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|  | Steroids and Hyperbaric Oxygen for Sudden Sensorineural Hearing Loss (SHOOSH): a randomised controlled trial.[Keyline divider beneath titleDr Susannah Sherlock, Royal Brisbane and Women’s Hospital (RBWH), Anaesthesia and Hyperbaric Medicine, Burns, Trauma and Critical Care Research Centre (BTCCRC), University of Queensland (UQ), BrisbaneDr Sharon Kelly, RBWH, Dept of ENT Surgery, BrisbaneProf Michael Bennett, Dept of Diving and Hyperbaric Medicine, Prince of Wales Medical School (UNSW) and Prince of Wales Hospital (POWH), SydneyDr David Cooper, Intensive Care and Hyperbaric Medicine, University of Tasmania, Royal Hobart Hospital (RHH), HobartDr David Kramer, RBWH, Hyperbaric Medicine, Brisbane.Dr Alexis Tabah, Intensive Care (Redcliffe) and Hyperbaric Medicine RBWH, BTCCRC (UQ), BrisbaneDr Neil Banham, Fiona Stanley Hyperbaric Unit, Perth, WADr Chris Jelliffe, Townsville Hyperbaric Unit, Townsville, QLD.Dr Andrew Fock, The Alfred Hospital Hyperbaric Unit, Melbourne, Vic.Ms Carla Rose, Audiology Team Leader, Audiology Dept, RBWH, BrisbaneMs Mandy Way, Biostatistician, QIMR Berghoffer Institute, Brisbane |

# 1.0 Introduction

#### 1.1 Background

The diagnosis, incidence, pathology, treatment and natural history of idiopathic sudden sensorineural hearing loss (ISSHL) are all areas of controversy. It is defined by the National Institute on Deafness and Other Communications Disorder (NIDOCD) as the ‘sudden loss of hearing over three contiguous pure-tone frequencies of 30dB or more that develops over 72 hours or less’.[1]Because the aetiology (by definition) remains unclear, it is not surprising many therapies have been tried: among them hyperbaric oxygen therapy (HBOT), rheological agents, anti-viral agents, acupuncture, vitamins and steroids.[2, 3]The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) recently released clinical practice guidelines suggesting HBOT could be useful up to three months after onset of symptoms, however the hyperbaric literature suggests best outcomes if utilised within two weeks of symptoms.[4-7] Our recently published retrospective outcome study suggested best outcomes with HBOT may extend up to four weeks from onset.[8]

#### 1.2 Rationale for the use of HBOT

ISSHL may be due to ischaemia following vascular occlusion or an immune-associated process. The cochlea is prone to ischaemia due to the paucity of arterial supply and the high oxygen requirement of the Organ of Corti and perilymph oxygen tension decreases in association with ISSHL.[9] HBOT is known to increase perilymph oxygen tensions and also modulate immune responses.[10, 11]

#### 1.3 Current evidence

There are a few small controlled trials to support HBOT in the treatment of ISSHL and although a Cochrane review included seven randomized controlled trials (RCTs) and found some evidence of benefit, the authors suggested functional improvement was not proven and RCTs are warranted.[12] This review suggested some improvement with HBOT versus control after two weeks of treatment for patients treated within two weeks of onset, both in pure tone average hearing thresholds (see Figure 1) and the proportion of individuals achieving a 25% improvement in hearing thresholds.



**Figure 1**: Mean improvement over all frequencies after HBOT (dB), Source: [12]

A more recent meta-analysis of 16 comparative trials in the use of HBOT only found a benefit in those with severe hearing loss.[13] There is insufficient evidence at this time to convince the majority of practitioners in this area that referral for HBOT is appropriate or cost-effective and considerable clinical equipoise exists. The use of corticosteroids in ISSHL has become widely accepted despite low evidence. A meta-analysis of trials comparing medical therapy to medical therapy plus steroids found only three RCTs all with fewer than 58 patients.

