END OF TRIAL SUMMARY REPORT

07/04/16

Effectiveness of transtympanic steroids in unilateral Meniere's disease: A randomised controlled double-blind trial

Chief Investigator	Professor Adolfo Bronstein
EudraCT Number	2008-004803-78
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Funder(s)	Meniere's Society UK
Sponsor(s)	Imperial College Healthcare NHS Trust
Name of Test Drug/Investigational Product	Methylprednisolone (steroid)
Indication Studied	62.5mg/ml per injection

Chief Investigator: *Signature* _____ Professor Adolfo Bronstein

Date: 07-04-16 _____ DD-MM-YYYY

This trial study was carried out in compliance with International Conference on Harmonisation (ICH) and Good Clinical Practise (GCP).

Contents

List of Abbreviations and Definition of Terms

MD	Meniere's disease
AAO-HNS	American Academy of Otolaryngology – Head and Neck Surgery
VEMP	Vestibular evoked myogenic potentials
UCF	Utricular centrifugation
ENG	Electronystagmography
VSS	Vertigo symptom scale
AFS	Aural fullness scale
DHI	Dizziness handicap inventory
THI	Tinnitus handicap inventory
FLS	Functional level scale

1. Summary of Study

Background: This study compared intratympanic methylprednisolone (steroid) to gentamicin in intractable unilateral Meniere's disease. Intratympanic gentamicin is the current standard therapy for attacks of vertigo in unilateral Meniere's disease but can cause a loss of hearing and chronic symptoms of dizziness and unsteadiness. Intratympanic steroid can also reduce the number of attacks of vertigo without such side-effects. We performed a 2-year follow-up study comparing intratympanic steroid or gentamicin for unilateral Meniere's disease.

Trial Design: This was a double-blind randomised controlled study conducted at two UK sites, Charing Cross Hospital, London and Leicester Royal Infirmary, Leicester. Power calculations showed that thirty patients in the two arms were needed (n=60). The study recruited its target of sixty patients between 2009-2013 and were followed-up for two years during which time treatment was repeated or swapped if necessary. One patient was lost to follow-up at the six month stage (patient could not be contacted by any means) though a successful response to treatment was observed. One patient withdrew participation before treatment. Data is based on the fifty-nine patients who completed the two-year follow-up period. The study protocol was approved by the National Research Ethics Committee (London-Fulham) and interventions approved by the Medicines Health Regulatory Association (MHRA). The Sponsor of this study is Imperial College London, AHSC Joint Research Compliance Office, 5th Floor Lab Block, Charing Cross Hospital, Fulham Palace Road, London. W6 8RF.

Outcome measures: The primary outcome was control of vertigo in the final 6 months and 1 month of the two year follow-up compared to before treatment. Secondary outcome was change in hearing.

Eligibility criteria: Eligibility was definite or probable unilateral Meniere's disease with attacks of vertigo according to AAO-HNS guidelines not having responded to medical treatment for at least 6 months previous, between 18-70 years old, without severe disability or serious concomitant illness, other neuro-otological disorder, ear pathology which could interfere with treatment, history of adverse/allergic reactions to gentamicin or steroid. Other exclusions were pregnancy.

Methods: Patients were double-blindly and randomly assigned to a methylprednisolone (steroid, phase II) or gentamicin (phase III) arm from a pre-generated randomisation list designed by an external member of the group (DB) and held by pharmacy aseptic units. Patients were followed-up over a two-year period and audiovestibular assessments were performed at baseline (0 months), 1 month, 2 months, 6 months, 12 months, 18 months and 24 months. Audiovestibular tests were PTA, speech discrimination, caloric test, VEMP, UCF and ENG. VSS, DHI, THI, AF and FLS questionnaires were completed. Number of vertigo attacks before treatment (6 months and one month before) and after treatment (final 6 months and one month) were obtained.

Patients were assessed by an unblinded neurologist when vertigo attacks continued or returned during the two-year follow-up period. The consultant screened the patient for other conditions or bilateral involvement (no patient developed bilateral Meniere's disease in the course of this trial). The patient was deemed a non-responder if vertigo attacks were associated with relapse and prescribed a further course of double-blinded intratympanic injections made by aseptic unit, to begin on the same day. The clinician had the choice to prescribe the same drug or swap, basing this decision on the severity and frequency of vertigo attacks compared to before treatment and the patient's response to previous injections.

Results: The two arms were balanced at baseline for disease characteristics including mean numbers of attacks of vertigo. Two patients in the steroid arm experienced relapsing attacks of vertigo after further injections of

steroid and were crossed-over to the gentamicin arm. The results were analysed on an intention-to-treat basis and after removing the two drug failures; however no results were affected by removing the two patients from the statistical analysis. We found that both gentamicin and steroid significantly decreased the number of attacks of vertigo in the final 6 and 1 month of the trial compared to before treatment. There was no significant difference between the steroid and gentamicin arm. There was also no significant difference between steroid and gentamicin treatments over the 24 months follow-up for the secondary outcomes: Change in hearing. We found no difference in the number of injections required per patient between the steroid and gentamicin arms. Neither drug produced safety concerns.

Conclusions: The project achieved its objectives. In intractable unilateral Meniere's disease injections of gentamicin or steroid are equally as effective at reducing attacks of vertigo. Disability, measured with the Functional Level Scale, is improved equally so after steroid or gentamicin treatments. However, gentamicin treatment is well-known to have side-effects; the potential for hearing loss and acute vertigo and dizziness which could lead to chronic dizziness and being unsuitable in bilateral Meniere's disease owing to its ablative action.

2. Ethical Review

The study protocol and amendments were approved by the National Research Ethics Committee (London-Fulham) and interventions approved by the Medicines Health Regulatory Association (MHRA). The study was sponsored by Imperial College London, AHSC Joint Research Compliance Office, 5th Floor Lab Block, Charing Cross Hospital, Fulham Palace Road, London. W6 8RF. The study was conducted in accordance with GCP principles and the Declaration of Helsinki and Imperial College London procedures.

3. Introduction

Background: Intratympanic gentamicin is a proven to reduce or prevent attacks of vertigo in intractable unilateral Meniere's disease. However, well recognised limitations include the risk of hearing loss, acute vertigo and the potential development of chronic dizzy symptoms. New indications suggest that intratympanic steroid has the potential to suppress vertigo episodes without such side-effects. For this reason intratympanic steroid is regarded as a potential substitute for gentamicin therapy in unilateral Meniere's disease, yet no definitive comparison of these treatments exists. Here, we address the gap in knowledge by conducting the first randomised controlled double-blind clinical trial comparing intratympanic gentamicin and steroid.

Objectives:
The main objectives were:
1). To clarify the effectiveness of intratympanic steroid vs the more established gentamicin for vertigo control in a controlled study.
2). Compare the effects of intratympanic steroids and gentamicin on hearing.
Both objectives were achieved in this study.

4. Methods

Primary and Secondary outcomes: The primary outcome was number of attacks of vertigo in the final 6 months and 1 month of the two year follow-up compared to before treatment. Secondary outcome was change in hearing.

Trial design: This was a double-blind randomised controlled study comparing the effectiveness of methylprednisolone (steroid) to the current standard treatment gentamicin in the control of vertigo in MD. The treatment comprised two blind injections after confirmation of diagnosis from pre-evaluation tests. We monitored disease characteristics over a two year follow-up period, that is hearing and vestibular function and questionnaires on the disease symptoms. Informed consent was taken before randomisation as shown in Figure 1. Based on power calculations, 60 patients in total (30 patients in each drug arm) were needed to achieve good statistical power (5% significance, 80% power).

The patients were initially fully assessed and informed and provided written information sheets. The two treatment injections were allocated randomly and administered intratympanically under local anaesthesia in a double-blind manner to patients with refractory Meniere's disease. The pharmacy retained a randomisation list, allocating subject numbers (1-60) to the starting medication, either methylprednisolone or gentamicin.

- Methylprednisolone – Administered intratympanically. Methylprednisolone is a synthetic cortico-steroid drug. It has predominant anti-inflammatory properties with some anti-allergic and mineralocorticoid effects. The treatment is 2 doses (spaced 2 weeks apart) of 1ml of 62.5mg/ml.

- Gentamicin – also administered intratympanically. Gentamicin is commonly used as an antibiotic but used for its vestibular suppressant action, i.e., reducing vestibular function and vertigo attacks. There is central compensation of reduced vestibular function following treatment. The treatment is 2 doses (spaced 2 weeks apart) of 1ml of 40mg/ml.

In the case where there was a hearing loss of > 20db in two adjacent frequencies after gentamicin, the second injection was normal saline (Nacl 0.9%) NOT gentamicin. This hearing test was blindly performed by hospital audiologists and screened by the trial's audiological physician who instructed pharmacy to dispense the appropriate 2nd injection.

When vertigo attacks returned, the unblinded consultant decided on further management after fully re-assessing the patient. That is, re-injecting the patient with the same drug if it appeared to show signs of benefit or changing drug if there was no response. The number of courses of injections was not limited, though patients were free to decline treatment and remain on the trial. Re-injections were performed on the same day as consultation.

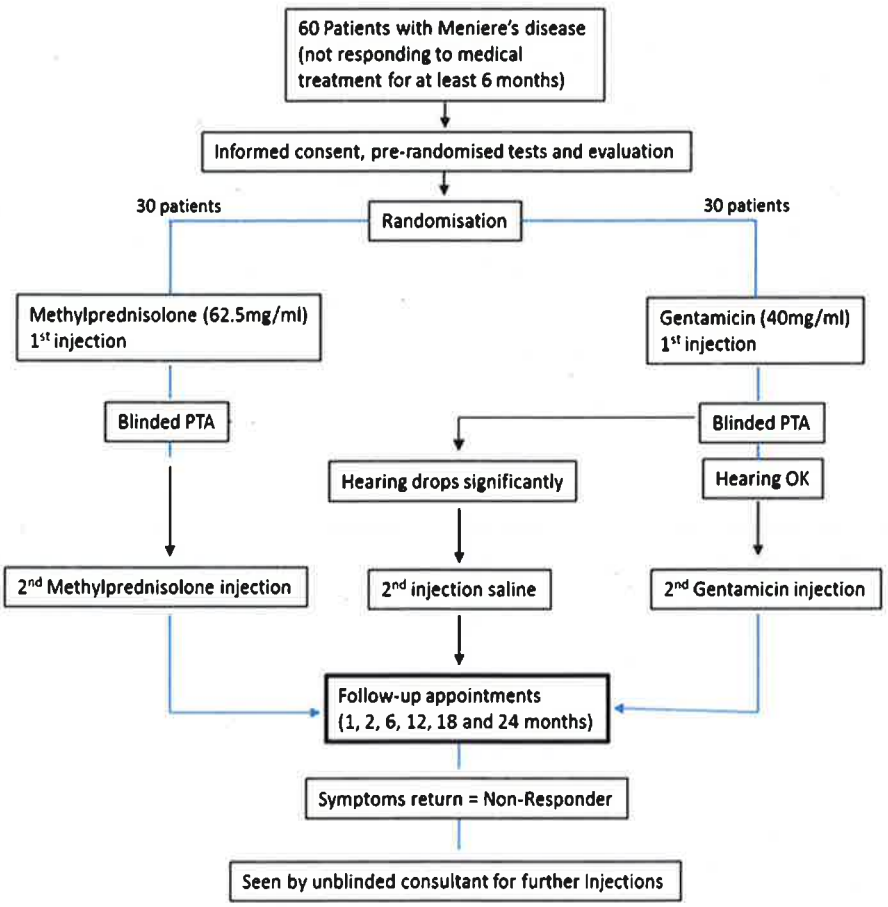


Figure 1: Trial design

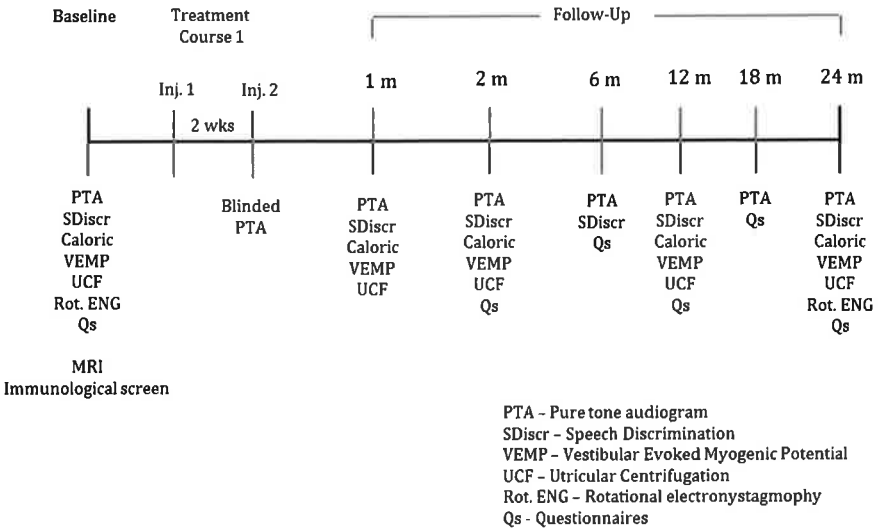


Figure 2: Follow-up schedule

Sample size and withdrawals: The study recruited its target of 60 patients from 2009-2013 in outpatient clinic settings. One patient withdrew from the study before treatment and the number allocated to this patient was re-used. The patient wished to pursue oral medication which is the basic treatment in MD. Fifty-nine patients provided the final outcome measure.

Changes to trial design: One protocol deviation (19.12.2009) was issued before the randomisation of the first patient. Oto-acoustic emission testing (OAE), which is another diagnostic test, was removed owing to non-availability of the test but is not relevant to the primary outcome.

Participants: The inclusion criteria for participation are patients between the ages of 18-70 with definite or probable Unilateral Meniere's disease (AAO-HNS criteria), hearing loss, recurrent spinning attacks of vertigo longer than 20 minutes each time, received medical treatment for at least 6 months and signing consent for participation. The exclusion criteria are concomitant illness preventing follow up or other active neuro-otological disorders and middle ear disease confirmed by MRI scan, family history of unexplained deafness, known allergic reactions to gentamicin or steroids or being pregnant. One patient was withdrawn at 12 months owing to loss of contact.

Study settings: The study was started at Charing Cross Hospital (Imperial College London Healthcare Trust), London, sponsored by Imperial College London. In September 2012, Leicester Royal Infirmary (University Hospitals of Leicester NHS Trust) was added as a secondary site to boost recruitment figures. Injections were performed by blinded, fully trained, ENT consultant surgeons at Charing Cross Hospital and Leicester Royal Infirmary. Study co-ordinators conducted all administration and tests in the Audiology and Balance departments at Charing Cross Hospital or Leicester Royal Infirmary.

Interventions: After randomisation, the intervention was administrated by way of two injections, spaced two weeks apart. To mask any clues about which drug was injected, the treatment protocol was identical for both drugs, i.e., two injections spaced two weeks apart per course. An unremarkable syringe containing the drug was provided by the hospital aseptic unit. A label with the participant's initials, trial ID number, trial name and injection number was attached to the syringe.

The treatments were injected intratympanically into the affected ear of the patient in a routine outpatient clinic.
The patients lay supine on a couch with the head turned away from the treated ear. The ear canal was sprayed with 2 to 3 squirts of Lidocaine spray (Xylocaine spray™ 10mg/spray). After 60 seconds the ear canal was completely aspirated. The injection syringe, provided by the pharmacy was attached to a 22Gauge spinal needle. Under microscopic control the needle was inserted in the inferior aspect of the pars tensa and the injection continued until a fluid level could be seen to fill the tympanic cavity. The patient was asked not to swallow or speak for 20 minutes. The volume of injected fluid was recorded. After this period they mobilized and left the clinic if there were no adverse symptoms. They were instructed to keep the ear dry for 3 days after the injection.

Drug continuation: Patients were advised to remain on any oral medication for Meniere's disease during the drug trial. Medications for other illnesses were not restricted and patients were advised to see their GP for general medical care. All medication was recorded before entry into the trial in each subject's Case Report Form.

Randomisation: The randomisation sequence was constructed using a block design by a technician who played no other part in the study.

The randomisation list containing patient details was retained by Charing Cross Hospital aseptic unit and later by Leicester Royal Infirmary aseptic unit. Upon consenting to the trial, the investigator completed a New Starter form for each patient and entered and ID number from 1-60. This number corresponded to a number on the randomisation list for the allocation of treatment. This record of the patient's details and their allocation was kept by the aseptic unit of the relevant hospital. Assignment of intervention was kept blind to all investigators and patients apart from the unblinded consultant.

Similarity of interventions: Measures were taken to ensure that the IMP (methylprednisolone) and control drug (gentamicin) were indistinguishable. They were delivered in identical syringes and injected with identical schedules and procedures.

Statistical methods: Demographic and baseline characteristics were compared between groups with paired t-tests (two sided) to check for similarity at baseline. Demographic characteristics were age, gender, disease duration and disease side. General linear model ANOVA (2x2 design) were performed to investigate the difference between pre and post treatment (time, 2 levels: Baseline vs 24months) and arm differences (arm, 2 levels: gentamicin vs steroid).

Analyses were performed firstly with the intention-to-treat population then again after removing patient failures. P-values were adjusted for multiple comparisons. All analyses were performed with SPSS version 21. Data were statistically analysed on an intention-to-treat basis and again after removing any drug failures; that is patients who crossed-over drug treatments. All data was complete for the primary outcome. For the secondary and tertiary outcome any missing data was filled in with the mean value.

Trial team

Chief Investigator & Trial Design: Professor Adolfo Bronstein (Professor of Neuro-Otology, Honorary consultant neurologist)
Secondary Investigators: Mr Jonny Harcourt (ENT consultant surgeon, Charing Cross Hospital) & Dr Mohamed Hariri (Audiology consultant, Charing Cross Hospital).
Study Co-ordinators: Dr Kiran Agarwal (19.06.09-25.07.11) & Mitesh Patel PhD (25.07-11-11.04.15)
Unblinded Consultant: Dr Barry Seemungal (Consultant neurologist Charing Cross Hospital)
Statistician & Trial design: Professor John Golding (Imperial College London & University of Westminster)
Principle Investigator at Leicester Royal Infirmary: Mr Peter Rea (ENT consultant surgeon).
Aseptic injection dispensing and pharmacy log: Andrea Davis-Cook (Charing Cross Hospital)

5. Main Findings of the Study

The intention-to-treat population comprised all 60 patients, 30 patients in the gentamicin arm (15 female, 12 right-sided) and 30 patients in the steroid arm (10 female, 13 right side).

Participant flow: During the study, one patient (subject 34, AC) was withdrawn one year into the two year follow-up stage as the patient was unreachable by any means (telephone/post). The patient received treatment which had a positive effect on symptoms. Before treatment this patient had experienced 42 attacks of vertigo in the preceding 6 months. After treatment, the number of attacks fell to 1, 6 months after treatment at the last time of contact. All other patients provided data at each follow-up assessment.

Two patients allocated to the steroid arm crossed-over to gentamicin during the follow-up period at 7 months and 18 months. Both patients were considered drug failures and were removed for the second analysis (by protocol, see supplementary appendix) which also showed no significant difference at baseline between patients in the two drug allocation arms.

Baseline data:

Baseline characteristics were not significantly different between the two drug allocation arms: i.e., the two arms were balanced (table 1).

Characteristic (Mean ± SD)	Gentamicin (n=30)	Methylprednisolone (n=30)
Age (Years)	53.3 (10.8)	51.6 (10.2)
Disease Duration (Years)	4.9 (5.6)	4.1 (3.2)
Baseline no. attacks (6 months)	19.9 (16.7)	16.4 (12.5)
Baseline no. attacks (1 month)	6.9 (7.3)	5.3 (6.5)
Pure-tone average (dB)	51.5 (11.3)	53.3 (21.2)
Speech discrimination (%)	72 (22)	65 (29)
Caloric asymmetry (%)	72 (22)	65 (29)
VEMP asymmetry (%)	31 (26)	30 (31)
UCF weakness (%)	14 (84)	41 (60)
Vertigo Symptom Scale (/60)	25 (13)	22 (11)
Dizziness Handicap In. (/100)	59 (21)	51 (21)
Aural Fullness Scale (/10)	6.6 (3.1)	5.3 (3.0)
Tinnitus Handicap In. (/100)	46 (30)	39 (25)
Functional Level Scale (/6)	4.0 (0.9)	3.5 (0.9)

Table 1: Baseline characteristics between the two drug allocation arms.

Outcomes and estimation:

Primary Outcome: *Vertigo control*

Almost all patients had a marked reduction of vertigo attacks at 24 months compared to baseline.

As shown in Figure 3A, in intention-to-treat analysis, the mean (± SD) number of vertigo attacks in the preceding 6 months at baseline was 19.9 ± 16.7 in the gentamicin arm and 16.4 ± 12.5 in the steroid arm. At 24 months, both arms had significantly fewer number of vertigo attacks in the preceding 6 months compared to baseline (P<0.001). The mean number of vertigo attacks fell to 2.5 ± 5.8 in the gentamicin arm and 1.6 ± 3.4 in the steroid arm. There was no significant difference between drug arms (no *time* x *arm* interaction; P=0.514).

The second analysis omitting the two failures in the steroid group showed that the number of attacks in the preceding 6 months at baseline was 16.8 ± 12.8 which fell significantly to 1.2 ± 3.1 at 24 months (*time;* P<0.001). There was no difference between gentamicin and steroid arms (no *time x arm interaction*; P=0.65).

Number of vertigo attacks in preceding 1 month

Figure 3B shows that for intention-to-treat, the mean (± SD) number of vertigo attacks in the preceding 1 month at baseline was 6.9 ± 7.3 in the gentamicin arm and 5.3 ± 6.5 in the steroid arm. At 24 months, both groups had significantly fewer number of vertigo attacks in the preceding 1 month compared to baseline (*time*; P<0.001). The mean number of vertigo attacks fell to 0.7 ± 2.8 in the gentamicin arm and 0.4 ± 1.4 in the steroid arm. There was no significant difference between drug arms (no *time* x *arm interaction;* P=0.65).

Omitting the two failures in the steroid arm showed that the number of attacks in the preceding 1 month at baseline was 5.5 ± 6.7 which fell significantly to 0.5 ± 1.4 at 24 months (*time*; P<0.001). There was no difference between gentamicin and steroid arms (no *time x arm interaction*; P=0.54).

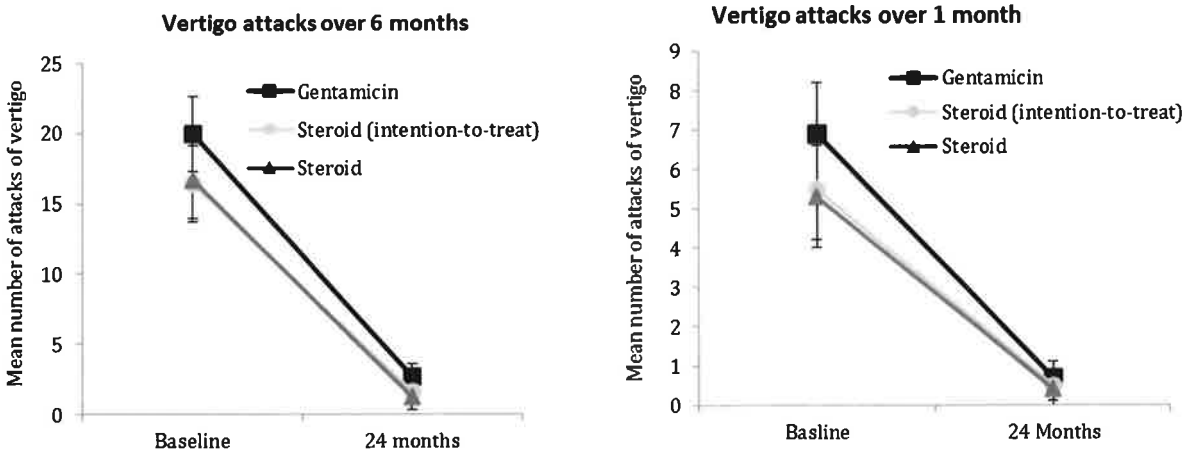


Figure 3: Mean ± SEM number of vertigo attacks for A. the preceding 6 months and B. the preceding 1 month at Baseline and at 24 months.

Vertigo symptoms, dizziness, tinnitus, aural fullness and functional level scale

Symptoms dramatically reduced two months after the first injection as shown in Figure 5. After this time, symptoms generally remained constant.

As shown in Figure 5A, Vertigo Symptom Scale mean scores significantly decreased over the 24 months follow-up in both arms for intention-to-treat (*time*; P<0.001) and after removing patient failures (*time*; P<0.001). There was no significant difference between arms for intention-to-treat (no *time x arm interaction*; P=0.74) or after removing patient failures (no *time x arm interaction*; P=0.37).

Figure 5B shows that Dizziness Handicap Inventory mean scores significantly decreased from baseline over the 24 months follow-up period in both arms for intention-to-treat (*time*; P<0.001) and after removing the patient failures (*time*; P<0.001). There was no significant difference between arms for intention-to-treat (no *time x arm interaction*; P=0.99] or after removing the patient failures (no t*ime x arm interaction*; P=0.99).

Figure 5C shows that Tinnitus Handicap Inventory mean scores significantly decreased from baseline over the 24 months follow-up period in both arms for intention-to-treat (*time*; P<0.001) and after removing the patient failures (*time*; P<0.001). There was no significant difference between arms for intention-to-treat (no *time x arm interaction*; P=0.57] or after removing the patient failures (no *time x arm interaction*; P=0.50).

Figure 5D shows that Aural Fullness Scale mean scores significantly decreased from baseline over the 24 months follow-up period in both arms for intention-to-treat (*time*; P<0.001) and after removing the patient failures (no *time x arm interaction*; P<0.001). There was no significant difference between arms for intention-to-treat (no *time x arm interaction*; P=0.50) or after removing the patient failures (no *time x arm interaction*; P=0.61).

Figure 5E shows that Functional level Scale mean scores significantly decreased from baseline over the 24 months follow-up period in both gentamicin and steroid arms for intention-to-treat (*time*; P<0.001) and after removing the patient failures (*time*; P<0.001). There was no significant difference between the drug arms for intention-to-treat (no *time x arm interaction*; P=0.98) or after removing the patient failures (no *time x arm interaction*; P=96).

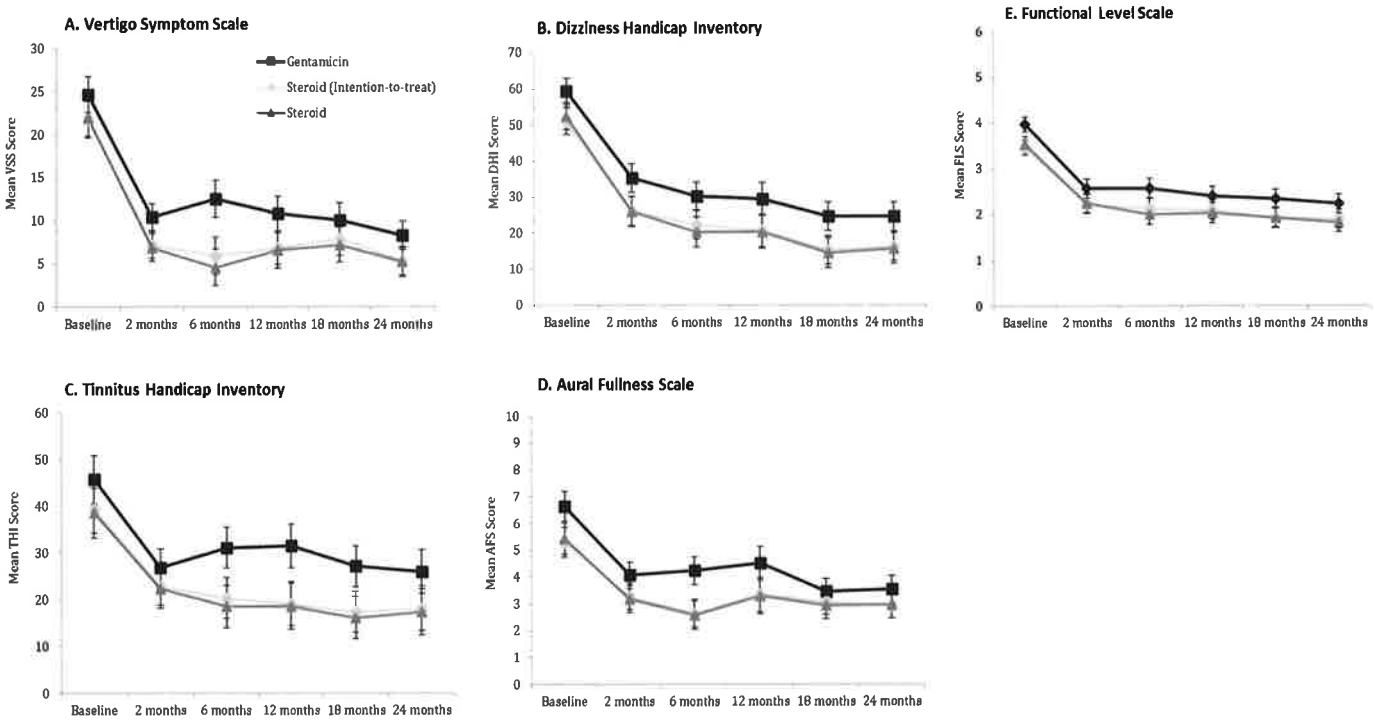


Figure 5: Mean ± SEM for A. Vertigo Symptom Scale, B. Dizziness Handicap Inventory, C. Tinnitus Handicap Inventory, D. Aural Fullness Scale and E. Functional Level Scale.

Secondary Outcomes: Change of Hearing

Hearing loss as shown by pure-tone audiometry and speech discrimination was similar between the gentamicin and steroid arms in the affected ear over the 24 months follow-up, see Figure 6.

Pure-tone Audiometry

For intention to treat, hearing loss did not significantly change from baseline over the 24 months follow-up (*time*; P=0.065). There was no significant difference between the drug arms (no *time x arm interaction*; P=0.18).

After removing patient failures from the steroid group, hearing loss significantly improves from baseline over the 24 month period (*time*; P=0.037). There was no significant difference between drug arms (no *time x arm interaction*; P=0.10).

Speech Discrimination

For intention to treat, speech discrimination fluctuated over the 24 months follow-up (*time*; P=0.029). Whereas there was an eventual drop in speech discrimination in the gentamicin arm, there was an increase in the steroid

arm. There was no significant difference between drug arms when taking into account all responses (no *time x arm interaction*; P=0.13).

Removing patient failures from the steroid group did not change the results. Speech discrimination fluctuated from baseline over the 24 months follow-up (*time*; P=0.038). There was no difference between drug arms taking into account all responses (no *time x arm interaction*; P=0.063).

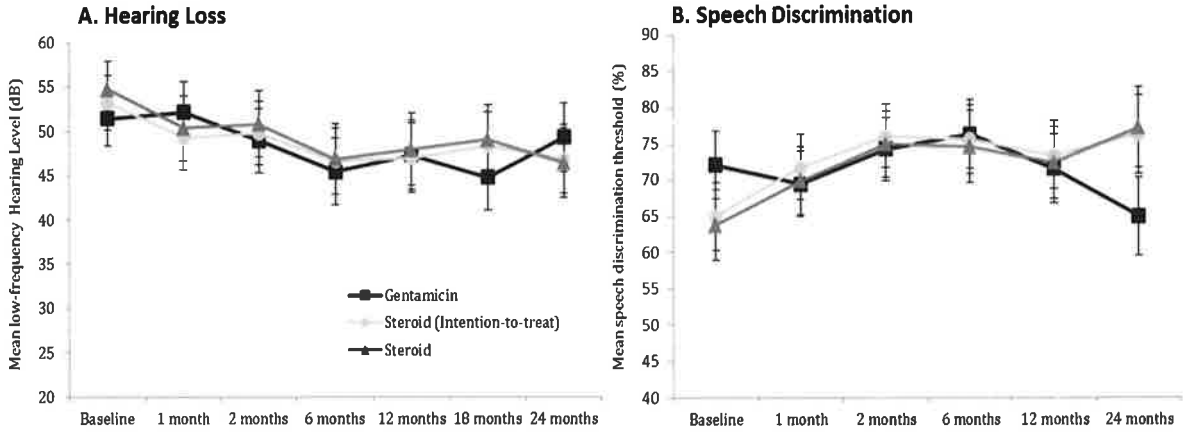


Figure 6: Mean ± SEM A. Mean low-frequency (average 0.5, 1, 2 and 3KHz) pure tone audiometry level and B. Mean speech discrimination threshold over the 24months follow-up.

Vestibular Function tests

Vestibular function as measured with VEMP asymmetry, caloric paresis, UCF weakness and rotational ENG time constant reduced in the injected ear following gentamicin injections and remained at a low level but there was no change after steroid injections.

Non-responders

In the gentamicin arm 8/30 patients required further courses of injections whereas in the intention-to-treat steroid arm 15/30 patients required further courses of injections. The two crossover patients in the steroid arm deemed failures were also given repeat courses of gentamicin. Chi-square analysis showed no significant difference between the numbers of non-responders in the gentamicin arm compared to steroid (p=0.11). The mean number of injections per patient was 2.7 (± SD 1.7) in the gentamicin arm, 3.7 (± SD 2.5) in the intention to treat steroid arm and 3.2 (± 1.6) in the steroid arm after omitting the patient failures. Chi-Square analysis showed no significant difference between drugs for intention to treat (P=0.09) or after removing failures (P=0.31).

Harm: Both the IMP (methylprednisolone) and the control drug (gentamicin) are used routinely in ENT clinics in the UK and globally as a standard treatment for patients with refractory Meniere's disease. There are some risks with both IMP's and all have been previously documented; Methylprednisolone via trans-tympanic

injections: Acute and chronic dizziness and Gentamicin via intratympanic injections: Temporary dizziness and imbalance lasting up to about 3 months and may result in some hearing loss in small group of patients.

There were no Suspected Unexpected Serious Adverse Reactions (SUSAR), Serious Adverse Reactions (SAR) or Serious Adverse Events (SAEs). The most common adverse event was repeated ear infections experienced by three patients, one in the gentamicin arm and two in the steroid arm. Two patients refused further injections after the first for pain. One patient was in the gentamicin arm and one patient was in the steroid arm.

A double-blinded hearing test was performed before the second injection to screen for hearing loss. A significant hearing loss was found in 14/60 patients; 9/30 followed gentamicin treatment and 5/30 followed steroid treatment, presumably associated with the disease fluctuations. Chi-square analysis showed no significant difference between drug arms (p=0.36).

The definition of adverse events was in line with ICH GCP guidelines. There were no reported Suspected Unexpected Serious Adverse Reactions (SUSAR), Serious Adverse Reactions (SAR) or Serious Adverse Events (SAEs). The most common adverse event was repeated ear infections experienced by three patients, one in the gentamicin arm and two in the steroid arm. Two patients refused further injections after the first for pain. One patient was in the gentamicin arm and one patient was in the steroid arm.

Adverse Events in the recording period
Subject 15: Lump found under tongue requiring day-surgery for removal. The event was not related to the IMP and not serious.
Subject 21: Split retina requiring surgery to correct. This was resolved without residual effects, was of moderate severity and was not related to the IMP. It was not serious.
Subject 29: Repeated ear infections which cleared up after repeated medical treatment.
Subject 30: Repeated ear infections which cleared up after repeated medical treatment.
Subject 36: Small abdominal schwanomma found and being monitored elsewhere but does not require surgery.
Subject 57: Repeated ear infections which cleared up after repeated medical treatment.

Location of Data
All data is stored in accordance to Imperial College Healthcare NHS Trust policy at Charing Cross Hospital, Fulham Palace Road, London.

6. Discussion

Repeated and unpredictable attacks of vertigo are the main cause of disability in MD. Accordingly the primary outcome in this study was reduction in the number of vertigo attacks.

Although non-invasive treatments for MD have shown little or no benefit [1,2], it is customary to delay invasive treatments such as intratympanic injections for months or years. This is a reasonable approach, at least for three reasons. Firstly, Ménière's disease is notorious for spontaneous fluctuations and remissions. Secondly, the intratympanic drug validated as useful (gentamicin) exerts its effects through its well-known ototoxic properties. Accordingly, patients and doctors are cautious before starting such treatments because acute vertigo, a permanent reduction in vestibular function and hearing loss are possible after the injection. The latter has been described in 25% of cases in a Cochrane review [3] but negligible in other meta-analyses [4,5].

Thirdly, there is an up to 50% progression of cases to bilateral MD in the long term [6] and, therefore, inducing a fixed audio-vestibular deficit on one side with gentamicin is problematic if the other side is likely to require a similar treatment. For these various reasons, intratympanic steroidal injections have recently become a popular alternative as it is assumed that no permanent cochlea-vestibular damage could arise from their use. However, no prospective, double-blind RCT validation of this new treatment was available. Neither a consensus document for the use of intra-tympanic steroids is available and many otologists are sceptical about their value [7,8].

In this trial we compared intratympanic gentamicin, the current first line treatment for patients with refractory (or "intractable") unilateral Ménière's disease, with a similar regime of intratympanic methylprednisolone. Both arms of the trial provided an active drug as it would have been unethical to compare methylprednisolone against placebo once patients reach the disabling refractory phase of the disease. Comparing the steroid injection against the established effectiveness of gentamicin is therefore a sensible alternative. Hence, steroids would be considered superior to gentamicin if the reduction in vertigo symptoms (primary outcome) was similar with the two drugs but hearing function (secondary outcome) was better in the steroid arm. A main strength of this trial is the long term follow up of patients (2 years) in an attempt to minimize the impact of the natural fluctuations in this condition and in line with current recommendations [9].

Primary outcome:

The main result is that both drugs were equally effective in controlling vertigo. There was no significant difference in outcome between the two groups. The overall reduction in vertigo attacks in the final month of follow up compared to pre-treatment was 92% for steroid injections and 88% for gentamicin. There was total abolition of attacks in the same time period for 83% across both treatment groups. All results in this trial held equally for the number of attacks over a final six months for intention to treat and for the secondary analysis after treatment failures were excluded. In full agreement with the direct reduction in the number of vertigo attacks, the vestibular validated questionnaires employed here, the Vertigo Symptom Scale (VSS), the Dizziness Handicap Inventory (DHI) and the Functional Levels Scale (FLS), also showed a clear and significant reduction in scores with both drugs. The main difference with respect to the straight count of the number of attacks is that these questionnaires incorporate a number of additional factors, including shorter duration vertigo attacks (VSS_V) and function-based, psychological and autonomic components (FLS, VSS_A, DHI), which all add to the aggregate disability of these patients.-Most of the reduction in symptoms was already established at the first follow up two months after the injections and, from then on, levels remained fairly constant up to trial conclusion two years later.

Hearing function - secondary outcome:

For hearing function (pure tone audiometry and speech discrimination), there was also no difference between the two drugs although a trend for better discrimination was suggested for steroids over gentamicin. On average, hearing function remained stable over the 2-year follow up in both groups and this conclusion also applies to related audiological variables such as the Tinnitus Handicap Inventory and Aural Fullness Scale.

Non-responders:

Given the disabling nature of the vertigo attacks in Ménière's disease we felt it would be unethical to deprive patients who did not respond to the initial programmed two injections from further treatment. Therefore, non-responders, defined as patients experiencing two or more episodes of vertigo lasting 20 minutes or longer, received 1-5 new courses of injections. We found no statistically significant difference between arms for mean number of injections per patient over the two year follow-up period, both for intention-to-treat or after removing patient failures. Given that the number of non-responders is numerically higher in the steroid group (8 in the gentamicin arm and 15 in the methylprednisolone arm) we carried out further statistical analysis but this showed that the frequency of non-responders was not significantly different between the two groups (Chi-square P=0.11).

Vestibular function:

Tests of vestibular function were not a trial outcome measure because they generally correlate poorly with clinical disability and symptom load [10,11]. These tests, however, were an essential part of the study as an objective way of monitoring vestibulo-toxic effects of the administered drugs and/or progression of the underlying disease process. In the case of gentamicin, vestibular function tests would also document that the injected drug reaches the inner ear and acts in the expected manner. Figures 10A-E undoubtedly show that gentamicin has seriously compromised vestibular function on the injected side, with all measures of canal, utricular and saccular function dropping significantly at the 2-month follow up, after the first course of injections (Caloric, Utricular centrifugation and VEMP tests, respectively). These drastic drops in vestibular function, combined with a reasonable preservation of hearing is what is expected as gentamicin is more toxic for the vestibular than the cochlear epithelium [12]. From a practical point of view, the data shows that our dosage choice (40mg/ml gentamicin), based on the literature on intratympanic gentamicin [5,13], was appropriate. Higher concentrations of gentamicin might have avoided the need for further injections in some patients but, inevitably, the risk of inducing an unwanted hearing loss would have been greater [12].

General discussion and conclusions:

In this double blind RCT comparing intratympanic injections of either gentamicin or methylprednisolone (steroid) we found no significant differences between these two drugs in terms of controlling vertigo (primary outcome) and vestibulo-related symptoms. Both drugs were highly effective in reducing the number of vertigo attacks and associated disability. It could have been expected that the number of repeated injections would be higher in the steroid group and this was indeed the case but the differences were not statistically significant.

Most published studies comparing one or both of these two drugs suffer from several limitations, including a retrospective approach, unbalanced and unjustified patient numbers, poor follow up adherence and, above all, the lack of randomisation and blinding [3,14]. In the words of the authors of one such study "due to the retrospective nature of this study, the presence of bias caused by loss of subjects from follow-up cannot be ruled out"[15]. Fortunately, this is not a limitation of our study. Notwithstanding these drawbacks, many studies have reported credibly good results using intratympanic steroids [15,16] and the trend for a slightly better hearing outcome with steroids described in some of them [15] is a similar finding in the current RCT. The conclusion that gentamicin, in contrast, to steroids is a definitive treatment is not supported by our results - additional

injections were required in 8/30 patents who received gentamicin and this could reflect variable rate of diffusion through the window or different susceptibility of the labyrinthine epithelium in different subjects. It is well known that certain individuals have extremely high sensitivity to gentamicin through mitochondrial RNA inheritance [17]. Furthermore a variable penetration of gentamicin through the round window has been observed [18], both in the presence of middle fibrosis caused by previous infection or without any visible macroscopic obstruction. Both mechanisms may contribute to inconsistent outcomes with intratympanic drug administration. It should be noted that for both drugs, relapse tended to be controlled by further injections of the same drug.

We therefore conclude that both treatments are equally effective for the control of vertigo due to severe unilateral Ménière's disease. Patients and clinicians now have a choice of two effective treatments but, on the basis of clinical wisdom and trends in our data, one may favour one or the other drug in specific circumstances. For instance for a patient with no geographical access to repeat injections, nor afraid of a post-injection vertigo attack and not relying professionally on his hearing (say a non-musician), gentamicin may be appropriate. For a patient with easy access to further injections, concerned about any further hearing loss and not wishing to experience a post injection vertigo episode (e.g. a musician with a busy schedule), intratympanic steroid seems more appropriate.

Mechanism of action of the drugs:

The action of gentamicin in the inner ear has been extensively investigated and it has been shown to accumulate predominantly in Type 1 vestibular hair cells and cause subsequent atrophy of these cells as well as the whole of the neuro-epithelium [19]. The action of steroids on the inner ear remains speculative [20]. There are both gluco-corticoid and mineralo-corticoid receptors in the vestibular and cochlear systems. Steroids may have an effect on ion homostasis functions as well as immune modulation [21] via both types of receptor. They have also been shown to have an effect on the aquaporins [21] which are a family of small transmembrane water transporters, and they have been shown to play a role in regulating homeostasis in the inner ear fluids. Furthermore steroids have been shown to have an effect on absorption and osmotically coupled water flux [22,23].

Interpretation: Steroid injections are equally as effective as gentamicin injections for vertigo control in intractable unilateral Meniere's disease over a 24 month period and has no serious side-effects.

7. Conclusions

Both treatments were equally effective in the control of vertigo due to severe unilateral Meniere's disease. Patients and clinicians now have a choice of two effective treatments but, on the basis of data from previous non-controlled studies, clinical wisdom and trends in our data, one may favour one or the other drug in specific circumstances. For instance for a patient with no geographical access to repeat injections, nor afraid of a post-injection vertigo attack and not relying professionally on his hearing (say a non-musician), gentamicin may be appropriate. For a patient with easy access to further injections, concerned about any further hearing loss and not wishing to experience a post injection vertigo episode, intratympanic steroid seems more appropriate.

8. Other information

Protocol: The Protocol and all records are to be retained securely at Charing Cross Hospital, London, W6 8RP.
Funding: The Meniere's Society, UK and the Medical research Council funded this study.

9. Arrangements for Disseminating Findings

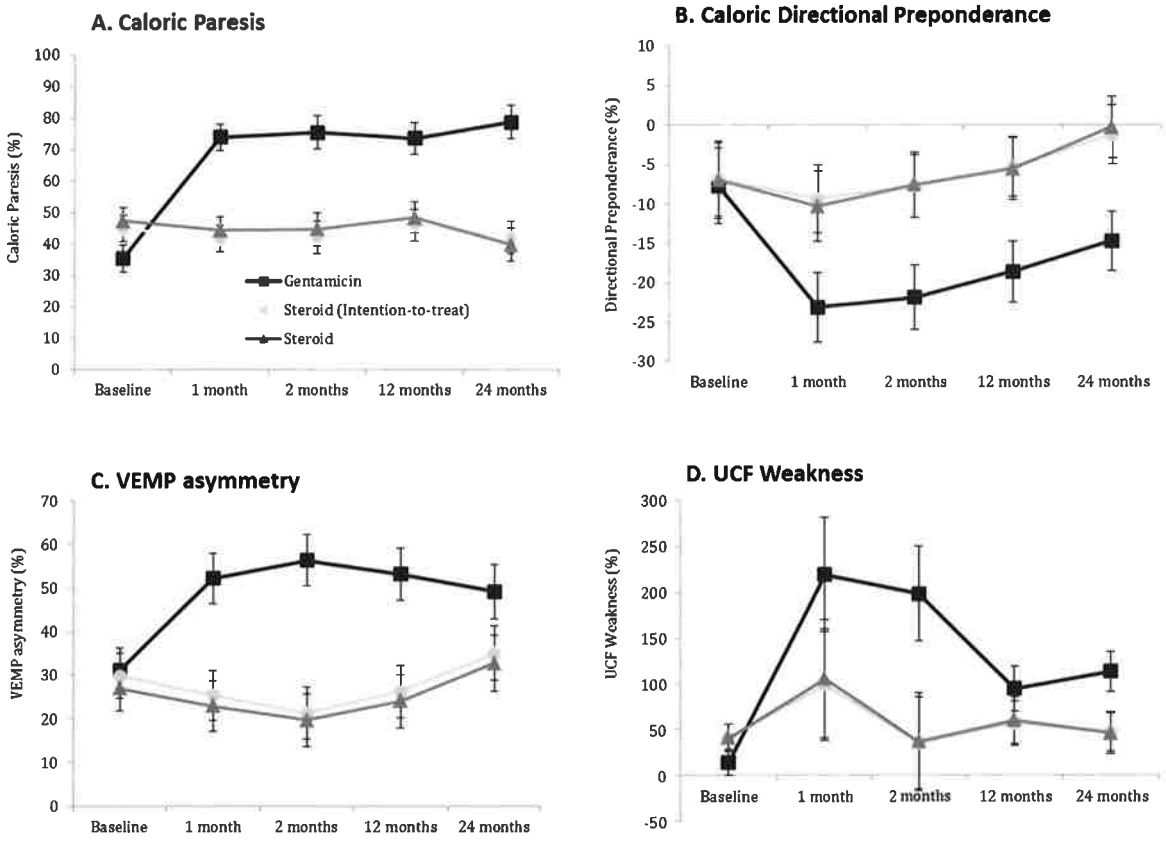
Results have been conveyed to the Meniere's Society, UK, who funded the clinical trial. The results were presented at the British Society of Neuro-Otology (BSNO) conference, London, on the 9th of October 2015 to an audience of audiovestibular physicians and scientists. The manuscript is set to be submitted for peer-review.

10. Feedback to patients

Participants will be informed of their medication after the study has been published. The general population will be informed by the Meniere's Society who will publish the results through their own patient-focussed magazine "Spin" and website http://www.menieres.org.uk/.

11. Appendices

Vestibular function test data



Vestibular test results over the 24months follow up A. Caloric Paresis, B. Caloric Directional Preponderance, C. VEMP asymmetry, and D. Utricular Centrifugation (UCF) Weakness.

Protocol

Imperial College London

Effectiveness of Transtympanic Steroids in unilateral Ménière's disease: a Randomised Controlled Double-Blind Trial

Version No. 3

MAIN SPONSOR: Imperial College London
FUNDERS: Ménière's society and Medical Research Council

REC reference: 08/H0712/95
EudraCT reference: 2008-004803-78

Sponsor

Imperial College is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance Manager at:

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Sir Alexander Fleming Building
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This protocol describes the study 'Effectiveness of Transtympanic Methylprednisolone in unilateral Ménière's disease: a Randomised Controlled Double-Blind Trial' and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

List of Abbreviations used:

AAO-HNS: American Academy of Otolaryngology-Head and Neck Surgery.
ENG: Electronystagmography.
Inj: Injection.
Imm: Immunological tests.
m: months
OAE: Oto acoustic emissions.
PTA: Pure tone audiometry.
QA: Questionnaire assessment.
Rot.ENG: Rotational tests with ENG.
SDS: Speech discrimination score.
TIA: Transient ischemic attacks.
TT: Transtympanic.
Tymp: Tympanometry.
UFT: Utricular function tests.
VEMP: Vestibular evoked myogenic potentials.
wk: week
+ve: positive

1. SCIENTIFIC ABSTRACT:

There is no established treatment for Ménière's disease, nor agreement on whether Ménière's disease is a single clinical entity or an umbrella syndrome covering different aetiologies and pathophysiological mechanisms. Lately, local (transtympanic, TT) treatments have been advocated and TT gentamicin injections have been established for refractory attacks of vertigo in Ménière's disease. This treatment however carries an inherent risk of aggravating the hearing loss and alternatives have been sought. Of these, local treatment with steroids (TT steroids) has shown to be promising in that no hearing deterioration is expected and indeed some studies report improvement in hearing. Although most ENT surgeons use TT steroids in selected patients, the effectiveness has not been fully established. In these proposals we aim to: 1) clarify the effectiveness of TT steroids vs. the more established TT gentamicin treatment in a controlled study; 2) compare the effects of TT steroids vs. TT gentamicin on hearing function; 3) ascertain if the reasons for variable outcome in TT steroids studies relates to different underlying mechanisms mediating Ménière's disease, i.e. immune mediated Ménière's disease 4) establish a new technique for assessing unilateral vestibular function in Ménière's disease during TT trials which does not rely on caloric testing (which is contraindicated after invasive TT treatments).

2. Purpose of investigation and statement of scientific value or applicability:

2.1. Introduction and background:

Ménière's disease is characterised by recurrent attacks of disabling vertigo and progressive hearing loss. It is postulated that the underlying mechanism producing symptoms is endolymphatic hydrops however the aetiology triggering hydrops remains unknown. It has been suggested that an underlying inflammatory or autoimmune inner ear process may cause Ménière's disease, at least in some patients (1). Indeed, systemic autoimmune disorders (e.g. systemic lupus eythematosus, vasculitis) may present with a Ménière's -like syndrome (2). In addition, autoimmune inner ear disorder is a specific clinical entity causing isolated local progressive inner ear disease without general manifestations or markers of connective tissue (3). This is relevant with regards to the current controversy as to whether local treatment with steroids (TT steroids) is effective in refractory Ménière's disease.

Interest in TT therapies developed after the general acceptance within the otological and neuro-otological communities that TT gentamicin is the treatment of choice for refractory vertigo in Ménière's disease. Gentamicin, however, is an ototoxic agent and carries an inherent risk of permanent and severe cochlear damage. The reported incidence of worsening of hearing loss is between 13 and 34.7% of treated patients, being profound loss in 6.6%, depending on the dose and regimen used (4) In this regard, TT treatment with steroids was initially well received because steroids do not have a deleterious effect on hearing and indeed some degree of hearing improvement and tinnitus reduction

has been reported in Ménière's disease (5-9). At this point in time, however, it is not fully established whether TT steroids is an effective therapy in Ménière's disease.

2.2. Purpose of the investigation:
A review of the studies assessing the response of TT steroids treatment in Ménière's disease shows a few limitations: a) many studies do not have an appropriate control group, b) most studies have not quantified the vestibular response to treatment in the injected ear, which is understandable because caloric testing would be contraindicated after invasive TT treatments, c) follow up has been too short, for a chronic relapsing disease as Ménière's disease, d) no attempt has been made to identify Ménière's disease patients with a suspected immune/inflammatory cause who would be more likely to respond to TT steroids.

In this proposal we will directly address these four limitations by 1) clarifying the effectiveness of TT steroids on vertigo vs. the more established TT gentamicin treatment in a controlled study; 2) compare the effects of TT steroids vs. TT gentamicin on hearing function; 3) ascertain if the reasons for variable outcome in TT steroids studies relate to possible underlying mechanisms mediating Ménière's disease, i.e. immune mediated Ménière's disease; 4) establish a new technique for assessing unilateral vestibular function in Ménière's disease which does not rely on caloric testing. Thus, we propose a randomised double blind controlled trial in unilateral Ménière's disease, comparing TT methylprednisolone vs. TT gentamicin. A positive methylprednisolone outcome (with respect to gentamicin) would be similar vertigo control *and* similar hearing outcome with the two treatments. This would imply that methylprednisolone is as effective as gentamicin. Since gentamicin can cause hearing deterioration in some patients it can be expected that methylprednisolone may fair better than gentamicin. In patients with immune-mediated disease, methylprednisolone should be far superior to gentamicin, both for hearing and vertigo, and it may be possible to conclude that steroids be regarded as the first choice treatment in this patient group.

2.3. Scientific value or applicability:
The clinical value of this proposal is to compare an established (gentamicin) vs. a new (methylprednisolone) treatment. The added scientific value is that we will:
a) compare appropriate control groups,
b) investigate a possible immune-basis and will relate this to the success of steroid treatment in Ménière's disease patients,
c) validate a new tool for assessing unilateral vestibular function in Ménière's disease patients undergoing TT treatment.

3. METHODS OF RESEARCH:
3.1. Type of study: Randomised double-blind controlled trial of transtympanic methylprednisolone vs. gentamicin in patients with unilateral Ménière's disease.

3.2. Patient groups: 60 patients will be recruited: 30 patients to the methylprednisolone group (trial) and 30 to the gentamicin group (control). Patients with Ménière's disease attending ENT and Neuro-otology services at Imperial College NHS Trust (Charing Cross and St. Mary's Hospitals) will be asked to participate. Patients will also be recruited from ENT clinics at Northwick Park Hospital and West Middlesex hospital.

3.3. Inclusion criteria: Patients with Ménière's disease (definite or probable, according to AAO-HNS criteria 1995) in Shea stages II and III (i.e. with hearing loss and presenting with recurrent vertigo) not responding to medical treatment for at least 6 months will be included. Patients above 18 years of age will only be included.

3.4. Exclusion criteria:
a) Patients with Ménière's disease in later stages (not having vertigo attacks).
b) Age: patients older than 70 years at the start of the trial.
c) Severe disability (e.g. neurological, orthopaedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow up.

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b) Age: patients older than 70 years at the start of the trial.
c) Severe disability (e.g. neurological, orthopaedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow up.

d) Active additional neuro-otological disorders that may mimic Ménière's disease (e.g. vestibular migraine, vertebro-basilar TIAs, acoustic neuroma) and thus will make the objective follow up difficult.
e) Concurrent ear pathology that may interfere with TT (e.g. active middle ear disease).
f) Family history of unexplained deafness (possibility of genetic susceptibility to gentamicin toxicity).
g) History of known adverse/allergic reaction to steroids or gentamicin.
h) Pregnant women.

3.5. Duration: The treatment phase will be 2 weeks and the follow-up phase will be 24 months. The trial design includes an option for additional TT injections in patients with unsatisfactory vertigo control (see 3.9.i. below).

3.6. Pre-randomisation evaluation (Clinical and Laboratory assessment):
The diagnostic criteria defined by the American Academy of Otolaryngology-Head Neck Surgery 1995 will be used (10). Before the TT injections are initiated the following questionnaire assessments and laboratory tests will be performed;

a) **Questionnaires and symptom load assessment**: The subjective symptoms like vertigo, tinnitus, aural fullness and functional levels will be assessed by:
i) Vertigo symptom scale (Yardley; 11) - a symptom specific questionnaire which measures the severity of vertigo and somatic anxiety.
ii) Dizziness Handicap Inventory (12) - widely used for self-reporting of functional, emotional and physical impairment due to dizziness.
iii) Tinnitus Handicap Inventory (13) - universally used tinnitus questionnaire for symptom assessment and to report treatment outcomes
iv) Functional level scale - a six-point scale recommended by the AAO-HNS for clinical trials in Ménière's disease.
v) Subjective improvement scale of aural fullness (8) - on a scale of 0-10.

b) **Audiology**: Pure Tone Audiometry, Speech audiometry, Transient evoked and Distortion Product Oto-Acoustic Emissions (14), Tympanometry.

c) **Vestibular tests**:
i) Caloric tests and full Electronystagmography (ENG), including rotational tests, are routinely done in our clinics.
ii) Vestibular evoked myogenic potentials (VEMP), an established test of unilateral vestibular (probably saccular) function.
iii) Unilateral utricular centrifugation: a new utricular function test (UFT). We will undertake, for the first time in the UK, a new test that allows examination of peripheral vestibular function unilaterally. This technique requires a highly specialised rotating chair which the Neuro-otology Unit at Charing Cross Hospital acquired in 2006 and is now fully available for patient use. A very recent study (15) reported abnormalities in Ménière's disease patients. Additional details are provided in 'Appendix A'.

d) **Immunological tests**: systemic and inner ear-specific investigations will be implemented.
i) Systemic: A standard battery of blood tests for immunological disorders will be performed to identify systemic immunological or inflammatory disease producing endolymphatic hydrops, including: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum immunoglobulins, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibody (ANCA), antiendothelial cell antibody (AECA), antiphospholipid/anticardiolipin antibodies, antithyroid antibodies, rheumatoid factor and VDRL.
ii) Inner ear specific:
-We have pioneered a technique which allows identification of autoantibodies directed against specific compartments of the inner ear, in patients with cochlear and vestibular (3) disorders.

Dr Agrup, who developed this technique, is a co-applicant in this proposal and has committed herself to this work; see 'Appendix B'.
-The OTOblot test™ is a commercially available test that claims to be specific for immune-mediated inner ear diseases. However, the antigen used is heat shock protein 70 (hsp 70) from bovine kidney tissue and therefore lacks ear-specificity. Accordingly, there have been mixed reports of utility of this particular test (16-18). We will compare this commercially available kit against inner ear specific western blot technique to define their true value in Ménière's patients.

e) Other investigations (radiological or laboratory) will be performed as the need arises, as accepted guidelines for diagnosis of Ménière's disease emphasise that 'other causes have to be excluded' (10).

3.7. Treatment groups: The treatment will be given in a randomised way in two groups: Methylprednisolone and Gentamicin. The course will be 2 transtympanic injections at an interval of 2 weeks (one per week):
- Methylprednisolone group: 2 doses of 1 ml of 62.5mg/ml at interval of 2 weeks.
- Gentamicin group: 2 doses of 1 ml of 40mg/ml at interval of 2 weeks. If significant hearing loss is found during treatment, gentamicin will be replaced by normal saline (1 ml). The trial's pharmacist (unblinded but not part of the trial team) will provide the active drug (or saline) to the surgeon (blinded) on the basis of a report by an audiological physician (blinded) to the pharmacist. If the average hearing loss is >20dB in a week, the patients in the gentamicin group will receive saline instead of the active drug, while remaining blinded

The flow chart of the trial is as below:

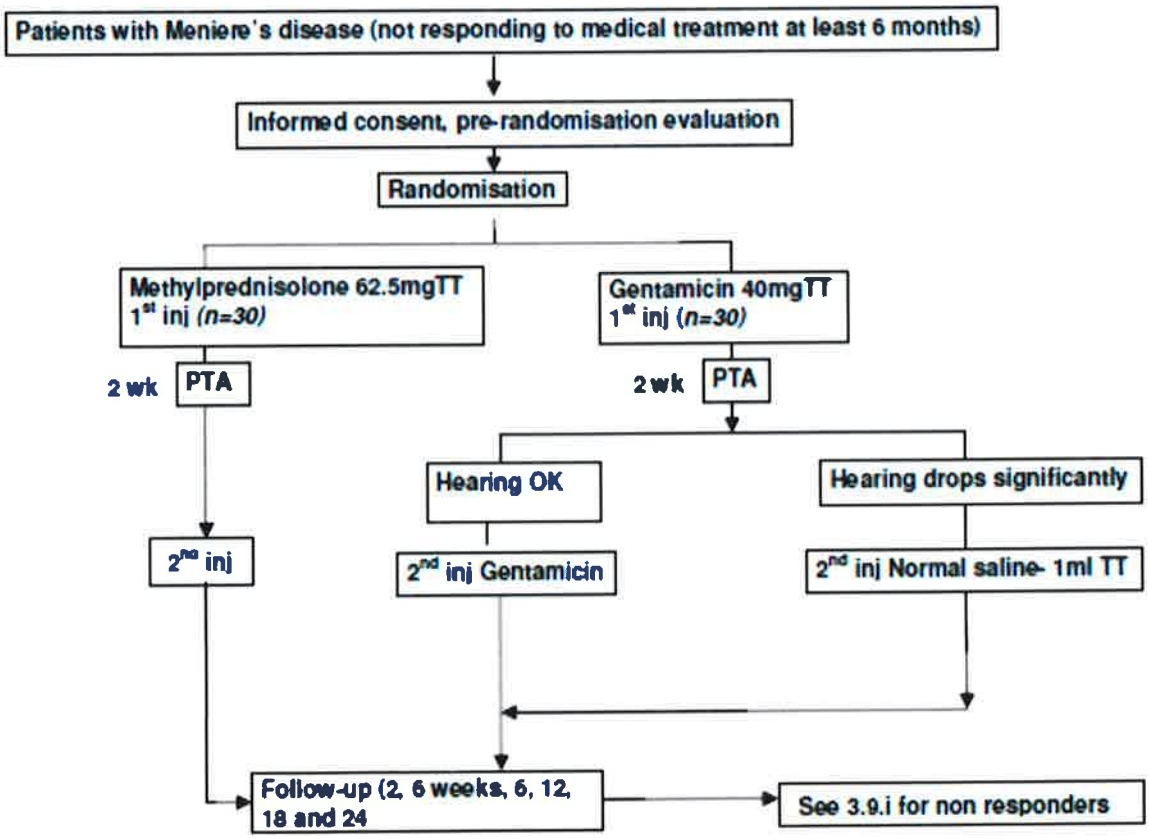


Fig 1: Flow Chart Diagram of the trial.

3.8. Technique for transtympanic injections: The treatments will take place in the ENT Out-Patient Department at Charing Cross Hospital. The patient, having been laid supine on a treatment table and head turned by 45 degrees to contra lateral side will have the affected ear cleaned under the microscope and then anaesthetised with topical Lignocaine. Transtympanic injections will be given using a 1ml syringe via a spinal needle (22 G) into the postero-inferior quadrant of the tympanic membrane. An attempt will be made to fill the middle ear space with the drug as much as possible. The patient will be asked to remain lying down on the couch with head turned for 20 mins and try to avoid swallowing following the injection.

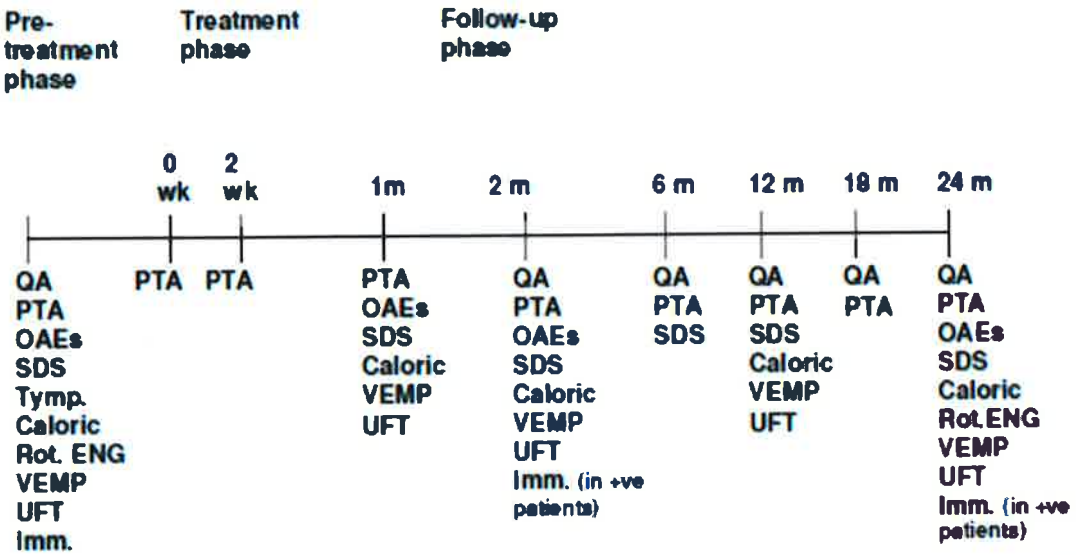
3.9. Follow-up: After both injections, the patients will be followed up at 1 month, 2, 6 months and then every 6 months for 2 years. For patients with persistent, frequent or disabling vertigo attacks after receiving a full course of injections, further treatment has been planned by repeating injections (see 3.9.i.below).

3.9.i. Further treatment options for non-responders: There may be some patients who do not have a satisfactory response to the above mentioned treatments. If at follow-up a patient is having persistent disabling vertigo (confirmed by high scores on questionnaire assessments); the trial team will consult an outside independent consultant. This consultant will then assess the patient and contact the pharmacy to get the drug information. He will provide further advice to the pharmacy to supply the same drugs (methylprednisolone or gentamicin) as before to the trial team, or decide any other course of action.

4. EVALUATION: The following measures (Fig 2) have been planned to investigate the effects of the transtympanic treatment.

4.1. Evaluation to detect acute effects:

- PTA will be done prior to each injection.
- PTA, SDS, OAEs (transient evoked and distortion product), Caloric tests, Utricular function test, and VEMP, will be done after the second injection to note any acute changes in hearing and in vestibular function. These will be done two weeks after the last injection.



nb: 'Imm' in follow up refers to immunological systemic markers only, in patients with initially +ve results.

Fig 2. Evaluation chart

4.2. Evaluation in the follow-up phase:
2 months: Questionnaire assessments, PTA, SDS, OAEs (transient evoked and distortion product), Caloric tests, VEMP and UFT to note clinical and audio-vestibular changes following treatment. Blood tests for systemic immunological markers will be repeated in patients who had positive results on pre-randomisation evaluation.
6 months: Questionnaire assessments, PTA, and SDS will be done.
12 months: Questionnaire assessments, PTA, SDS, caloric tests, VEMP and UFT will be done to note whether effects of treatment are sustained.
18 months: Questionnaire assessments and PTA.
24 months: Clinical and questionnaire assessments and all the audiovestibular investigations (PTA, SDS, OAEs (transient evoked and distortion product), Caloric test, rotational ENG VEMP, and UFT) will be repeated. Blood tests for systemic immunological markers will be repeated again in patients who had positive results on pre-randomisation evaluation.

4.3. Outcome measures:
a) Primary: relief from vertigo attacks (Vertigo symptom scales, Dizziness Handicap Inventory) as per committee of hearing and equilibrium guidelines.
b) Secondary: Preservation of hearing (Pure Tone Audiometry, Speech Discrimination Scores).

4.4. Statistics and data analysis:
Power calculations (5% significance with 80% power) indicate that the number of patients suggested for this study (n= 30x2) is adequate. Questionnaire items or physiological measurements will be compared between the groups using nonparametric and parametric tests as appropriate to the variable under consideration, with adjusted 'p' values for multiple significance tests. Possible relationships between variables will be explored using bivariate correlations and factor analysis. We may employ posthoc data analysis with logistic regression if other features (demographics, duration of disease, others) become apparent.

5. PHARMACOVIGILANCE
5.1 DEFINITIONS
Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (eg investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). *When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

Serious Adverse Event (SAE) or **Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

5.2 CAUSALITY

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the investigators should inform the Principal Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the trial management team in the first instance. A flowchart is given below to aid in the reporting procedures.

5.3.1 Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form within one month of the form being due.

5.3.2 Serious AR/AEs

Fatal or life threatening SAEs and SUSARs should be reported on the day. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e.

unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be recorded within 5 days if the reaction has not resolved at the time of reporting.

SAEs

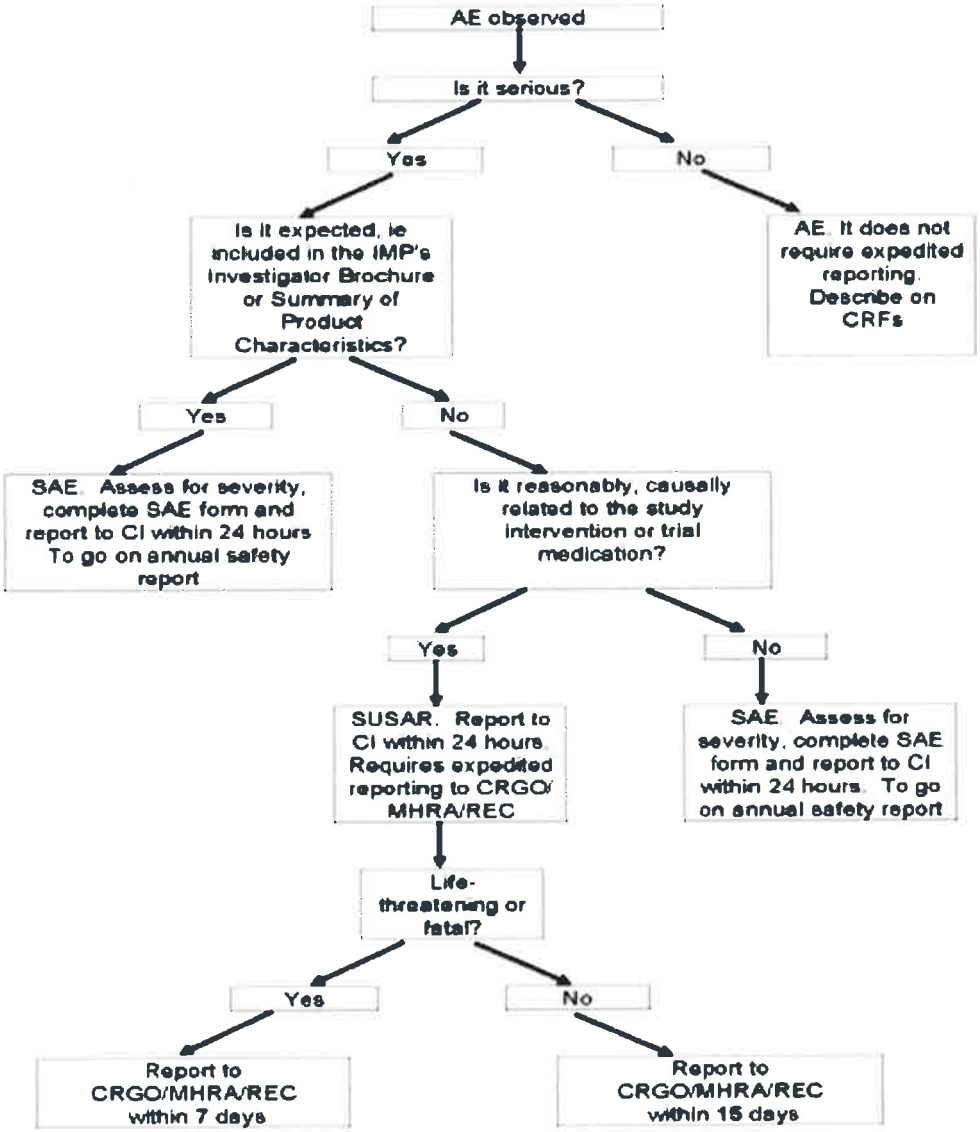
An SAE form should be completed within 24 hours. However, relapse of Meniere's disease and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

SUSARs

In the case of serious, unexpected and related adverse events, the investigator should complete the SAE case report form & record it immediately (within 24 hours), signed and dated together with relevant treatment forms and anonymised copies of all relevant investigations.

The principal investigator will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study.

The investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.



6. REGULATORY ISSUES

6.1 CTA
This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA. Reference: xxx

6.2 ETHICS APPROVAL
The Trial management group has obtained approval from the xxx Research Ethics Committee. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

6.3 CONSENT
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

6.4 CONFIDENTIALITY
Participants' identification data will be required for the registration process. The Trial Management Group will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

6.5 INDEMNITY
Imperial College holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

6.6 SPONSOR
Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

6.7 FUNDING
Ménière's society and Medical Research Council are funding this study.

6.8 AUDITS AND INSPECTIONS
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP.

7. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group.

8. REFERENCES:

1. Savastano M, Giacomelli L, Marioni G. Non-specific immunological determinations in Meniere's disease: any role in clinical practice? Eur Arch Otorhinolaryngol. 2007; 264(1):15-9.

2. Broughton SS, Meyerhoff WE, Cohen SB, Immune-mediated inner ear disease: 10 year experience. Semin Arthritis Rheum. 2004; 34: 544-548.

3. Agrup C, Keir G, Thompson EJ, Bronstein AM. Systemic autoantibodies against discrete inner ear compartments in bilateral vestibular loss. Neurology 2005; 65(1):167.

4. Chia SH, Gamst AC, Anderson JP, Harris JP. Intratympanic gentamicin therapy for Meniere's disease: a meta-analysis. Otol Neurotol 2004; 25: 544-552.

5. Shea JJ Jr, Ge X. Dexamethasone perfusion of the labyrinth plus intravenous dexamethasone for Meniere's disease. Otolaryngol Clin North Am. 1996; 29(2):353-8.

6. Shea JJ Jr. The role of dexamethasone or streptomycin perfusion in the treatment of Meniere's disease. Otolaryngol Clin North Am. 1997; 30(6):1051-9.

7. Sennaroglu L, Sennaroglu G, Gursel B, Dini FM. Intratympanic dexamethasone, intratympanic gentamicin, and endolymphatic sac surgery for intractable vertigo in Meniere's disease. Otolaryngol Head Neck Surg. 2001; 125(5):537-43.

8. Garduño-Anaya MA, Couthino De Toledo H, Hinojosa-González R, Pane-Pianese C, Ríos-Castañeda LC. Dexamethasone inner ear perfusion by intratympanic injection in unilateral Ménière's disease: a two-year prospective, placebo-controlled, double-blind, randomized trial. Otolaryngol Head Neck Surg. 2005; 133(2):285-94.

9. Hamid. Intratympanic dexamethasone perfusion vs. natural history of Meniere's disease. Paper presented at the 6th Meeting of the British Society of Neuro-otology. Imperial College London, 30th November 2007.

10. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Menière's disease. American Academy of Otolaryngology-Head and Neck Foundation, Inc. Otolaryngol Head Neck Surg. 1995; 113(3):181-5.

11. Yardley L, Masson E, Verschuur C, Haacke N, Luxon L. Symptoms, anxiety and handicap in dizzy patients: development of the vertigo symptom scale. J Psychosom Res. 1992; 36(8):731-41.

12. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg. 1990; 116(4):424-7.

13. Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. Arch Otolaryngol Head Neck Surg. 1996; 122(2):143-8.

14. Perez N, Espinosa JM, Fernandez S, Garcia- Tapia R. Use of distortion-product otoacoustic emissions for auditory evaluation in Meniere's disease. Eur Arch Otorhinolaryngol. 1997; 254: 329-342.

15. Helling KA, Schonfield U, Clarke AH. Treatment of Meniere's disease by Low-Dosage Intratympanic Gentamicin Application: Effect on Otolith Function. Laryngoscope 2007; 117: 2244-2250.

16. Moscicki RA, San Martin JE, Quintero CH, Rauch SD, Nadol JB Jr, Bloch KJ. Serum antibody to inner ear proteins in patients with progressive hearing loss. Correlation with disease activity and response to corticosteroid treatment. JAMA. 1994; 272(8):611-6.

17. Yeom K, Gray J, Nair TS, Arts HA, Telian SA, Disher MJ, El-Kashlan H, Sataloff RT, Fisher SG, Carey TE. Antibodies to HSP-70 in normal donors and autoimmune hearing loss patients. Laryngoscope. 2003; 113(10):1770-6.

18. Samuelsson AK, Hydén D, Roberg M, Skogh T. Evaluation of anti-hsp70 antibody screening in sudden deafness. Ear Hear. 2003; 24(3):233-5.

Appendix A

The Unilateral Utricular Centrifugation Test:

New developments in rotational equipment have allowed the development of a test that can stimulate one utricle at a time. Essentially the technique consists of slowly accelerating a subject to reach high angular velocities (e.g. 300-400deg/s). Once the nystagmic response from the semicircular canals has died down (e.g. ca. 1 min), a secondary linear motor shifts the chair sideways ca. 4 cm so that the earth-vertical axis of rotation passes through one utricle. At this point the centred utricle receives no centrifugal input whereas the eccentric input receives a horizontal centrifugal acceleration of ca. 0.2-0.3g (g = gravity = 9m/s/s). Hence, ocular torsional effects, which can easily be measured by standard visual vertical procedures or with 3-D video-oculography, are due to the action of the eccentrically placed utricle. The subject's chair is then linearly shifted to the contra lateral position and the output of the ocular responses indicates the strength of the right and left utricle. Due to the low acceleration and deceleration rate the procedure is perfectly well tolerated by subjects.

This elaborate technique is now available in our laboratory thanks to our core MRC grant which allowed us to purchase the system from *Neurokinetics (USA)*. This system pioneered by Dr Clarke in Germany and Prof Wuyts in Belgium has been validated and, very recently, used in Ménière's disease patients undergoing TT Gentamicin (Helling et al 2007). This study, from Dr Clarke's group, reported a lower rate of abnormalities in Ménière's patients than with other tests, but this may be due to their use of a lower rotation rate than the one we use [in agreement with Dr Wuyts' technique (Wuyts et al 2003)]. We will therefore have the possibility of assessing vestibular function unilaterally in our trial, on the side injected with TT Dexamethasone or Gentamicin. This will provide objective evidence of the action of the drug in a situation where conventional unilateral tests of vestibular function (e.g. caloric tests) will be contraindicated.

1. Helling K, Schönfeld U, Clarke AH. Treatment of Ménière's Disease by Low-Dosage Intratympanic Gentamicin Application: Effect on Otolith Function. Laryngoscope. 2007; 117: 2244-2250

2. Wuyts FL, Hoppenbrouwers M, Pauwels G, Van de Heyning PH. Utricular sensitivity and preponderance assessed by the unilateral centrifugation test. J Vestib Res. 2003; 13(4-6):227-34.

Appendix B

Inner ear specific western blot technique:

Sera from all patients will be collected, before transtympanic injections are initiated, and the presence of autoantibodies against specific inner ear proteins will be studied using the Western-blot technique. This allows the detection of inner ear specific immune disease in cases where general inflammatory or autoimmune markers are not raised (Agrup et al 2005). Separate dissected inner ear tissues (i.e. organ of Corti, stria vascularis, semicircular canals with the ampullary tissue, utricle and endolymphatic sac) from pigmented guinea pigs are used as antigen substrates. Renal medulla and brain are used as negative control tissues. After the antigens have been extracted, they are separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). These filters are then incubated overnight with patient's serum (dilution 1/1000) followed by incubation with anti-human IgG secondary antibody (dilution 1/2500) for 2 hours. Detection will be performed with an enhanced chemiluminescent substrate for detection of horseradish peroxidase. The same amount of protein from various tissues is loaded on each gel to enable semi quantitative evaluation.

1. Agrup C, Keir G, Thompson EJ, Bronstein AM. Systemic autoantibodies against discrete inner ear compartments in bilateral vestibular loss.

Protocol Deviations

OAE tests and western blots removed from protocol owing to difficulties with obtaining equipment for technique.

Statistical Methods (Full Details)

We used previous data on the preservation of hearing levels following steroid or gentamicin injections published by Sennaroglu and colleagues [24] to calculate our sample size. Power calculations (5% significance with 80% power) showed that 60 patients, 30 patients in each treatment arm, provided adequate power to detect a significant change in hearing. It should also be noted that 60 unilateral Ménière's disease patients were used in recent "open-label" intratympanic studies of steroid or gentamicin [13,25].

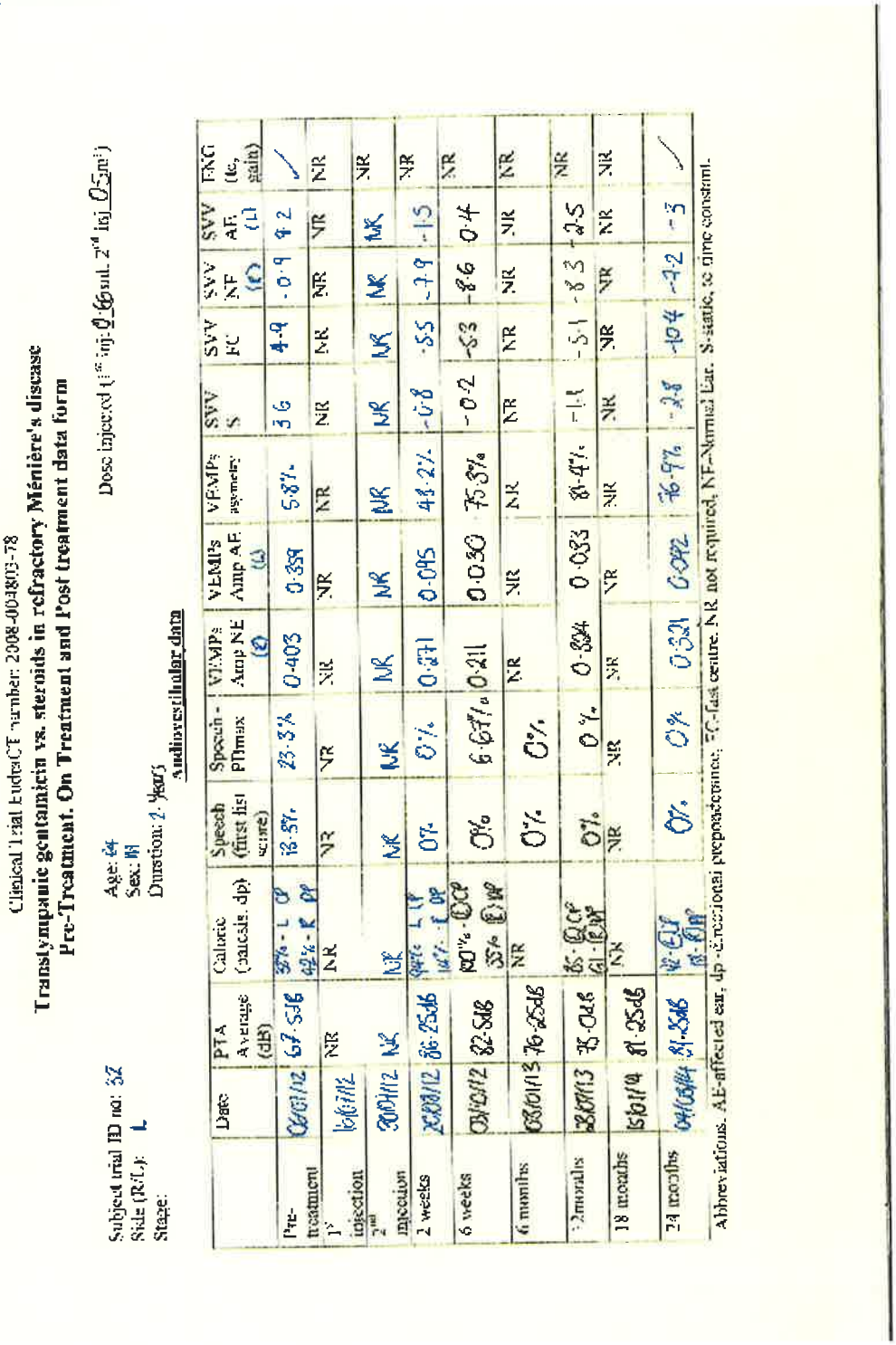
When patients were unable to complete a test a mean value was fitted for data. All primary and secondary measures were completed by the sixty patients over the 24month follow-up period. Six patients never performed the UCF assessment owing to availability of equipment (5 cases) or refusal (1 case). Three patients were unable to perform a caloric test owing to previous grommet insertion (2 cases) or a thin tympanic membrane (1 case).

Demographic and baseline characteristics were compared between groups with paired t-tests (two sided) to check for similarity at baseline. Demographic characteristics were age, gender, disease duration and disease side.

General linear model ANOVA (2x2 design) were performed to investigate the difference between pre and post treatment at each measured interval (time) and arm differences (arm, 2 levels: gentamicin vs steroid).

Analyses were performed with the intention-to-treat population then after removing patient failures. Intention to treat analysis, as defined by NICE (www.nice.org.uk) is an assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. Chi-square analyses were performed when appropriate, as described in the text. P-values were adjusted for multiple comparisons. All analyses were performed with SPSS version 22.

Sample Case Report Form



Clinical Trial EudraCT number: 2008-004803-78

Transtympanic gentamicin vs. steroids in refractory Ménière's disease

Pre-Treatment and Post treatment data form

Subject trial ID no: 32 Age: 64

Side (R/L): L Sex: M

Stage: Duration: 2 years

Dose injected (1st inj) 0.6mL 2nd inj 0.5ml

Audiovestibular data

	Date	PTA Average (dB)	Caloric (paresis, dp)	Speech (first list score)	Speech - PTmax	VEMPs Amp NE (Ø)	VEMPs Amp AE (Ø)	VEMPs asymetry	SVV S	SVV FC	SVV NF (°)	SVV AF (°)	ENG (ie, gain)
Pre-treatment	06/03/12	67.5dB	39% - L DP 42% - R DP	18.8%	23.3%	0.403	0.359	58%	3.6	4.9	-0.9	9.2	✓
1st injection	16/04/12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2nd injection	30/04/12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2 weeks	20/05/12	86.25dB	100% - L DP 100% - R DP	0%	0%	0.271	0.095	48.2%	-0.8	-5.5	-7.9	-1.5	NR
6 weeks	03/07/12	82.5dB	100% - L DP 35% - R DP	0%	6.67%	0.211	0.030	75.8%	-0.2	-5.3	-8.6	0.4	NR
6 months	03/01/13	76.25dB	NR	0%	0%	NR	NR	NR	NR	NR	NR	NR	NR
12months	28/07/13	75.0dB	85% - L DP 61% - R DP	0%	0%	0.324	0.033	81.4%	-1.1	-5.1	-8.3	-2.5	NR
18 months	15/01/14	81.25dB	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
24 months	04/06/14	81.5dB	100% - L DP 85% - R DP	0%	0%	0.321	0.092	76.7%	-2.8	-10.4	-7.2	-3	✓

Abbreviations: AE-affected ear, dp -directional preponderance, FC-fast centre, NR not required, NF-Normal Ear, S-static, to nine constant.

