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Long-Term Follow-Up of Intratympanic Methylprednisolone Versus Gentamicin in Patients With Unilateral Menie`re's Disease

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Structured Abstract

Objective:

To determine whether long term (>48 months) symptomatic vertigo control is sustained in patients with Menière's disease who were involved in a previous comparative trial of intratympanic methylprednisolone versus gentamicin. This study also aims to determine if the two treatment arms remain similar at long-term follow-up, as original trial results at 24 months found no significant difference between drug treatments.

Patients:

Adult patients with definite unilateral refractory Menière's disease, who previously received either intratympanic methylprednisolone or gentamicin.

Intervention:

A mail survey of patient's symptoms was conducted to determine long-term follow-up results of trial participants who received random double-blind allocation of intratympanic injection of gentamicin (40mg/mL) versus methylprednisolone (62.5mg/mL).

Outcome measures:

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

Secondary outcomes: 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 the first treatment injection in the previous trial. In an intention-to-treat analysis, vertigo attacks in the 6 months prior to receiving the current survey reduced by 95% compared to baseline in both drug groups (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.

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. [1-31-31-3]

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. [4-8] Although a recent international consensus document has supported intratympanic steroids (ITS) as appropriate second-line management when non-invasive treatments have failed, there has been much scepticism in the literature regarding steroid treatment over the last two decades.[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

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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 two year comparative effectiveness trial of intratympanic methylprednisolone versus gentamicin, completed in April 2015 [9], were invited to complete a follow-up survey 48-95 months after baseline treatment and contacted by post, email and/or telephone.[1,8,14] 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.

In the original study patients were randomly assigned (1:1) and the trial was double blinded. The trial protocol involved two injections of either intratympanic methylprednisolone (62·5 mg/mL) or gentamicin (40 mg/mL), the second injection 2 weeks after the first. Those with a diagnosis of migraine were excluded.

After the trial period ended some patients went on to have 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. Patients were allowed to refuse additional treatment as it would otherwise be deemed

unethical.

Methylprednisolone was chosen rather than dexamethasone for scientific as well as practical reasons: higher endolymphatic concentrations, high perilymph concentrations, greater mineralocorticoid receptor binding and also 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 after the original study and before this follow-up survey.

In the survey we 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].

Lastly, patients were 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, based on the view that depriving patients from further treatment with disabling vertigo attacks who did not respond to the initial programmed two injections would be

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unethical. Following the end of 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. The exact details of what drug regimen was used in their local ENT unit, and date administered, was not 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.

Primary and secondary outcomes were the same as those from the original study except for hearing and speech discrimination levels, which were not included 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.

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, 22/46 patients received additional injections. 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). From this, 8/46 patients had additional injections between 24months and long-term follow-up (i.e., post-trial). 5/22 patients (23%) had further injections between the 24 month follow-up and long-term follow-up in the methylprednisolone group, which included 1 new patient who had not

previously required further treatment between baseline and 24 months follow-up, and 3/24

patients (13%) 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).

No safety concerns about either drug were raised.

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 treatment modalities

(betahistine, diuretics, positive pressure therapy, endolymphatic sac surgery) have all

concluded that there is insufficient evidence to support their use.[6,24-26]

A literature review of ITS for Menière's disease was undertaken by one of our co-authors in

2017.[27] 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

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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 (AAO-HNS Class A) at 2 years follow-up of 71% (IQR 42-81%). No significant reduction of hearing was identified in any study.

The previous longest follow-up of 8 years was in a retrospective study using dexamethasone, which found that there was a plateau of satisfactory vertigo control beyond 2 years follow-up.[28] 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.[29]

As we have highlighted the main strengths of this study are the length of follow-up, as well as the high response 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.

We acknowledge that there are several limitations with this 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.[30,31]

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.[32] 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.[33] 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.

