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

Summary

EudraCT number	2008-004803-78
Trial protocol	GB
Global end of trial date	04 May 2015

Results information

Result version number	v1 (current)
This version publication date	14 May 2016
First version publication date	14 May 2016
Summary attachment (see zip file)	End of Trial Summary Report (EndOfTrialReport_08_H0712_95.pdf)

Trial information

Trial identification

Sponsor protocol code	1.1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington, London, United Kingdom,
Public contact	Dr Mitesh Patel, Imperial College London, 0044 208 223 7241, Mitesh.Patel1@imperial.ac.uk
Scientific contact	Dr Mitesh Patel Professor Adolfo Bronstein, Imperial College London, 0044 208 223 7241, Mitesh.Patel1@imperial.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2015
Global end of trial reached?	Yes
Global end of trial date	04 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

There are 20-24% of patients with Meniere's disease who do not respond to first line treatment with diet modification and oral drugs. One of the well established alternative treatment option is the minimally invasive transtympanic treatment, where drugs are injected locally through the ear drum. The most commonly used drug for injection is Gentamicin. Gentamicin provides effective control of vertigo by toxic action on the labyrinth. But it is potentially harmful to hearing organ also and may produce further hearing deterioration in 25% of patients and profound loss in 7%. Recently, steroids are used as an alternative by many ENT surgeons with reports that it provides relief of vertigo without hearing loss or maybe hearing improvemnet also. However, this has not been proven. The main research question is to compare the two drugs and establish their role in Meniere's patients who are not responding to medical treatment.

Protection of trial subjects:

An audiogram was obtained before the second injection (2 weeks after the first) which was assessed by a blinded consultant (MH) and reported to the pharmacy. Following a 20dB (decibel) drop in hearing across any two consecutive frequencies, the pharmacy (without informing the trial team) switched gentamicin for saline (Figure 1). As steroids do not disturb hearing, patients randomised to steroid were given a second steroid injection.

Non responders: If vertigo attacks returned (=non-responder) an unblinded consultant (BMS) prescribed a further course of intratympanic injections but the patient and everybody else remained blind. The clinician had the choice to prescribe the same drug or swap, basing this decision on the patient’s response to previous injections.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between November 2009-May 2013

Pre-assignment

Screening details:

Inclusion criteria were patients 18-70 years of age with definite unilateral MD having experienced at least 2 episodes of rotational vertigo lasting at least 20min in the previous 6 months and shown no response to standard medical treatment.

Pre-assignment period milestones

Number of subjects started	60
Number of subjects completed	60

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

The double-blind randomisation sequence was generated by constructing 15 blocks of 4 possible combinations, containing 2 Steroid and 2 Gentamicin treatments, to keep drug allocation roughly equal throughout recruitment. The randomisation sequence was retained and concealed by the Charing Cross Hospital and Leicester Royal Infirmary pharmacy aseptic units

Arms

Are arms mutually exclusive?	Yes
Arm title	Gentamicin (control)

Arm description:

Gentamicin – 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 was 2 doses (spaced 2 weeks apart) of 1ml of 40mg/ml.

Arm type	Active comparator
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intratympanic use

Dosage and administration details:

2 initial doses (spaced 2 weeks apart) of 1ml of 62.5mg/ml. Repeat injections if necessary over 2 years. 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 was attached to a 22Gauge spinal needle which, under microscopic control, was inserted in the inferior aspect of the pars tensa. The injection continued until a fluid level could be seen to fill the tympanic cavity and the volume injected was recorded. The patient was asked not to swallow or speak for 20 minutes. Immediately after treatment, all 60 patients were issued the same (Cawthorne-Cooksey) rehabilitation exercises and instructed to begin performing them after 3 days, twice daily, beginning slowly and grading their intensity progressively over 4 weeks.

Investigational medicinal product name	Gentamicin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Intratympanic use

Dosage and administration details:

2 initial doses (spaced 2 weeks apart) of 1ml of 40mg/ml. Repeat injections if necessary over 2 years. 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 was attached to a 22Gauge spinal needle which, under microscopic control, was inserted in the inferior aspect of the pars tensa. The injection continued until a fluid level could be seen to fill the tympanic cavity and the volume injected was recorded. The patient was asked not to swallow or speak for 20 minutes. Immediately after treatment, all 60 patients were issued the same (Cawthorne-Cooksey) rehabilitation exercises and instructed to begin performing them after 3 days, twice daily, beginning slowly and grading their intensity progressively over 4 weeks.

Arm title	Methylprednisolone

Arm description:

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 was 2 doses (spaced 2 weeks apart) of 1ml of 62.5mg/ml.