Clinical Tri[redacted]aCT number: 2008-004803-78[redacted]

Transtympanic gentamicin vs. steroids in refractory Ménière's disease
Pre-Treatment, On Treatment and Post treatment data form

Subject trial ID no: 32
Questionnaires due:

Questionnaires	Date	VSS	DHI (total)	DHI (E)	DHI (F)	DHI (P)	THI (total)	THI (F)	THI (E)	THI (C)	FLS	AFS
Pre-treatment	26/07/12	24	60	24	22	14	0	0	0	0	3	0
6 weeks	08/10/12	6	12	0	4	8	0	0	0	0	2	1
6 months	08/01/13	1	10	0	4	6	0	0	0	0	2	0
12 months	26/07/13	0	4	0	2	2	0	0	0	0	1	0
18 months	15/01/14	1	10	0	4	6	0	0	0	0	3	0
24 months	04/08/14	0	0	0	0	0	0	0	0	0	1	0

VSS(Vertigo symptom scale); DHI (Dizziness Handicap inventory); THI (Tinnitus handicap inventory); FLS(Functional level scale); AFS (Aural fullness scale)

CV's of study team

Curriculum Vitae

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EDUCATION

June 2007-May 2009	Lund University Hospital, Sweden PhD Thesis Title: Postural Control and Adaptation to Threats to Balance Stability: **Defended on 16th May 2009.**
September 2001 - July 2006	University of the West of England, Bristol Bsc(Hons)Sw Applied Biological Sciences Degree Classification: **First**

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25th July 2011 - Date	Department of Neuro-Otology, Charing Cross Hospital, London. Supervisor: Professor Adolfo Bronstein.
May 2009-March 2011	Post-Doc research scientist at the Otorhinolaryngology department, Lund University Hospital, Lund, Sweden. Supervisors: Professor Måns Magnusson MD PhD and Associate Professor Per-Anders Fransson PhD CivEng.
September 2006 - May 2007	Assistant in the physiology department at the University of the West of England, Bristol

PRESENTATIONS include

Effects of 24 and 36 hours of sleep deprivation on human postural control and adaptation. **Presented by M Patel.** Bárány Meeting, Kyoto, Japan. May 2008.

Motor control and adaptation are affected by one night of total sleep deprivation. **Presented by M Patel.** Motor Network Conference, Lund University, Sweden. October 2008.

Difficulties in the clinical assessment of balance using foam surfaces. **Presented by M Patel.** 14th Congress on Research in Biomedical Sciences at the University of Iceland, Reykjavik, Iceland, January 2009.

Foam surfaces and standing balance testing: The balance perturbing effects, the perturbing mechanisms and considerations for clinical and experimental practice. **Presented by M Patel.** Bárány Meeting, Reykjavik, Iceland. August 2010.

Change of body movement coordination during cervical proprioceptive disturbances in older adults. **Presented by M Patel.** Bárány Meeting, Reykjavik, Iceland. August 2010.

PUBLICATIONS

Changes in multi-segmented body movements and EMG activity while standing on firm and foam support surfaces. PA Fransson, S Gomez, **M Patel**, L Johansson. European Journal of Applied Physiology. 2007; 101 (1): 81-89.

Effects of 24-h and 36-h sleep deprivation on human postural control and adaptation. **M Patel**, S Gomez, S Berg, P Almbladh, J Lindblad, H Peterson, M Magnusson, R Johansson, PA Fransson. Experimental Brain Research. 2008 Feb; 185(2): 165-173.

The effect of foam surface properties on postural stability assessment while standing. **M Patel**, PA Fransson, D Lush, S Gomez. Gait & Posture. 2008; 28(4): 649-656.

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2 Page CV for Research Projects

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Qualifications

1988	**MA: First Class Honours** Cambridge University Medical Science Tripos
1991	**BM BCh:** Oxford University Medical School
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2001	**Intercollegiate Examination in Otolaryngology: Gold Medal**

- 0 -

Mr Peter Anthony REA

Sub-speciality interest

In 2004 I took over as lead clinician at the **"hearing and balance centre"** at the Leicester Royal Infirmary, and now with colleagues have grown it into a large centre with 5,500 appointments per year. This unit has built up an international reputation as a centre of excellence for the investigation and management of patients with dizziness, vertigo and balance problems. This allows me to investigate patients with hearing and balance complaints to the very highest standard. I have a varied training in all aspects of otology and balance having trained at outstanding units such as The Royal National Throat Nose and Ear Hospital, London, The National Hospital for Neurology and Neurosurgery, Queen's Square, London, and a prestigious Fellowship period investigating and treating middle and inner ear disease in Sydney in both children and adults, each with internationally recognised experts. I have authored research articles, and written chapters in leading ENT textbooks.

I oversee the management of 30-40 often complex patients with inner ear disease every week. Many are referrals from other ENT surgeons from around the UK.

I also am directly involved in novel and cutting edge research in balance disorders, tinnitus, and inner ear disease both with the University and through clinical studies of patients with balance problems and tinnitus.

Most Recent Book Publications

Rea P, Graham J. *Acute suppurative otitis media.* **Scott Brown's Otorhinolaryngology, Head and Neck Surgery - 7th Edition. Paediatric volume.** Arnold. April 2008

Rea P. *Otosclerosis: Management with Hearing aids.* **Scott Brown's Otorhinolaryngology, Head and Neck Surgery - 7th Edition. Otology volume.** Arnold. April 2008

ReaP, Tange R. *Otosclerosis: Surgical Management.* **Scott Brown's Otorhinolaryngology, Head and Neck Surgery - 7th Edition. Otology volume.** Arnold. April 2008

Rea.P. *Vertigo and Balance Disorders.* **Ballantyne's Deafness 7th Edition** 2009

Most Recent Patent

The head thrust device – a new tool to investigate patients with balance disorder. Patent application in progress 2012

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	MA (Oxon)	1992
	FRCS (Eng) - Clinical Surgery-in-General	1992
	FRCS (Eng) - Otolaryngology	1993
	FRCS (ORL)	1997

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D.Phil. Experimental Psychology, University of Oxford (1980).
Chartered Psychologist (1990) with current Practising Certificate.

Current Post
2006 - Professor of Applied Psychology, Dept. of Psychology, University of Westminster, Londc

Previous Posts
1978-1979 Research Associate, M.R.C. funded Delta-9 THC Cannabis project, Clinical Psychopharmacology Unit, The Medical School, University of Newcastle upon Tyne.
1979-1982 Senior Research Fellow, Industry funded Nicotine project, Department of Experimental Psychology, University of Oxford.
1982-1987 Senior Research Associate, M.R.C./Wellcome funded Pain project, Clinical Psychopharmacology Unit, The Medical School, University of Newcastle upon Tyne.
1987-1990 Senior Psychologist, Human Factors Division (Navy), Institute of Naval Medicine, Gospc Hants.
1990-94 Senior Psychologist, Head of Vestibular Physiology Section, Special Senses Division, RA Institute of Aviation Medicine, Farnborough
1994-95 Deputy Head Neurosciences Division, Defence Research Agency, Centre for Human Sciences, Farnborough.
1995- 2005 Senior Lecturer, Dept. of Psychology, University of Westminster, London.

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Recent Publications:

John F. Golding, Smitha Arun, Elizabeth Wortley, Kahina Wotton-Hamrioui, Sian Cousins, Michael A. Gresty. (2009) Off Vertical Axis Rotation (OVAR) of the Visual Field and Nauseogenicity. **Aviat Space Environ Med** 2009; 80: 516-521.

Gresty MA, Golding JF. (2009) Impact of vertigo and spatial disorientation on concurrent cognitive tasks. **Ann NY Acad Sci** 2009; 1164 : 263-267.

Denise P, Vouriot A, Normad H, Golding JF, Gresty MA (2009) Effect of temporal relationship between respiration and body motion on motion sickness. **Autonomic Neuroscience** 2009; 151: 142-6.

Adolfo M Bronstein, John F Golding, Michael A Gresty, Marco Mandalà, Daniele Nuti, Anu Shetye, Yvonne Sllove. (2009) The Social Impact of Dizziness in London and Siena. **J Neurol** 2009 [Epub ahead of print]

Rosalind Potts, Robin Law, John F Golding, David Groome. (2010) The Reliability of Retrieval-Induced Forgetting. **European Psychologist** 2010 (in press)

David A Green, Junhao Leon Zhu, Anand Shah, John Golding, Michael A Gresty. (2010) Slalom Walking with Prism Disorientation: Impact on Verbal and Spatial Tasks. **Aviat Space Environ Med** 2010; 81:728-734.

John F. Golding, Olena Prosyanikova, Maria Flynn, Michael A Gresty. (2011) The effect of Smoking Nicotine Tobacco *versus* Smoking Deprivation on Motion Sickness. **Autonomic Neuroscience: Basic and Clinical** 2011; 160: 53-58.

Rachael Hornigold, John F Golding, Robin E Ferner, Rosalie E Ferner. (2011) Neurofibromatosis 2: A Novel Risk Factor for Hypertension? **Am J Med Genetics** (in press)

Michael A Gresty, Wei Lin Sung, Neeraj Kohli, Shamim Q'adir, John F Golding, Adolfo M Bronstein. (2011) Respiratory Vulnerability to Vehicle Buffeting. **Clin Autonom Res** (in press)

5/7/11

Curriculum Vitae

Name: Kiran Agarwal (Gaba) **Date of Birth**: 17 Jan 1978
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Current Appointments:

- Clinical Research Fellow to Professor Bronstein, Academic Department of Neurotology, Imperial College London, Charing Cross Hospital. *Sept 2008 till date*
- Honorary Clinical Assistant, Department of Neurotology, Charing Cross Hospital, Fulham Palace Road. *Nov 2006 till date*
- Honorary Clinical Assistant, National Hospital of Neurology and Neurosurgery, Queen Square, London. *June 2007 till date*

Primary Medical Education: Bachelor of Medicine and Bachelor of Surgery **(MBBS)**- Medical College and Hospitals, Calcutta (University of Calcutta), *1995- 2001*

Postgraduate Qualifications:

- **DOHNS**, *2010*
- **MRCS Part A**, *2011*
- **Doctor of Medicine by Research (MD)** *Sept 2008 till date* - Imperial College London

[Thesis: 'Physiological and immunological response in Meniere's disease patients undergoing Transtympanic treatment: basic and applied study']

- **Master of Surgery (MS)** *2003-2006* - Vardhaman Mahavir Medical College and Safdarjung Hospital (University of Delhi)

[Thesis: 'Evaluation and workup to detect regions of disproportionate anatomy and its subsequent management in patients of snoring and OSA' - Best Oral Paper award for the same in SLEEPCON, 2005, New Delhi]

Previous posts:

Sept 2006-Oct 2006: Clinical Research Consultant, Neurotology Unit, Imperial College London.
May 2003-April 2006: Postgraduate Surgical Trainee, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India. [Department of ENT; Department of Pulmonary Critical Care and Sleep Medicine]
October 2001-April 2003: Junior Surgical Officer (General Surgery), Aditya Hospital, Kolkata, India.
Aug 2001- Sept 2001: Intern, Cardiology and Respiratory Medicine, Safdarjung Hospital, New Delhi.
May 2001- Aug 2001: Intern, Obstetrics and Gynaecology, Safdarjung Hospital, New Delhi
April 2001- May 2001: Intern, General Medicine, Medical College and Hospitals, Kolkata.
Jan 2001- Mar 2001: Intern, Community Medicine, Medical College and Hospitals, Kolkata.
Oct 2000-Dec 2000- Intern, General Surgery, Medical College and Hospitals, Kolkata.

Andrea Davis-Cook (nee Davis)

Employment History

September 1995 – September 1997 Dartford and Gravesham NHS Trust
(Joyce Green Hospital)
- Student Pharmacy Technician: Dispensary
- MTO 1 Dispensary based Technician

September 1997 – July 2000 Queen Mary's Hospital Sidcup NHS Trust
- MTO 1 Rotational Technician
- MTO 2 Rotational Technician
- MTO 2 Deputy Senior Preparative Services

July 2000 until present day Imperial College NHS Health Trust — Charing Cross Hospital London
- MTO 3 Lead Senior For Parentral Nutrition
- MTO 3 ** Lead Senior Technician
- Band 6 Senior Technician PN & Clinical Trials

Current Role: Senior Pharmacy Technician Clinical Trials Aseptic Services
- Negotiation and liaison with other staff groups
- Development of training procedures
- Training staff of various grades and experience
- Departmental procedure writing and development
- Collation of statistical data
- Development of clinical trial worksheets
- Qualified NVQ assessor
- Clinical Trial technician responsibilities for Charing Cross Aseptic unit.

Membership

Register Pharmacy Technician with the Royal Pharmaceutical Society of Great Britain
Membership number: PT1095605

Affiliate member of The Institute of Clinical Research

Education

January 2009 — **Introduction to EU clinical trails directive 2001/20/EC Directive (Online)**

November 2008 — **Principles of ICH-GCP (Online)**

March 2004 — St Charles NVQ Centre

A1 Assessing Candidates using a range of methods

September 1995 until July 1997 — North West Kent College
Dartford, Kent

BTEC National Certificate in Pharmaceutical Sciences

September 1989 until July 1994 — Swanley School
Kent

Nine General Certificate in secondary education (GCSE) Grades A-D

04 FEB 2010

Curriculum Vitae

Name: **Mohamed A Hariri,**
Consultant Audiological Physician
Honorary Senior Clinical Lecturer
Charing Cross Hospital
Fulham Palace Road, London W6 8RF
Tel 020 8846 1004 Fax 020 8846 1200
Email Mohamed.hariri@imperial.nhs.uk

GMC No. **03364383**

Qualification:

MSc, Master of Science Audiological Medicine, Manchester University	1992
FRCS. Fellowship in Otolaryngology The Royal College of Surgeon, Edinburgh	1985
DLO Diploma in Laryngology and Otology Royal College of Surgeons, England	1984
MD Medical Doctor, Damascus University	1978

Areas of Expertise:

- Assessment and management of hearing loss, tinnitus and dizziness in adults.
- Assessment and management of congenital or acquired hearing loss in. neonates and children.
- Special experience in assessing hearing in children with multiple mental or physical disabilities.

Previous Employment:

- Training Program in ENT surgery 1982-1989
  In hospitals in the UK.
- Training Program in Audiological Medicine 1990-1993
  Manchester Royal infirmary and
  Department of Audiology, Manchester University

4/8/11

CURRICULUM VITAE

BARRY SEEMUNGAL

30/06/2011

Born: Port-of-Spain, Trinidad, W.I., 21-06-1967
British citizen.
Married with 2 children.

CURRENT POSITION
Academy of Medical Sciences & Health Foundation Clinician Scientist Fellow
Senior Lecturer & Honorary Consultant Neurologist, Imperial College & ICH NHS Trust.

EDUCATION

Intercal. BSc Physiology	2.1 Cardiff University,1989
MB BCh	Cardiff University, 1993
MRCP (UK)	Royal Coll Physicians, 1996
PhD	University College London, fON 2005

CLINICAL EMPLOYMENT

Medical PRHO	University College Hospital., Cardiff.	1993
Senior HO	St Mary's; Central Middx; Royal Free, London.	1994-96
Gen Medicine SpR	Oxford Deanery. Milton Keynes & Oxford Radcliffe.	1997-99
Neurology SpR	London Deanery. West London rotation.	2003-08
Consultant	Locum neurology consultant. ICH NHS Trust.	May-Oct 2008
	Honorary consultant neurologist, ICH NHS Trust.	Oct 2008-present

GRANTS & SCHOLARSHIPS

MRC Intercalated BSc Scholarship. 1988	£2,000
Dix Foundation. 1999	£100,000
Acad Medical Sciences & Health Foundn Clinician Scientist Fellowship. 2008	£677,504.

EDITORIAL & REVIEWER ACTIVITIES
Editorial board: Frontiers in Neuro-Otology.
Reviewer for: Neurology, Movement Disorders, Journal of Neurology Neurosurgery and Psychiatry, Experimental Brain Research, Journal of Neuro-Endocrinology, Journal of Vestibular Research, , Gait and Posture, Ophthalmic and Physiological Optics.Grant reviews for Action Research.

RESEARCH SUPERVISION
Primary supervisor for 2 PhD students
Co-supervisor for 1 clinical fellow and 1 PhD student.

INVITED TALKS IN 2011
Keynote speaker - Medical Ophthalmology Society. Birmingham. March 2011.
British Society of Audiology. London. March 2011.

Invited speaker - Basic & Clinical Ocular Motor & Vestibular Research. Buenos Aires. March 2011.
Hallpike Symposium. London March 2011.

PUBLICATIONS
Guzman J, Silvanto J, Seemungal BM. Visual motion adaptation increases the susceptibility of area V5/MT to phosphene induction by transcranial magnetic stimulation. Clin Neurophysiol. 2011. *In Press.*

Arshad Q, Kaski D, Gresty M, seemungal BM, Bronstein AM. A new clinical test of otolith function. Audiology & Neurotology.2011. *in press.*

Seemungal BM, Masaoutis P, Green DA, Plant GT, Bronstein AM. Symptomatic Recovery in Miller Fisher Syndrome Parallels Vestibular-Perceptual and not Vestibular-Ocular Reflex Function. Frontiers in Neurology. 2011;2:2.

Seemungal BM, Arshad Q, Guzman J, Walsh V, Schultz S, Yousif N. Vestibular Activation Differentially modulates Human V1 and V5/MT Excitability and Response Entropy. Curr Biol. - *Under review.*

3/7/11

CURRICULUM VITAE

NAME:	**BRONSTEIN, Adolfo Miguel**
DATE OF BIRTH:	22.5.50
PLACE OF BIRTH:	- Buenos Aires (Argentina)
NATIONALITY:	- British
MARITAL STATUS:	- Married, two children
QUALIFICATIONS/:	- Medico (MD), Universidad de Buenos Aires, Argentina,1975
ACCREDITATION	- PhD, University of London, Faculty of Medicine, 1990 Thesis on: Sensory Interactions in Balance and Eye Movement Control - FRCP (UK), 2002 - Specialist in Neurology, Ministry of Health, Buenos Aires, 1980. - Full Medical Registration with the General Medical Council (UK), 1985 - Completion of Specialist Training (GMC 'T' entry), 1991 - GMC Specialist Registrar (Neurology), 1996
MEMBERSHIP TO SOCIETIES:	- Barany Society; Association of British Neurologists; British Society of Audiology; British Society of Audiological Physicians; Physiological Society; British Society of Neuro-Otology; American Neurological Association - 2008: awarded the Nylen-Hallpike Prize by the Barany Society for outstanding contribution to clinical neuro-otology

CURRENT POSITION:
- Professor of Clinical Neuro-Otology, Imperial College School of Medicine.
- Head, Neuro-otology Unit, Department of Clinical Neuroscience, Division of Neuroscience and Mental Health, Imperial College London.
- Consultant Neurologist, Charing Cross Hospital, Fulham Palace Road, London
- Consultant Neurologist, National Hospital (UCLH), Queen Square, London.
- Honorary Professor, Institute of Neurology, Queen Square, UCL, London

CURRENT/RECENT INTERNATIONAL EDITORIAL ACTIVITIES
- Associate Editor, Gait and Posture.
- Ad Hoc Editor (Neuro-otology and Neuro-ophthalmology), Current Opinion in Neurology.
- Member, Editorial Board: Journal of Vestibular Research, Auris-Nasus-Larynx.

Ad Hoc Reviewer: Acta Otolaryngologica (Stockholm), Age and Ageing, Annals of Neurology, Brain, Brain Research, Brain Research Bulletin, British Journal of Audiology, Experimental Brain Research, J of Audiological Medicine, J of the International Neuropsychological Society, J of Neurology, J of Neurology Neurosurgery and Psychiatry, J of Vestibular Research, Movement Disorders, Proceedings of the American Academy of Science, Neuroscience, J of Neurophysiology and others.

Randomisation and concealment

The randomisation sequence (Table 2) was generated by constructing 15 blocks of 4 possible combinations containing 2 Methylprednisolone and 2 Gentamicin treatments. This was done to keep the allocation of either drug roughly equal throughout recruitment in the event of early termination or poor recruitment. The randomisation sequence was retained and concealed by Charing Cross Hospital aseptic unit and later by Leicester Royal Infirmary aseptic unit who prepared each injection and documented the drug history for each patient.

1	G	21	M	41	M
2	M	22	G	42	G
3	M	23	M	43	G
4	G	24	G	44	M
5	G	25	M	45	M
6	G	26	M	46	M
7	M	27	G	47	G
8	G	28	G	48	M
9	M	29	M	49	G
10	M	30	G	50	G
11	G	31	G	51	M
12	M	32	G	52	M
13	G	33	M	53	G
14	G	34	G	54	G
15	M	35	M	55	G
16	M	36	G	56	M
17	G	37	M	57	G
18	G	38	G	58	M
19	M	39	M	59	M
20	M	40	M	60	G

Table 2: Randomisation sequence

Audit Log

Imperial College London

Imperial College Healthcare NHS Trust

Joint Research Office (JRO)
Imperial College London & Imperial College Healthcare NHS Trust
St. Mary's Hospital, Faculty of Medicine
Room GM14
Ground Mezzanine Floor
Praed Street Wing
W2 1PG

CLINICAL TRIALS MONITORING VISIT AND AUDIT LOG

STUDY TITLE: Effectiveness of Transtympanic Steroids in unilateral Ménière's disease: a Randomised Controlled Double-Blind Trial

CHIEF INVESTIGATOR: Professor Adolfo M Bronstein

PRINCIPAL INVESTIGATOR: Professor Adolfo M Bronstein

SPONSOR NUMBER: cro1135

EUDRACT NUMBER: 2008-004803-78

STUDY SITE: Charing Cross Hospital

Date	Type Of Visit	Study Monitor Name	Study Monitor Signature	Study Representative Name	Study Representative Title	Study Representative Signature
05/07/11	RMV2	Susana murphy	S. Murphy	Kieran Nolan	Clinical Research Fellow	
"	"	"	"	MELANIE CAMPBELL	PHARMACIST	M Campbell
24/07/12	RMV 3	Susana murphy	S. Murphy	[illegible]	chief [illegible]	
25/07/12	RMV 3	Susana murphy	S. Murphy	MELANIE CAMPBELL	PHARMACIST	M Campbell
30/07/13	RMV4	Susana murphy	S. Murphy	MITESH PATEL	RESEARCH ASSOCIATE	
31/07/13	RMV4 add	Susana murphy	S. Murphy	MITESH PATEL	RESEARCH ASSOCIATE	
"	"	"	"	ANDREA DAVIS-COX	LEAD PHARMACY TECHNICIAN	
28/10/14	RMV5	Susana murphy	S. Murphy	MITESH PATEL	RES ASSOCIATE	
29/10/14	RMV5	Susana murphy	S. Murphy	ANDREA DAVIS-COX	LEAD PHARMACY TECHNICIAN	
30/10/14	RMV5	Susana murphy	S. Murphy	MITESH PATEL	RESEARCH ASSOCIATE	
04/11/14	RMV5	Susana murphy	S. Murphy	MITESH PATEL	RES ASSOCIATE	

Steroid vs Gentamicin in unilateral Meniere's disease

EudraCT Number: 2008-004803-78

REC Reference Number: 08/H0712/95

Sponsor Reference Number: CRO1135

Close-Out visit

Imperial College Healthcare NHS
NHS Trust

Imperial College
London

Joint Research Compliance Office
Imperial College Academic Health Science Centre
Room 5L01, 5th Floor, Lab Block
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Professor Adolfo M Bronstein
Academic Neuro-otology
10L 15b Lab Block
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Dear Professor Bronstein,

Close Out Visit Report

I would like to thank Dr Mitesh Patel and Andrea Davis-Cook for attending the Close Out Visit for the study below. This report details the findings and follow-up actions.

Close Out Visit Report

Trial Information		
Title of Trial: Effectiveness of Transtympanic Steroids in unilateral Ménière's disease: a Randomised Controlled Double-Blind Trial.		
Chief Investigator: Professor Adolfo Bronstein		**Principal Investigator:** Professor Adolfo Bronstein
Sponsor ref: cro1135 **Study Trust ref:** BROA2010	**Ethics no:** 08/H0712/95	**EudraCT no:** 2008-004803-78
Name of IMP (s): Methylprednisolone, Gentamicin		**Number of Recruited Subjects:** 60 (Fully recruited)
Monitoring Visit Details		
Name of Monitor: Nihaad Abbass	**Site Visit Date & Time:** 30 Jun 2015, 10.30 AM	**Address of Site Monitored:** Lower Ground – Academic

12. References

1. Adrion C, Fischer CS, Wagner J, et al. Efficacy and safety of betahistine treatment in patients with Meniere's disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial (BEMED trial). Bmj 2016;352:h6816.
2. Harcourt J, Barraclough K, Bronstein AM. Meniere's disease. Bmj 2014;349:g6544.
3. Pullens B, van Benthem PP. Intratympanic gentamicin for Meniere's disease or syndrome. The Cochrane database of systematic reviews 2011:CD008234.
4. Cohen-Kerem R, Kisilevsky V, Einarson TR, Kozer E, Koren G, Rutka JA. Intratympanic gentamicin for Meniere's disease: a meta-analysis. The Laryngoscope 2004;114:2085-91.
5. Huon LK, Fang TY, Wang PC. Outcomes of intratympanic gentamicin injection to treat Meniere's disease. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 2012;33:706-14.
6. Stahle J, Friberg U, Svedberg A. Long-term progression of Meniere's disease. Acta oto-laryngologica Supplementum 1991;485:78-83.
7. Hu A, Parnes LS. Intratympanic steroids for inner ear disorders: a review. Audiology & neuro-otology 2009;14:373-82.
8. Cope D, Bova R. Steroids in otolaryngology. The Laryngoscope 2008;118:1556-60.
9. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. American Academy of Otolaryngology-Head and Neck Foundation, Inc. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 1995;113:181-5.
10. Palla A, Straumann D, Bronstein AM. Vestibular neuritis: vertigo and the high-acceleration vestibulo-ocular reflex. Journal of neurology 2008;255:1479-82.
11. Patel M, Arshad Q, Roberts RE, Ahmad H, Bronstein AM. Chronic Symptoms After Vestibular Neuritis and the High-Velocity Vestibulo-Ocular Reflex. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 2016;37:179-84.
12. Webster JC, McGee TM, Carroll R, Benitez JT, Williams ML. Ototoxicity of gentamicin. Histopathologic and functional results in the cat. Transactions - American Academy of Ophthalmology and Otolaryngology American Academy of Ophthalmology and Otolaryngology 1970;74:1155-65.
13. Casani AP, Piaggi P, Cerchiai N, Seccia V, Franceschini SS, Dallan I. Intratympanic treatment of intractable unilateral Meniere disease: gentamicin or dexamethasone? A randomized controlled trial. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2012;146:430-7.
14. Phillips JS, Westerberg B. Intratympanic steroids for Meniere's disease or syndrome. The Cochrane database of systematic reviews 2011:CD008514.
15. Boleas-Aguirre MS, Lin FR, Della Santina CC, Minor LB, Carey JP. Longitudinal results with intratympanic dexamethasone in the treatment of Meniere's disease. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 2008;29:33-8.
16. Garduno-Anaya MA, Couthino De Toledo H, Hinojosa-Gonzalez R, Pane-Pianese C, Rios-Castaneda LC. Dexamethasone inner ear perfusion by intratympanic injection in unilateral Meniere's disease: a two-year prospective, placebo-controlled, double-blind, randomized trial. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2005;133:285-94.
17. Usami S, Abe S, Akita J, et al. Prevalence of mitochondrial gene mutations among hearing impaired patients. Journal of medical genetics 2000;37:38-40.
18. Silverstein H, Rowan PT, Olds MJ, Rosenberg SI. Inner ear perfusion and the role of round window patency. The American journal of otology 1997;18:586-9.

19. Lyford-Pike S, Vogelheim C, Chu E, Della Santina CC, Carey JP. Gentamicin is primarily localized in vestibular type I hair cells after intratympanic administration. Journal of the Association for Research in Otolaryngology : JARO 2007;8:497-508.
20. Hamid M, Trune D. Issues, indications, and controversies regarding intratympanic steroid perfusion. Current opinion in otolaryngology & head and neck surgery 2008;16:434-40.
21. Fukushima M, Kitahara T, Uno Y, Fuse Y, Doi K, Kubo T. Effects of intratympanic injection of steroids on changes in rat inner ear aquaporin expression. Acta oto-laryngologica 2002;122:600-6.
22. Pondugula SR, Sanneman JD, Wangemann P, Milhaud PG, Marcus DC. Glucocorticoids stimulate cation absorption by semicircular canal duct epithelium via epithelial sodium channel. American journal of physiology Renal physiology 2004;286:F1127-35.
23. Trune DR, Kempton JB, Harrison AR, Wobig JL. Glucocorticoid impact on cochlear function and systemic side effects in autoimmune C3.MRL-Faslpr and normal C3H/HeJ mice. Hearing research 2007;226:209-17.
24. Sennaroglu L, Sennaroglu G, Gursel B, Dini FM. Intratympanic dexamethasone, intratympanic gentamicin, and endolymphatic sac surgery for intractable vertigo in Meniere's disease. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2001;125:537-43.
25. Albu S, Chirtes F, Trombitas V, et al. Intratympanic dexamethasone versus high dosage of betahistine in the treatment of intractable unilateral Meniere disease. American journal of otolaryngology 2015;36:205-9.