The number of patients involved in this multicentre trial, and particularly the number available for long-term follow-up is not large, but reflects the incidence of this disease and the acknowledged response bias difficulties of using mail surveys, despite telephone and email contact to those who did not respond initially. Prospective hearing and formal balance testing/neurotological clinical examination at long-term follow-up was not in the scope of available resources in this unfunded follow-up study. Attempts were made to collect recent audiology for patients by contacting their local provider but numbers obtained were too small to include in our analysis. Similarly, detailed information about further injections after the formal 2 year trial had ended was limited by the patients being recruited nationally and thus had follow-up treatment with their local ENT unit.

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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 the known long-term risks of gentamicin ototoxicity.[31,34]

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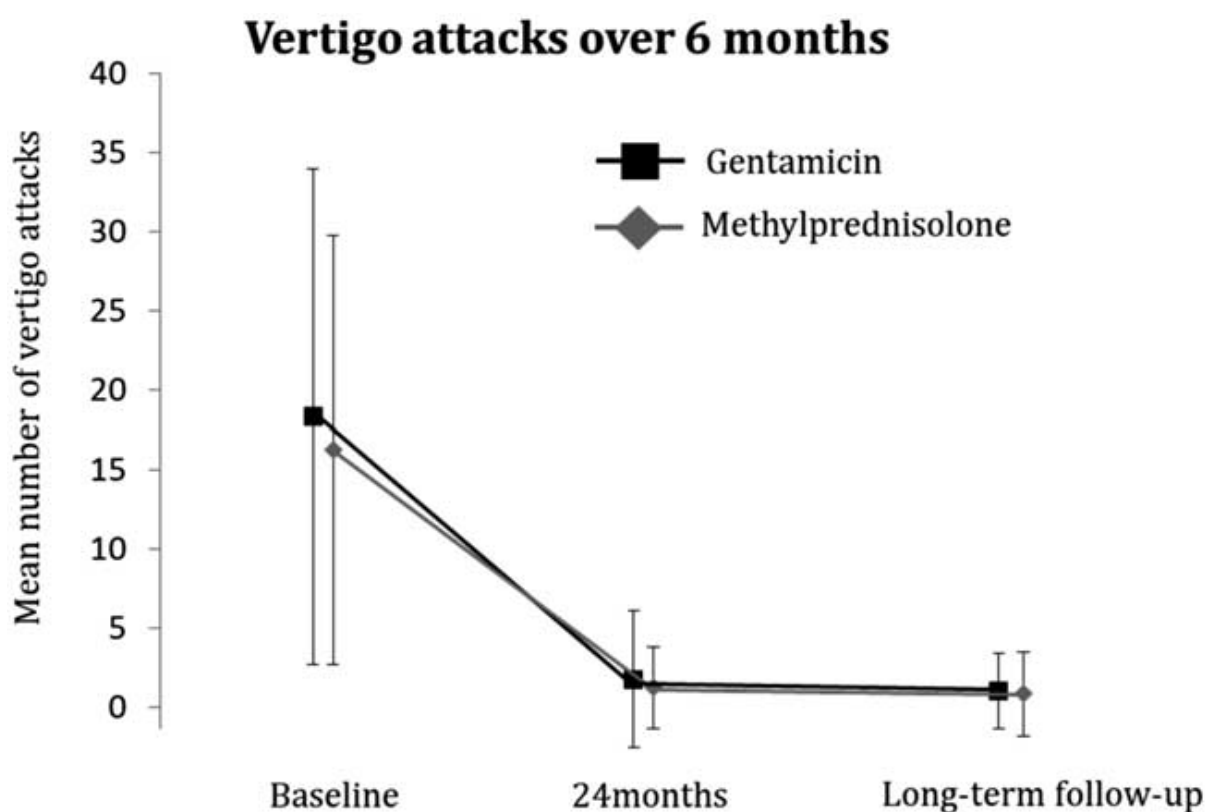
FIGURES

Figure 1. Mean number of attacks of vertigo at Baseline (within the 6 months before