Arm type	Active comparator
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intratympanic use

Dosage and administration details:

2 initial doses (spaced 2 weeks apart) of 1ml of 62.5mg/ml. Repeat injections if necessary over 2 years. 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 was attached to a 22Gauge spinal needle which, under microscopic control, was inserted in the inferior aspect of the pars tensa. The injection continued until a fluid level could be seen to fill the tympanic cavity and the volume injected was recorded. The patient was asked not to swallow or speak for 20 minutes. Immediately after treatment, all 60 patients were issued the same (Cawthorne-Cooksey) rehabilitation exercises and instructed to begin performing them after 3 days, twice daily, beginning slowly and grading their intensity progressively over 4 weeks.

Number of subjects in period 1[1]	Gentamicin (control)	Methylprednisolone
Started	30	30
Completed	29	28
Not completed	1	2
Transferred to other arm/group	-	2
Lost to follow-up	1	-

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: Two patient crossed over from methylprednisolone to gentamicin due to non-response One patient in the gentamicin arm was lost to follow-up.

Baseline characteristics

Reporting groups	
Reporting group title	Gentamicin (control)
Reporting group description:	
Gentamicin – 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 was 2 doses (spaced 2 weeks apart) of 1ml of 40mg/ml.	
Reporting group title	Methylprednisolone
Reporting group description:	
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 was 2 doses (spaced 2 weeks apart) of 1ml of 62.5mg/ml.	

Reporting group values	Gentamicin (control)	Methylprednisolone	Total
Number of subjects	30	30	60
Age categorical			
Inclusion criteria: 18-70 years of age			
Units: Subjects			
Adults (18-64 years)	25	25	50
From 65-84 years	5	5	10
Age continuous			
Units: years			
arithmetic mean	53.3	51.6	
standard deviation	± 10.8	± 10.2	-
Gender categorical			
Units: Subjects			
Female	14	10	24
Male	16	20	36

End points

End points reporting groups

Reporting group title	Gentamicin (control)

Reporting group description:

Gentamicin – 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 was 2 doses (spaced 2 weeks apart) of 1ml of 40mg/ml.

Reporting group title	Methylprednisolone

Reporting group description:

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 was 2 doses (spaced 2 weeks apart) of 1ml of 62.5mg/ml.

Primary: Attacks of vertigo (Primary Outcome)

End point title	Attacks of vertigo (Primary Outcome)

End point description:

End point type	Primary

End point timeframe:

18-24 months follow-up as per AAO-HNS recommendations.

End point values	Gentamicin (control)	Methylpredniso lone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: number				
number (not applicable)	2.5	1.6		

Statistical analyses

Statistical analysis title	Outcome measure stats

Statistical analysis description:

There was a significant reduction of vertigo attacks in the final six 6 months (time; F[1,58]65.0; P<0.001). Mean number of vertigo attacks fell from 19.9 to 2.5 in the gentamicin arm and from 16.4 to 1.6 in the steroid arm. There was no significant difference between drugs (drug; F[1,58]1.2;P=0·271, time x drug interaction; F[1,58]0.43; P=0.514).

Comparison groups	Gentamicin (control) v Methylprednisolone
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.514 [1]
Method	ANOVA

Notes:

[1] - No difference between drugs for primary outcome measure

Secondary: Change in Hearing threshold

End point title	Change in Hearing threshold

End point description:

End point type	Secondary

End point timeframe:

2 years follow-up as per AAO-HNS recommendations

End point values	Gentamicin (control)	Methylpredniso lone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[2]	30[3]		
Units: dB				
number (not applicable)	49.1	46.9		

Notes:

[2] - Intention-to-treat

[3] - Intention-to-treat

Statistical analyses

Statistical analysis title	Hearing Analysis (Secondary Outcome)
Comparison groups	Gentamicin (control) v Methylprednisolone
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	= 0.18 [5]
Method	ANOVA

Notes:

[4] - Hearing levels did not significantly change from baseline over the 24 months follow-up (time; F [6,54]2.13; P=0.065). There was no significant difference between drugs (drug F[1,58]0.03; P=0.964 ; time x drug interaction; F[6,54]1.55; P=0.18).

[5] - No significant difference between arms

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 2 years follow-up	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	RF2
Reporting groups	
Reporting group title	Adverse Events (Gentamicin)
Reporting group description: -	
Reporting group title	Adverse Events (Methylprednisolone)
Reporting group description: -	

Serious adverse events	Adverse Events (Gentamicin)	Adverse Events (Methylprednisolone)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 30 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Adverse Events (Gentamicin)	Adverse Events (Methylprednisolone)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)	3 / 30 (10.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Schwannoma	Additional description: Abdomen		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Buccal polyp			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Otitis media			
subjects affected / exposed	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences (all)	2	1	

Eye disorders Retinoschisis subjects affected / exposed occurrences (all)	 0 / 32 (0.00%) 0	 1 / 30 (3.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2009	Otoacoustic emission testing removed from audiological testing battery due to non-availability of equipment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported