Review articles

Hyperbaric oxygen therapy for acute idiopathic sudden sensorineural hearing loss; a systematic review with meta-analysis

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Abstract
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Introduction: Idiopathic sudden sensorineural hearing loss (ISSHL) is hearing loss of unknown cause with greater than 30 dB loss over 72 hours or less across three consecutive frequencies. Hyperbaric oxygen therapy (HBOT) is a widely accepted treatment for this condition. HBOT protocols and outcomes measured vary between studies.
Methods: To update a systematic review with meta-analysis of relevant randomised trials to both quantify and estimate the quality of evidence to support or refute the use of HBOT for ISSHL. We followed the Cochrane Handbook for Systematic Reviews of Interventions methodology. We conducted a focussed search of the following databases – AMED, BIOSIS Previews, CENTRAL, CINAHL, Embase, Emcare, Global Health, Medline, Scopus and Web of Science. There were no language or publication status restrictions. The updated search covered 1 April 2012 to 22 February 2023. A total of 148 papers were found with 24 randomised and pseudo-randomised studies identified of which seven contributed to the final analysis. Studies using usual treatment (steroids) plus HBOT or no treatment plus HBOT were included. The ROBB 2 tool for risk of bias and the GRADE tool for certainty of evidence were utilised.
Results: Data pooling was hampered by variation in reporting of changes in pure tone average across these studies. Pooled analysis from five studies suggested the chance of improvement following HBOT and steroids was greater than after steroids alone (RR 1.6, 95% CI 1.3 to 2.0). Pooled data from four trials suggested a greater mean improvement following HBOT (mean difference 15.6 dB, 95% CI 1.5–29.8).
Conclusions: There is moderate evidence that HBOT improves hearing when applied up to 30 days after the onset of ISSHL. HBOT in combination with steroids (oral or intra-tympanic) can be justified as a routine treatment. Future trials should address optimal dose and timing of HBOT and ensure outcomes enable pooling of data in future reviews, as well as addressing some measure of the functional significance of any improvement.

Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) is an acute hearing impairment that is usually one-sided and may be accompanied by tinnitus and vertigo. The US National Institute on Deafness and Other Communication Disorders defines ISSHL as a sudden sensorineural hearing loss of no identifiable cause, with greater than 30dB loss in at least three consecutive frequencies developing over 72 hours or less.[1] Sensorineural is further defined as "*abnormal functioning of the cochlea, auditory nerve, or higher aspects of central auditory perception or processing*".[1] While the most common proposed causes are vascular and viral, the aetiology remains elusive.

The incidence is estimated as 27 per 100,000 per year in the USA and is somewhat higher in patients 65 years and older (77 per 100,000) based on a pharmaceutical claims database.[2] A national epidemiological survey in Japan included 3,419 patients from 30 centres between 2014 and 2016 and found 31% were 65 years or older, 78% had tinnitus and 35% vertigo or dizziness. More than 90% of patients received corticosteroids, most commonly systemic.[3]

Historical treatments for ISSHL have mostly been designed to improve the blood circulation and oxygenation of the inner ear and include vasodilators, plasma expanders, steroids, anticoagulants, diuretics, contrast dye and antivirals. None have been proven of benefit in large, randomised trials or meta-analyses and for the most part the use of these agents has been abandoned.[4,5]

A UK clinical guideline recommends corticosteroids either orally, as intra-tympanic injections or a combination of both as first line-treatment for ISSHL despite no evidence supporting their benefit over placebo when given orally.[6] The guideline of the American Academy of Otolaryngology–Head and Neck Surgery Foundation additionally recommends hyperbaric oxygen therapy (HBOT) as either initial or salvage therapy in combination with steroids based on a systematic review of RCT evidence with a medium grade of confidence.[1]

The assessment of treatment response is complicated by a variable spontaneous recovery rate, with estimates ranging from 32% to 65% within 14 days quoted in the historical literature.[7] More recently, such high rates of resolution have been questioned.[1]

The variance in clinical practice in Australia and costs associated with increasing referrals for HBOT has prompted a review of the literature. The aim of this review was to perform meta-analysis, where possible, to assist in defining the benefit, if any, of the use of HBOT as adjunctive therapy to standard treatment in acute ISSHL. We specifically address the clinical question "*Does the additional administration of hyperbaric oxygen to people with idiopathic sudden sensorineural hearing loss result in an increase in the proportion attaining a useful improvement in hearing?*" We have not included any evidence concerning the treatment of long-standing hearing loss, nor any impact on the severity of the tinnitus that often accompanies acute hearing loss.

Methods

SEARCH STRATEGY

The Methodological Expectations of Cochrane Intervention Reviews (MECIR) reporting guideline was used. The same search algorithm which was used in previous updates was applied. This update was performed as it provides more up to date information to address health decisions. Electronic searches were conducted in 10 databases (Ovid Medline, Ovid Embase, Ovid Global Health, Ovid Emcare, AMED, CINAHL, Biosis Previews, Cochrane CENTRAL, Scopus and Web of Science). After an initial search for articles in MEDLINE and Embase, an analysis of the text words contained in the title and abstract, and of the index terms used to describe these articles was conducted. A second search using identified key words and subject index terms was then undertaken from database inception to 22 February 2023 across all ten databases. The search strategies used a combination of subject headings and free text terms that aimed to cover the areas of (1) sensorineural hearing loss or tinnitus, AND (2) hyperbaric oxygenation AND (3) randomised controlled trials/pseudo-randomised controlled trials.

Searches were adapted as appropriate to the specifications of each of the 10 databases. Hand-searching and reference checking of citations and reference lists was also undertaken to identify any studies that were not retrieved in the search.

There were no language or publication status restrictions, and we restricted publication date from 1 April 2012 to 22 February 2023 acknowledging the previous search had been performed on 2 May 2012. This protocol follows the standard protocol published in the Cochrane Handbook for Systematic Reviews of Interventions.[8]

Two review authors (AN and MB) independently screened the titles and abstracts of all retrieved citations against the inclusion criteria. Three authors (AN, MB, and MP) examined the electronic search results and identified studies that may have been relevant. These studies were retrieved in full and considered for inclusion in this review (see Figure 1). The same three authors reviewed these studies independently and reached a consensus decision on inclusion or rejection for this review. If included, the data were extracted using a form developed for the original review which follows the same process described in the Cochrane Handbook for Systematic Reviews used in previous systematic reviews.

STUDIES FOR INCLUSION

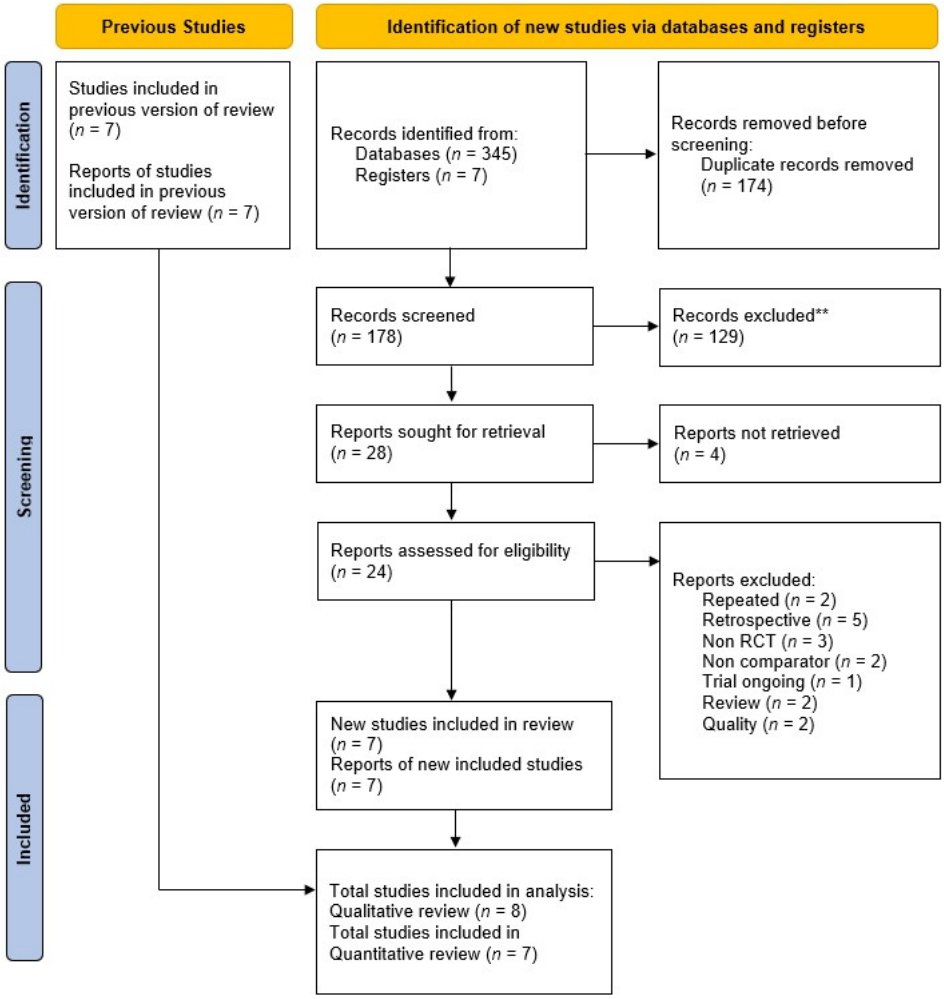
We identified and included all randomised and pseudo-randomised controlled trials that compared the effect of treatment for acute ISSHL (under two weeks versus over two weeks) in patients with ISSH, regardless of age where HBOT was included and compared to any treatment (or no specific treatment) in the absence of HBOT. We included studies irrespective of allocation concealment or blinding status.