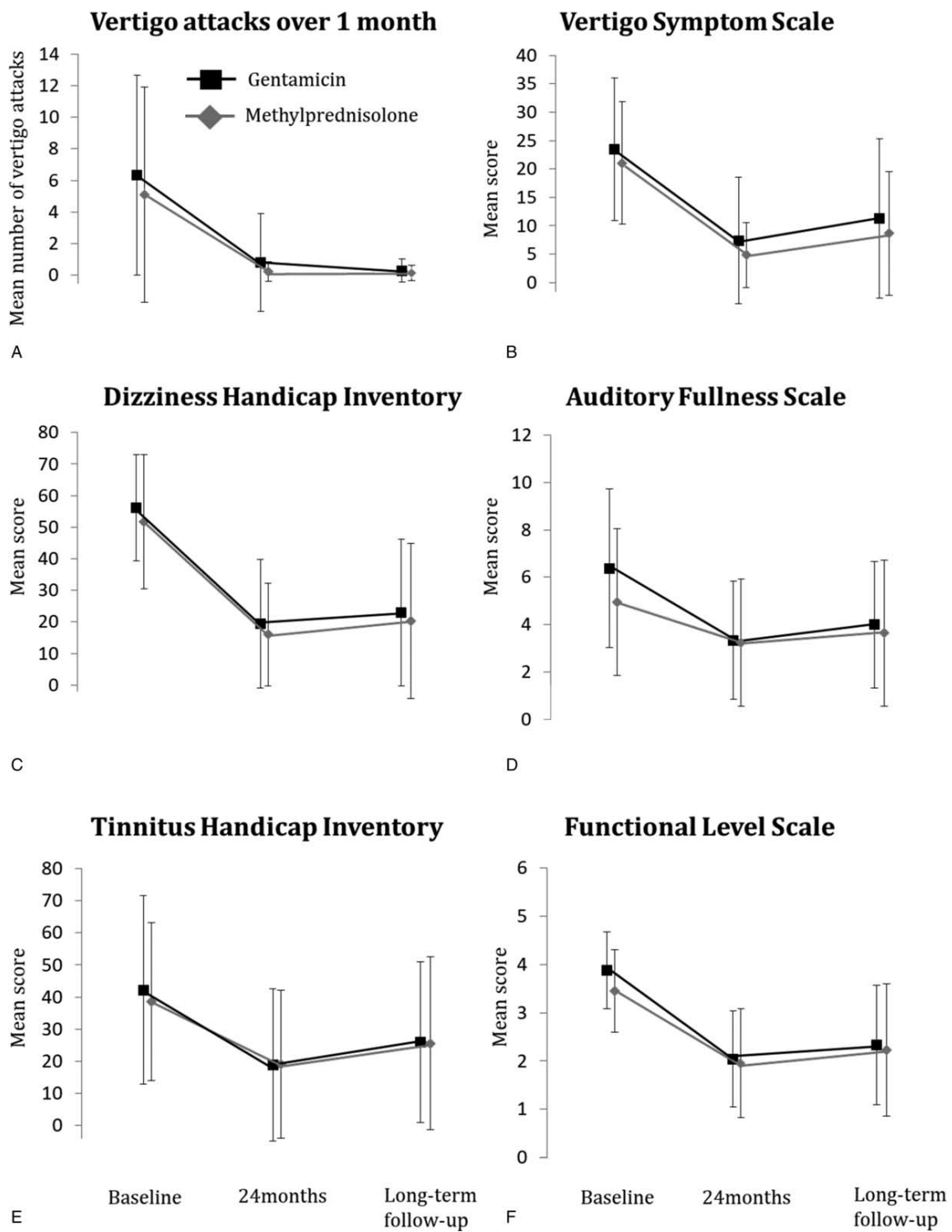treatment), at 24 months and at long-term follow up (>48 months). Bars are SDs.

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.