A recently published audit of practice in Australia and New Zealand revealed a huge disparity in treatments being offered to patients with ISSHL, with some hyperbaric units not receiving any referrals from Ear, Nose and Throat Surgeons (ENT) whilst other units had many referrals with significant financial cost for HBOT.[14]

#### 1.4 Need for a clinical trial

The rationale for the SHOOSH trial is as follows:

* ISSHL is common and may have grave permanent consequences in terms of disability or employment opportunities for individuals who require both ears or those who already have impairment in the contralateral ear.
* The disparity in clinical practice reflects the clinical equipoise in this area.
* The current evidence suggests a benefit from HBOT but the evidence is of low quality.
* The provision of emergency treatments out of hours incurs significant costs to the health service and a clinical trial will ascertain whether this is justified.

#### 1.5 Clinical significance

A well designed RCT which answers the following question will greatly assist with clinical decision-making in this important area:

“*For adult patients presenting within two weeks of the onset of sudden sensorineural hearing loss without clear cause (ISSHL), does the addition of HBOT to the current standard practice (including steroids), result in any clinically important improvement in hearing (measured by audiogram) or functional benefit (measured by quality of life scores)?*”

If this study shows benefit, more patients should have access to HBOT services and it would assist a funding application to MSAC for support of HBOT services as these are currently unfunded. If the study is negative, there will be less fiscal burden on health services to provide out of hours HBOT for ISSHL.

2.0 Study Design

#### 2.1 Aim

To conduct a well-designed multicentre RCT to determine if the addition of HBOT to steroids improves hearing with a clinically significant benefit to patients with ISSHL.

#### **2.2 Hypothesis**

This study will test the hypothesis that patients with ISSHL treated with steroids and HBOT will have better outcomes than patients treated with steroids alone.

#### **2.3 Design**

The SHOOSH study is a prospective, multicentre, open RCT. Patients presenting with ISSHL within two weeks of onset to participating ENT practitioners will be assessed for suitability, offered participation, consented and then randomised to either conventional steroid treatment or steroid treatment plus HBOT. 150 patients will be enrolled in each group.

Randomisation will be by computer generated random sequence (web based). This will occur after consent and by the ENT consultant or registrar in order to ensure allocation concealment.



3.0 Study Outcomes

#### 3.1 Primary Outcome

Hearing improvement as measured by speech discrimination scores.

#### 3.2 Secondary Outcomes

Proportion of patients with 50% return of hearing on PTA4 at treatment completion and at six months post therapy.

Hearing improvement in PTA4 (pure tone audiogram over 4 frequencies) as defined by Seigel’s classification of hearing improvement.

Grade 1; final hearing better than 25dB (complete resolution)

Grade 2; Moderate hearing gain (hearing threshold 26 to 45dB)

Grade 3; hearing threshold 46- 70 dB

Grade 4; hearing threshold 71- 90dB

Grade 5; hearing threshold >90dB

Quality of life improvement as defined with the Euro-QoL instrument (EQ5D)

Side effects of HBOT : MEBT / Refractory changes / major events

#### 3.3 Economic Evaluation

Cost analysis of treatment using Medicare Scheduled fee for treatment if it was funded based on other funded conditions (eg diabetic wounds) versus actual costs of HBOT to the health service.

# 4.0 Study Participants

#### 4.1 Study Setting

This study will be conducted in tertiary hyperbaric facilities in several sites across Australia. The primary site will be the Royal Brisbane and Women’s Hospital with satellite recruitment from other hospital ENT departments and private rooms (Brisbane Metro North and Metro South sites). The Prince of Wales Hospital and the Royal Hobart Hospital have expressed a desire to participate and have in principle support from ENT surgeons to recruit and randomise patients.

#### 4.2 Inclusion Criteria

1. Documented diagnosis of ISSHL as defined by the criteria of NIDOCD.
2. Presentation within two weeks of onset of symptoms.
3. Adult aged 18 or over.
4. Normal hearing in contralateral ear.
5. Exclusion of retro-cochlear mass.
6. No contraindication to oral steroids.
7. Fitness for compression in a HBOT chamber.

#### Exclusion Criteria

1. Contraindication to HBOT as assessed by a hyperbaric physician.
2. Unstable Type 1 diabetes.
3. Other causative agent for hearing loss suspected (e.g. drugs, acoustic trauma).
4. History of middle ear surgery which in the ENT surgeon’s opinion would exclude the patient from being able to be pressurized.

5.0 Study Interventions

#### **5.1 Study treatment regimens**

* 5.1.1 Steroids

Daily oral methylprednisolone 50 mg for 7 days then 25 mg for 7 days.

* 5.1.2 Hyperbaric oxygen treatment (HBOT)

Daily compression at 2.4 ATA in a multiplace or monoplace chamber according to unit protocols; allowing for unit variation of 85-90 mins at depth (Mon to Fri) for 20 treatments. The first 5 treatments will be consecutive regardless of weekday. A single air break mid treatment for 5 mins will be standard.

#### 5.2 Withdrawal of study treatment

Following randomisation, every effort will be made to ensure patients continue to receive the allocated treatment protocol. Unless a participant wishes to withdraw consent to participate in the study they will be included in the analysis on an intention to treat basis.

Withdrawal may occur for any of the following reasons

* Withdrawal of consent to be in the study
* Inability to compress (with or without necessitation of grommets)
* Inability to continue oral steroids
* The treating ENT surgeon believes the patient requires intra tympanic steroids
* Intercurrent illness which necessitates withdrawal
* Adverse or serious adverse events related to treatment irrespective of group allocation.

#### 5.3 Blinding

This is a single blinded study as patients will be aware of treatment group as will treating clinicians. The audiologist will be blinded to the study allocation group and the statistician will be blinded from patient identification details.

#### 5.4 Safety considerations

There is no additional risk to patients from participating in this study by taking steroids as this is usual care as defined by ENT published Clinical Practice Guidelines[4,].

HBOT is a safe procedure with a low incidence of serious side effects. [15]

# 6.0 Study Assessments

#### 6.1 Screening

Patients will be screened by ENT staff for eligibility in the study. A screening log to track recruitment from the patient population (all patients with ISSHL) will be kept.

#### 6.2 Randomisation

Patient demographics will be entered for eligibility criteria (answered with a yes/no response) into a web based randomisation system. Patients meeting all inclusion criteria and none of the exclusion criteria will then be randomised after consenting to participate.

#### 6.3 Baseline

Audiograms and quality of life score will be collected at presentation by the ENT registrar/ consultant or research nurse (depending upon time of presentation).

#### 6.4 Schedule of assessments

Audiograms will be repeated after 10 days of therapy and after 20 days.

#### 6.5 Follow up at 6 months

Repeat audiogram and quality of life score.

# 7.0 Safety Monitoring and reporting

#### 7.1 Adverse events

Any adverse event thought to be related to study assignment will be reported to the coordinating centre within 7 days. The principal site investigator will be responsible for determining causal relationship and notifying the chief investigator by scanned document via email or fax (Adverse Event form). All adverse events will be reported to the independent Data and Safety Monitoring Committee (DSMC).

* 7.1.1 Serious adverse events (SAEs)

These are defined as any event which:

* Results in death
* Is life threatening
* Requires admission to hospital
* Results in significant disability
* 7.1.2 Suspected unexpected serious adverse reactions (SUSARS)

Defined as unexpected event whose nature, severity, specificity or outcome is not consistent with either a steroid reaction or hyperbaric oxygen reaction.

* 7.1.3 Reporting SAEs and SUSARs

 All SAEs and SUSARs will be reported to the DSMC and HREC by the Chief Investigator within 24 hours.

#### 7.2 Data and safety monitoring committee

An independent DSMC will be formed to monitor recruitment, data storage, monitor follow up and SAEs and SUSARs. Each site will designate a Principal Site Coordinator to report to the Chief Investigator who is responsible for reporting to the DSMC.

All adverse reactions (both SAEs and SUSARs) will be promptly reported to the DSMC within 24 hours of the event. The report will contain patient name, trial identifier, details of event and outcome.

#### 7.3 Study termination

The study may be terminated at any time after consultation with the DSMC. Local and head HREC will be promptly informed and the Chief Investigator will provide details outlining the reasons. Funding bodies will also be informed.

