betahistine use in particular has been bolstered by the BEMED trial which found no reduction in vertigo attacks compared with placebo.[7] A recent international consensus document has supported intratympanic steroids (ITS) as appropriate second-line management when non-invasive treatments have failed, but despite this there remains scepticism in the literature regarding steroid treatment.[6,8-13]

Between 2009 and 2015 we carried out a prospective double-blind randomized comparative effectiveness trial of intratympanic injections of methylprednisolone versus gentamicin for unilateral refractory Menière's disease with two year follow-up of vertigo control and audio-vestibular function.[14] The trial concluded that the primary outcome, vertigo control, was equal in both treatment arms, thus providing the first high level evidence in support of the use of intratympanic methylprednisolone.

Based on the results of the original trial, the aim of the current study was to examine, in the same patient cohort, the effect of intratympanic treatment on refractory Menière's disease symptoms, beyond the 1995 American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS) guidelines on extended reporting (48 months from baseline).[1] Our aim was to

investigate whether the initial treatment effects were sustained, and whether any further treatments were required. An examination of long-term treatment effects is pertinent in Menière's disease because spontaneous relapse and remission is part of the natural history of the disease.[15]

Materials and Methods

Adult patients with definite unilateral Menière's disease, refractory to standard non-invasive treatments, who took part in a trial of intratympanic methylprednisolone versus gentamicin, completed in April 2015 [9], were invited to complete a follow-up survey 48-95 months (mean 70.8, SD17.0) after baseline treatment and contacted by post, email and/or telephone.[1,6,14] In the original double blinded study patients were randomly assigned (1:1) to two injections of either intratympanic methylprednisolone (62·5 mg/mL) or gentamicin (40 mg/mL); the second injection was 2 weeks after the first. Exclusion criteria included vestibular migraine.[8]

After the trial period ended some patients received further injections. These were carried out locally in many cases, did not necessarily follow trial injection protocol, and were un-blinded as patients had been told their original trial drug treatment by that time.

Methylprednisolone was originally chosen rather than dexamethasone because the former reaches high endo- and peri-lymphatic concentrations, has greater mineralocorticoid receptor binding and because high-dose dexamethasone (24 mg/mL) is not readily available in the UK and other countries.[16-18]

56 of the original 60 patients recruited were available to be contacted: one withdrew;

another was lost to follow-up after the original study; two died of unrelated causes.

The survey asked patients “How many attacks of rotational vertigo (lasting more than 20 minutes) have you had in the past 6 months?” and “How many attacks of rotational vertigo (lasting more than 20 minutes) have you had in the last month?” Patients also scored the severity of their symptoms in the 1 month prior to receiving the current survey with the same validated questionnaires used in the original trial: Vertigo Symptom Scale short form (VSS)[19], Dizziness Handicap Inventory (DHI)[20], Functional Level Scale (FLS)[1], Tinnitus Handicap Inventory (THI)[21] and Aural Fullness Scale (AFS)[22]. Patients were also asked whether further intratympanic injections or other treatments had been received after the original trial. In the original trial patients experiencing two or more vertigo episodes lasting more than 20 min (i.e. non-responders) received further injections, as it was deemed unethical not to do so. After the trial some patients similarly sought and received further injections either locally or through the original trial centres. We recorded where possible (from patient questionnaire responses) whether further injections were the same as their original trial treatment or if they crossed over to the other drug group.

Primary and secondary outcomes were the same as those from the original study except for hearing and speech discrimination levels, which were not available in this follow-up study.[14] The primary outcome was relief from vertigo (number of vertigo attacks in the 6 months prior to receiving the current survey (long-term follow-up) compared with the 6 months before the first injection (baseline). Secondary outcomes were number of vertigo attacks over 1 month at long-term follow-up compared with Baseline and symptom scores (VSS, DHI, FLS, THI and AFS).

Repeated-measures general linear model ANOVA was used, with factor labels ‘drug’

(methylprednisolone versus gentamicin), 'time' (baseline versus 24 months versus long-term follow-up), and drug x time interactions. Analyses were done in the intention-to-treat population and then per protocol. Paired t-tests were used to explore within group effects. Independent-samples *t* tests were used to assess differences between groups and chi-square analysis to compare the number of patients given further intratympanic injections after baseline treatment. Chi-square and exact tests were employed where relevant for categorical data. All analyses were done in SPSS, version 24.

All patients provided written informed consent before enrolment in the original trial, which was approved by the London-Fulham Research Ethics Committee, Imperial College Joint Research Compliance Office, and the Medicines and Healthcare Products Regulatory Agency. This study was done in accordance with the Declaration of Helsinki and International Council for Harmonisation's Good Clinical Practice.

Results

46 patients (23 female) completed the follow-up survey (77% response rate). There was no evidence of selection bias in those who were followed up; analysis of baseline characteristics of the long term follow-up sample demonstrated that it was representative of the entire original sample. There were also no significant baseline differences between the two treatment groups in the current study (independent-samples t tests, Table 1).

Primary Outcome:

In the intention-to-treat analysis, the mean number of vertigo attacks in the past 6 months at long-term follow-up compared with baseline decreased from 18.3 (SD 15.6) to 1.0 (SD 2.4) in the gentamicin group (95% reduction, p<0.001, paired *t* test analysis) and from 16.2 (SD 13.5) to 0.8 (SD 2.6) in the methylprednisolone group (95% reduction, p<0.001; mean difference at follow-up -0.2, 95% CI -1.3 to 1.7). There was no significant difference between treatment groups for the number of vertigo attacks over 6 months at baseline, 24 months or long-term follow-up (drug p=0.52; drug x time interaction p=0.90, primary outcome), Figure 1. An independent-samples *t* test confirmed no significant difference for the number of attacks of vertigo over 6 months between the two treatment groups at long-term follow-up (p=0.80).

Secondary Outcomes:

The mean number of vertigo attacks in the past 1 month at long-term follow-up compared with baseline decreased in the gentamicin group by 95% and in the methylprednisolone group by 99% (both p<0.001, paired *t* test analysis). There was no significant difference between treatment groups for the number of vertigo attacks over 1 month at baseline, 24 months or long-term follow-up (drug p=0.73; drug x time interaction p=0.59), Figure 2A. An independent-samples *t* test confirmed no significant difference for the number of attacks of vertigo over 1 month between the two treatment groups at long-term follow-up (p=0.85).

No significant difference was found between treatment groups for VSS score (drug p=0.19, drug x time interaction p=0.99), DHI score (drug p=0.33, drug x time interaction p=0.98), THI score (drug p=0.78, drug x time interaction p=0.93), AFS score (drug p=0.21, drug x time

interaction p=0.52) and FLS score (drug p=0.27, drug x time interaction p=0.71), Figure 2B-F. Independent-samples *t* tests showed no significant differences between the two treatment arms for any of the symptom questionnaires at long-term follow-up.

The per protocol analysis performed for primary and secondary outcomes confirmed the results of the intention-to-treat analysis; there were no significant differences between the two treatment groups.

Post-trial treatments:

Between baseline treatment and long-term follow-up, 13/22 patients (59%) in the methylprednisolone group had further injections to re-establish vertigo control and 9/24 patients (37%) in the gentamicin group (odds ratio 2.4, 95% CI 0.74 to 7.88; chi-square p=0.14, Fisher's exact test p=0.24). 8/46 patients had further injections between the 24 month follow-up and long-term follow-up. Of these 8 patients, 5 were from the methylprednisolone group, which included 1 new patient who had not previously required further treatment between baseline and 24 months follow-up, and 3 were from the gentamicin group, with 1 new patient (odds ratio 2.1, 95% CI 0.43 to 9.87; chi-square p=0.36, Fisher's exact test p=0.45).

Discussion

In this long-term follow-up study, we established that methylprednisolone and gentamicin are both equally effective for long-term vertigo control in unilateral refractory Menière's disease. The overall reduction of vertigo attacks at long-term follow-up compared to the 6 months prior to initial treatment was 95% for both methylprednisolone and gentamicin. There were also significant reductions for the secondary outcomes, number of vertigo attacks over a 1 month period and audio-vestibular symptom questionnaires, with no difference between the two drugs.