In addition, the trials included in the systematic review must have reported an outcome relevant to our pre-defined primary or secondary outcomes. Primary outcome: a documented assessment of pure-tone audiometric thresholds at a number of frequencies (pure tone average values – PTA) after treatment. Secondary outcomes: activities of daily living (ADLs); subjective or objective improvements in depression or mood disturbance; hearing handicap inventory change; word discrimination score; or any adverse events associated with HBOT and comparators.

ASSESSMENT OF RISK OF BIAS IN INCLUDED TRIALS

Two authors (AN and MB) undertook assessment of the risk of bias of the included trials independently, with the

Figure 1
PRISMA Study Flow Diagram for updated systematic review



following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions.*[8] This methodology (ROB2) assesses the potential of bias from six domains – sequence generation method, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'any other' potential bias detected by the reviewers. The GRADE methodology was also used as a tool for grading the certainty of evidence.

DATA SYNTHESIS

For proportions (dichotomous outcomes), we used risk ratio (RR). We used a fixed-effect model where there was no evidence of significant heterogeneity between studies (I^2 < 30%) and employed a random-effects model when such heterogeneity was likely. Where the 95% confidence interval (CI) did not include parity between treatments (RR = 1), we also calculated the number needed to treat (NNT) and 95% CI. For continuous data we compared the mean differences (MD) between hyperbaric oxygen and control groups and defined a statistically significant difference as existing if the 95% CI did not include a zero MD. We undertook all analyses using the RevMan Web© online systematic review tool.[9] We also intended to perform sensitivity analyses for missing data and study quality where possible. For missing data, we planned a 'best-case' and 'worst-case' approach to the imputation of missing data (best-case assumes none of the originally enrolled patients missing from the primary analysis in the treatment group had the negative outcome of interest whilst all those missing from the control group did. The worst-case scenario was the reverse). We also intended to conduct a sensitivity analysis by study quality based on our estimate of the risk of bias and an assessment of adequate sample size to detect the clinically important difference in outcome for which the study was designed.

Results

We present the main findings of this meta-analysis in Table 1.[10]

We repeated our original search strategies in February 2023 and in total, from 294 citations, we identified 24 randomised and pseudo-randomised studies of which seven contributed to this quantitative analysis (Figure 1).[11–25]

Table 1
Summary table for outcomes

Summary of all outcomes designed to show a differential improvement in hearing between HBOT and control; bold suggests benefit from HBOT; *according to Siegel's criteria; **no steroids used in trial; +calculated where proportional outcomes are statistically significant; #sensitivity analysis on removal of non-contributing studies and the mild hearing loss group reported in Topuz 2004[23]; CI – confidence interval; HBOT – hyperbaric oxygen treatment; MD – mean difference; NNT – number needed to treat; PTA – pure tone average; RR – relative risk

Outcome No.	Outcome name	Included trials	*n*	Event outcomes	Result Point est (95% CI)* (NNT and 95%CI)+
1.1	Proportion of participants with > 50% return of hearing	Cavallazi 1996[12] Fattori 2011[17]	114	HBOT: 35/64 Control 18/50	RR 1.5 (0.9–2.8)
1.2	Proportion of participants with > 25% return of hearing	Cavallazi 1996[12] Fattori 2011[17]**	114	HBOT: 50/64 Control 28/50	**RR 1.4 (1.1–1.8)** **NNT 5 (3–21)**
1.3	Proportion of participants with mean improvement of > 20 dB	Hoffmann 1995[18] Chi 2008	80	HBOT: 5/40 Control: 2/40	RR 2.2 (0.5–9.2)
1.4	Proportion of patients with a significant improvement*	Cavaliere 2022[11] Chi 2018[13] Cho 2018[14] Dova 2022[16] Hu 2020[19] Piniara 2022[25] Zhang 2022[24]	562	HBOT: 238/293 Control: 148/26	**RR 1.5 (1.2–1.7)** **NNT 4 (3–5)**
1.5	Mean improvement of PTA (% of baseline)	Fattori 2011[17] Hu 2020[19]	157	N/A	**MD 17.5% (2.5–32)**
1.6.1	Mean improvement (dB from baseline)	Pilgramm 1985[21] Piniara 2022[25] Hoffmann 1995[18] Schwab 1998[22] Topuz 2004[23] Zhang 2022[24]	341	N/A	**MD 13.0 dB (6.2–19.7)**
1.6.2#		Pilgramm 1985[21] Piniara 2022[25] Topuz 2004[23] Zhang 2022[24]	245	N/A	**MD 15.1 dB (8.2–22.0)**
1.7	Mean final PTA after treatment (dB)	Cho 2018[14] Hu 2020[19]	165	N/A	**MD 10.0 dB (2.7–17.3)**

The newly identified trials added to the analysis were published between 2012 and 2022, and the authors are aware of one possible ongoing randomised study at this time whose authors were uncontactable.[26] Four identified trials were unable to be retrieved as published in non-English publications. In total, these newly identified trials were added to historical Cochrane data resulting in 989 participants, 552 receiving HBOT and 437 control. All trials included participants with acute hearing loss of unknown aetiology, but other inclusion criteria, the dose of oxygen, comparator treatments and time to follow-up all varied across these studies. Trial details are included in Table 2. All included studies reported at least one clinical outcome of interest. Of the outcomes identified above, these trials reported data on the primary outcome (pure-tone audiometric documented change in hearing) but none of the secondary outcomes of interest.

RISK OF BIAS

The methodology of these trials was inconsistently reported. The assessments of risk of bias are summarised in Figure 2. Allocation concealment was not adequate in any of the studies. Randomisation procedures were only described in four studies where a computer-generated sequence was employed.[11,21,24,25] Allocation may not have

Table 2

Details of included studies; *three groups, HBOT/both/control; **three groups, HBOT daily/HBOT twice daily/control; #twice daily HBOT; HBOT – hyperbaric oxygen treatment; IT – intratympanic; IV – intravenous

Study	*n* Total (HBOT/control)	Intervention	Oxygen dose: kPa x mins and (number of sessions)	Maximum time from onset to treatment (days)	Control regimen	Final follow-up (days)
Cavaliere 2022[11]	171 (56/55/60)*	HBOT only	253 x 90 (15)	30	Oral steroids	20
Cavallazzi 1996[12]	62 (32/30)	HBOT + multiple drug treatment	243 x 60 (15)	Unclear	Multiple drug treatment	Treatment end
Chi 2018[13]	60 (30/30)	HBOT + oral steroids	253 x 90 (10)	14	Steroids + other drugs	180
Cho 2018[14]	60 (30/30)	HBOT + steroids (oral and IT)	253 x 60 (10)	8	Oral and IT steroids	90
Cvorovic 2013[15]	50 (25/25)	HBOT only	203 x 60 (20)	28	IT steroids	Treatment end
Dova 2022[16]	50 (25/25)	HBOT + IV steroids	223 x 80 (15)	11	IV steroids	90
Fattori 2001[17]	50 (30/20)	HBOT only	223 x 90 (10)	2	Oral vasodilator	Treatment end
Hoffmann 1995[18]	20 (10/10)	HBOT only	152 x 45 (10–20)	14	Nil	90
Hu 2020[19]	107 (38/27/42)**	HBOT + oral steroids	Not stated (10–20)	Unclear	Oral steroids	20
Krajcovicova 2018[20]	68 (47/21)	HBOT + steroids (oral and IV)	203 x 90 (10)	7	Oral and IV steroids	Treatment end
Pilgramm 1985[21]	37 (18/19)	HBOT + multiple drug treatment	253 x 60 (10)	14	Multiple drug treatment	28
Piniara 2022[25]	102 (50/52)	HBOT + steroids (IV and IT)	253 x 90 (10)	10	IV, oral and IT steroids	90
Schwab 1998[22]	75 (37/38)	HBOT only	152 x 45 (10–20)	14	Nil	28
Topuz 2004[23]	55 (30/21)	HBOT + multiple drug treatment	243 x 90 (25)	14	Multiple drug treatment including steroids	28
Zhang 2022[24]	70 (35/35)	HBOT + steroids	203 x 60 (20)	7	Steroids + other drugs	Treatment end

Figure 2
Risk of bias for all included studies across six domains

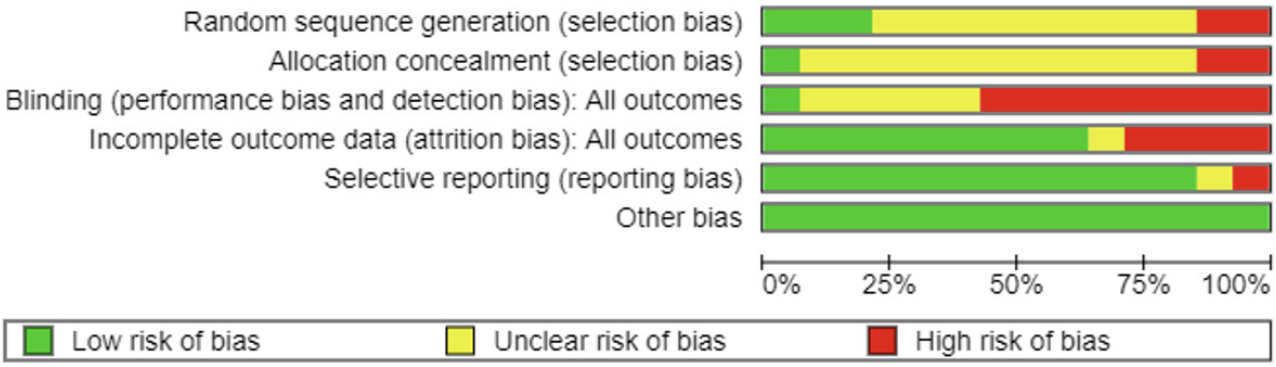
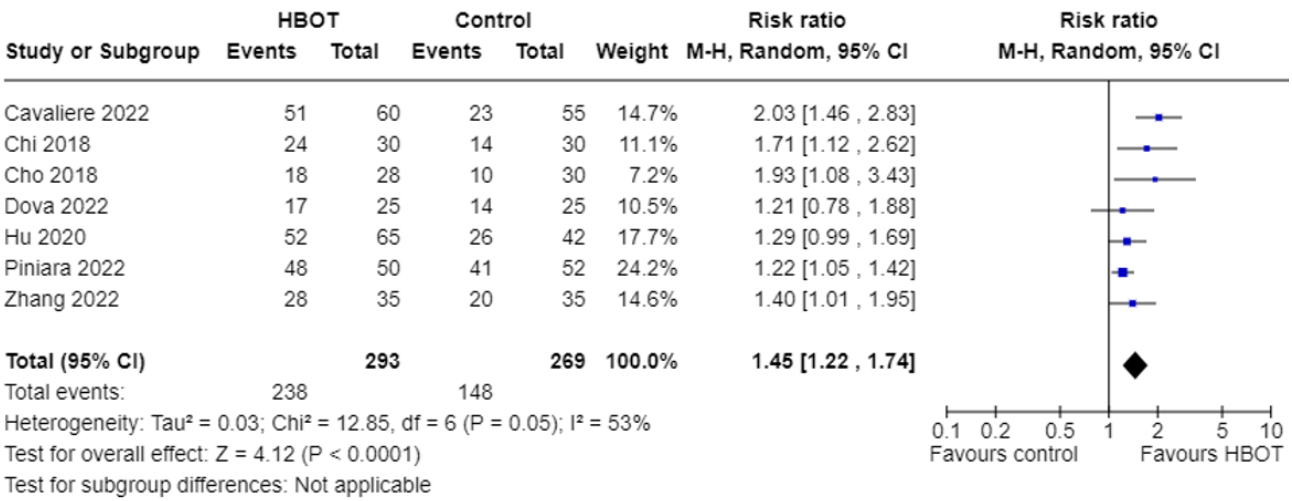


Figure 3
Forest plot for the proportion of participants with significantly improved pure tone average after treatment



been truly random for Cavallazi et al.,[12] while Hu et al. 2020 was pseudo-randomised by alternate allocation.[19] Only Hoffmann et al.,[18] described sham therapy with blinding of participants to the allocated therapy and only Piniara et al.,[25] clearly described blinding of the outcome assessors. One study enrolled 31 participants with both ISSHL and tinnitus, and 43 with one diagnosis or the other, making an intention-to-treat analysis for hearing loss problematic.[22] As no trials with potentially important losses to follow-up (less than 20 percent) reported any dichotomous outcomes, we have not performed sensitivity analysis making best and worst-case analyses. As there was relatively little variation in the risk of bias, we did not use study quality as a basis for sensitivity analysis.

EFFECTS OF THE INTERVENTIONS ON OUTCOMES

Together, these studies reported on seven different methods for assessing any improvement in PTA after treatment, hampering our ability to pool these results. Various groups have defined the different methods used including absolute change, percentage of change and percentage improvement. In general, there was reasonable evidence in favour of using HBOT for these patients with six of the eight synthesised analyses showing statistically important improvements. The results are summarised in Table 1 and the Forest plot in Figure 3 showing the proportion of participants with significantly improved pure tone average after treatment.

We were able to perform eight meta-analyses on these seven different means of measuring improved hearing across ten studies. The greatest number of studies contributing to any outcome was seven for the proportion of patients assessed as having a clinically important (defined as Siegel's criteria 'complete or partial recovery' or a similar assessment) improvement with HBOT versus the control intervention.[27] The chance of improvement following HBOT was greater than the control, RR 1.5 (1.2 to 1.7). This analysis suggests we would need to treat four patients with HBOT to improve one extra person's hearing by a clinically important amount. Six studies also reported the mean improvement from baseline PTA in decibels, but two did not give any estimate of the variance (e.g., standard deviation) and so could not contribute to the analysis. The remaining four trials together

suggested a greater mean improvement following HBOT the MD of improvement from baseline was 15.1 dB with a 95% CI of 8.2 dB–22.0 dB.

In summary of our analyses, with HBOT we found an improvement in the proportion of participants with > 25% return of hearing (RR 1.4, 95% CI 1.1–1.8). This analysis suggests we would need to treat five patients with HBOT to improve one extra person's hearing by 25% (NNT 5, 95% CI 3 to 21), an improvement in mean PTA expressed as a percentage of the baseline (MD 17.5%, 95% CI 2.5–32), and a better mean final PTA in decibels after treatment (MD 10.0 dB, 95% CI 2.7–17.3).

For the remaining two analyses, although the point estimate of effect was in favour of HBOT, any benefit was unclear as the 95% confidence intervals included no difference between the groups (the proportion of participants with either > 50% return of hearing (RR 1.5, 95% CI 0.9–2.8) or a mean improvement of > 20 dB (RR 2.2, 95% CI 0.5–9.2).

Only a single trial reported on any direct functional outcome.[14] These authors reported the word discrimination score (WDS) expressed as a percentage of words correctly identified on a standard test at three months after treatment and reported a better WDS following HBOT combined with both systemic and intratympanic (IT) steroids compared to the same steroid regimen alone (mean WDS at three months 66% [standard deviation14%] with HBOT versus 57% [19%] in the control group, $P < 0.05$).

ADVERSE EVENTS

None of these trials systematically reported adverse effects with HBOT or control therapies, although several did report a number of individuals who experienced some middle ear pain and effusion on compression with HBOT.[14–16,21] One study reported six participants who were withdrawn from HBOT with either aural barotrauma or confinement anxiety[21] and another reported two patients withdrawn for aural barotrauma and one with confinement anxiety.[25] For the other studies, the proportion of patients affected was 6% to 10% and all completed their planned treatment. Only a single study reported any adverse effects in the control group.[15] This study reported five of 25 patients (20%) complained of ear pain related to injection of IT steroids.

Discussion

This review has included data from 15 trials, and we believe these represent all randomised human trials in this area, both published and unpublished, at the time of searching the databases. We found reasonable evidence that HBOT improves hearing when applied as an early treatment in ISSHL (inclusion criteria for time from onset to treatment ranged from 48 hours to 30 days). These trials together reported on seven different approaches to assessing an improvement in PTA, of which five were statistically significant and the remaining two yielded a point estimate of effect in favour of those patients receiving HBOT. There was some indication from the analysis of pooled data from two trials that HBOT increases the proportion of patients gaining more than 25% improvement in hearing (RR 1.4).[12,17] The clinical significance of a 25% improvement in hearing from baseline is not clear and will depend greatly on the starting level of impairment.

An analysis of seven trials assessing a 'significant improvement' in hearing suggested those receiving HBOT had a 1.5 x better chance of improving compared to control. Six trials also suggested improvements in mean hearing measured in decibels following HBOT, with some evidence that more severely affected patients will improve most with the application of HBOT.[18,21–25] We found no evidence to support or refute the use of HBOT in those individuals with long-standing hearing loss.

Only a single trial reported any outcome designed to evaluate the functional impact of hearing loss on the individuals enrolled, and found a statistically significant benefit in word disrcrimination.[14] Other problems for this review were the poor methodological quality of many of these trials (see Figure 2), variability and poor reporting of entry criteria, the variable nature and timing of outcomes, and poor reporting of outcomes. Given the high rate of spontaneous recovery from ISSHL, there is a possibility of bias due to delay to entry in these small trials, as well as from non-blinded management decisions in all trials. The conclusions of this review are therefore to be interpreted with caution.

Previous trials were published over a 37-year period and are from a wide geographical area. We had planned to perform subgroup analyses with respect to the time between onset and therapy, the dose of oxygen received (pressure, time and number of treatments) and the nature of the comparative treatment modalities. None of these strategies were appropriate in the small number of pooled analyses. Response rates stratified by severity of hearing loss on presentation were reported by two studies.[12,23] Whilst one suggested a trend to greater treatment effect in those more severely affected,[23] this was not the case for the patients in the other,[12] and we cannot draw any firm conclusion.[23,24] The interpretation of outcomes by severity are complicated because for some methods of assessment, those with more severe hearing loss can improve to a much greater extent than those mildly affected (e.g., mean improvement in dB) while for other outcomes this is not the case (e.g., percentage return of hearing).

While we have made every effort to locate further unpublished data, it remains possible this review is subject to a positive publication bias, with generally favourable trials more likely to achieve reporting. Regarding long-term outcomes following HBOT and any effect on the quality of life for these patients, we have located no relevant data.

Conclusions

There is moderate quality evidence that HBOT improves hearing in patients with ISSHL who present up to 30 days after onset (however most patients included were of less than two weeks duration). Further good quality randomised trials are likely to improve our confidence in the effect estimate. There is no evidence available to establish or refute the functional importance of the improvements reported. The small number of studies available for pooled analyses, and the methodological and reporting inadequacies of the primary studies included in this review demand some caution and further studies are highly recommended, particularly addressing the impact of HBOT on functional and activities of daily living outcomes.

The evidence in favour of HBOT is stronger than for the established approaches with oral or IT steroids, and the routine use of HBOT in these patients can be justified. There is no compelling basis from this review for recommending HBOT solely as a rescue treatment following failure to respond to steroids.

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