# 8.0 Ethics

#### 8.1 Ethical Principles

This study will abide by the ethical principles of the Declaration of Helsinki and the NHMRC National Statement on ethical conduct in human research.

#### 8.2 HREC

This study will be reviewed by the RBWH HREC and the Research Governance Officer for site specific approval. Each satellite site will obtain local HREC approval prior to enrolling patients. Any amendment or protocol modification will have HREC approval prior to implementation unless the change is necessary to eliminate hazard to a patient, in which case, the HREC and DSMC should be notified as soon as possible hereafter.

Each Principal Site Investigator will be responsible for informing the local HREC of any event likely to affect patient safety or the conduct of the trial. A copy of that report will be provided to the Chief Investigator who will report also to the RBWH HREC.

The Chief Investigator will provide progress reports, adverse events reports and other documentation as directed by the HREC in accordance with their guidelines. Copies of all correspondence pertaining to HREC locally or satellite sites will be kept by the Chief Investigator. Copies of the same documents will also be kept with the Principal Site Investigator at each site.

#### 8.3 PICF and procedures

This study assesses the effectiveness of two treatment strategies already in place as usual practice and supported by both the AAO-HNS and Undersea and Hyperbaric Medical Society (UHMS) as indicated when available to improve clinical practice. Patients not enrolled in the trial will be treated at the discretion of the ENT surgeon. Patients who are enrolled in this trial will be offered a PICF (attached) to inform them of the nature of the study. This form will also have been assessed and approved by the local HREC.

#### 8.4 Privacy

All patient data will remain confidential and be stored in accordance with the local site regulations.

# 9.0 Data collection and Management

#### 9.1 Record retention

All patient data pertaining to this study will be stored in accordance with local regulations at each site and on a central hard drive at the completion of the study. If any site investigator retires, relocates or withdraws from the study a replacement investigator must be designated to take responsibility of records and the Chief Investigator (and DSMC and HREC) informed. The Chief Investigator must approve the change. All associated documentation is to be updated. The Chief Investigator will ensure all data is retained for at least 15 years after the completion of the study. This will be stored on a secure hard drive in a secure location on site at RBWH Hyperbaric Medicine Service. The Chief Investigator must inform the HREC of the principal site prior to any planned or accidental record destruction.

# 10.0 Quality Control

#### 10.1 Responsibilities of Chief Investigator

The Chief Investigator is responsible for the overall running of the study in accordance with the protocol and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice. Responsibilities include

* Provision of reliable, legible data as requested by HREC or DMSC in a timely fashion.
* Allow access of representatives to source documents

#### 10.2 Responsibilities of Principal Site Investigators

* Provision of SADRs and ADRs to Chief Investigator.
* Protocol adherence.
* Local HREC reports as required.
* Local data accuracy and storage.

#### 10.3 Management of protocol deviations

A protocol deviation may be an omission, addition or change to the protocol. No deliberate protocol deviations should occur unless pertaining to patient safety. All protocol deviations need to be recorded and sent to the Chief Investigator who will also inform the DSMC and HREC.

# 11.0 Statistical methods

11.1 Power calculation

We are currently performing a pilot study with HREC approval (LNR/2019/QRBW/57648) to calculate the sample size using the variation in speech discrimination scores of patients treated with HBOT. We will accept a power of 80% and a *p* value of <0.05.

11.2 Analysis Plan

The effectiveness of the intervention (HBOT) will be evaluated by an intention to treat analysis of all eligible patients who are randomised. The coordinating centre (RBWH) will undertake analysis of results with QIMR Berghofer, including interim reporting to the DSMC.

11.3 Interim analyses

An interim analysis will be performed after 50% of patients have been recruited and completed 6 month follow-up.

# 12.0 Publication and dissemination of results

It is envisioned that this trial will be of interest, whatever the outcome, and publishable in either general, ENT or Hyperbaric Medicine journals. As ISSHL is primarily an ENT emergency we will endeavor to publish in the ENT literature.

# 13.0 Proposed project timeline

Based upon our previous study and number of referrals at RBWH (2-3 per week) this study should take three years to complete (including follow up) if single center. We expect a reasonable time frame to be 2 years if multicentre for completion.

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