Our aim was to provide robust long-term evidence for the role of ITS treatment in this disease. Cochrane published the first systematic review of ITS for Menière's disease in 2011, and at that time only one small placebo controlled study was included, which provided limited support to using ITS treatment.[22,23] Cochrane reviews of other non-ablative treatment modalities (betahistine, diuretics, positive pressure therapy) have all concluded that there is insufficient evidence to support their use.[4,24,25] This is likewise the case for endolymphatic sac surgery.[26] Ablation with intra-tympanic gentamicin and vestibular nerve section, although shown to be effective for vertigo control, carry the added concern of non-neglibible hearing loss.[26-29] Dose-dependent hearing loss has been discussed, however, in recent studies with IT gentamicin, which have revealed that hearing outcomes can be comparable to IT steroids.[13,14]

A literature review of ITS for Menière's disease was undertaken by one of our co-authors in 2017.[30] 12 studies (6 prospective) meeting AAOHNS reporting guidelines were identified, of which 8 have been published since the 2011 ITS Cochrane paper. The review found results for over 600 patients treated with ITS (methylprednisolone or dexamethasone, with varying

doses/protocols, including 8 'as needed' study protocols) reporting median percentage of complete vertigo control (AAOHNS Class A) at 2 years follow-up of 71% (IQR 42-81%). No significant reduction of hearing was identified in any study. In a previous retrospective study with long follow-up (8 years) investigating intratympanic dexamethasone, it was found that there was a plateau of satisfactory vertigo control beyond 2 years follow-up.[31] To date our study has the longest follow-up reported for intratympanic methylprednisolone injection in Menière's disease and our results support these previous findings for dexamethasone. In 2017 Masoumi et al. published a randomised trial in 69 patients of intratympanic methylprednisolone versus intratympanic dexamethasone. The trial used the AAOHNS outcomes criteria for Menieres research. They identified no statistically significant difference between vertigo control in the two drug groups, but methylprednisolone showed statistically significant hearing improvement.[32]

As we have highlighted the main strengths of our study are the length of follow-up, as well as the high response (participation) rate of 77% from the original trial participants. Although not reaching statistical significance, there was a trend for a higher frequency of repeat injections required in the methylprednisolone than in the gentamicin group as perhaps expected, and recently reported in a retrospective series (n=33) using dexamethasone.[13]

We acknowledge that there are several limitations with this follow-up study, including the absence of a placebo arm. It was felt that it would have been unethical to leave patients in the severely symptomatic stage of Menière's Disease untreated for up to 2 years, particularly in view of the 2014 gentamicin Vs placebo RCT which was stopped early and the 2011 Cochrane review.[27,28] Similarly, there were ethical reasons for not collecting

prospective treatment-free symptom diaries in this significantly symptomatic group. The recognised limitation of recall bias which this has incurred, both in the retrospective collection of pre-baseline symptoms and the post-trial postal-survey reported here has been looked at in a recent paper by authors in our group.[33] In that study patients with Menière's Disease were asked to recall the number of attacks that they had experienced over 6 months and 1 month, and the number recalled was consistent with those produced from the large scale BEMED Menière's Disease intervention trial in which patients used a diary to record disease activity.[7] We would also argue that any recall bias would affect both drug groups equally, and the original trial and long-term follow-up study equally as the same methodology was used throughout.

Another limitation is that the number of patients involved, particularly for long-term follow-up, is not large and that prospective hearing assessment at long-term follow-up was not carried out. Attempts were made to collect recent audiology for patients by contacting their local health provider but numbers obtained were too small to include in our analysis. Similarly, detailed information about further injections (drug regimen used and date administered) after the formal 2 year trial had ended was limited and this is a confounder which could alter the results obtained. We are likewise unable to comment upon the amount of vertigo or other criteria used by different doctors for deciding when to perform repeat injections. These limitations reflect the transition of this study from recording results in the controlled setting of a clinical trial with research subjects, to retrospective analysis of clinical observations in a cohort of patients.

In summary, intratympanic methylprednisolone injections are safe and effective in

managing refractory Menière's disease, and provide excellent long-term symptom control. The choice between methylprednisolone and gentamicin, two equally effective treatments, should be made based on individual patient circumstances, and in particular, their hearing thresholds. In patients with mild to moderate hearing loss the possible risk of gentamicin ototoxicity may favour the initial use of intratympanic methylprednisolone.[27,34]

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FIGURE LEGENDS

Figure 1. Mean number of attacks of vertigo at Baseline (within the 6 months before treatment), at 24 months and at long-term follow up (>48 months). Bars are SDs.

Figure 2: Mean scores for Secondary outcomes (A) Mean number of attacks of vertigo 1 month before treatment at baseline (B) Vertigo Symptom Scale, (C) Dizziness Handicap Inventory, (D) Auditory Fullness Scale, (E) Tinnitus Handicap Scale and (F) Functional Level Scale before treatment at Baseline, 24 months and at long-term follow up (>48 months). Bars are SDs.