Hyperbaric oxygen therapy for idiopathic sudden sensorineural hearing loss

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Background

Idiopathic sudden sensorineural hearing loss (ISSNHL) is a form of sudden sensorineural hearing loss (SSNHL) with no identifiable cause despite adequate investigation. ISSNHL is defined as a decrease in hearing of ≥30 decibels (dB), across at least three consecutive frequencies and occurring within three days (Stachler 2012). SSNHL is a subset of sudden hearing loss (SHL) that is sensorineural in nature. It indicates an abnormality either in the cochlea, the auditory nerve or central auditory processing. In only 10 to 15% of patients a cause for SSNHL is defined at the time of presentation (Conlin 2007).

While the incidence of SSNHL is usually reported between 5 to 30 cases per 100,000 per year (Wu 2006, Nostrati 2007, Teranishi 2007), the true incidence may be higher due to underreporting. Some estimates are as high as 160 per 100,000 (Byl 1984, Klemm 2009). Spontaneous remission of hearing loss within the first 2-4 weeks of onset of deafness is a well-recognized phenomenon, but the historical rates of 40 to 89 % (Mattox 77) are arguably optimistic.

Clinical Presentation

ISSNHL is almost always unilateral. The primary presenting symptom is a sensation of aural fullness or blocked ear that is often overlooked by the patient until hearing loss dominates the clinical picture. While tinnitus almost always accompanies ISSNHL dizziness and in some cases vertigo may also be present (Rauch 2008, Kocaman 2010, Murphy-lavoie 2012). Because the treatment is different, it is important to distinguish between conductive hearing loss (CHL) and SSNHL, however, it should not delay the emergency treatment of SSNHL. Hearing impairment in ISSNHL is graded as slight (26dB-40 dB), moderate (41dB-60dB), severe (61dB-80dB) and profound (>81dB) (WHO 2011). The hearing loss configuration most frequently observed in patients with ISSNHL is either flat or descending, but may also be ascending in some cases. Bilateral SSNHL is rare, but requires careful differential diagnosis, as it may be associated with vascular, metabolic, autoimmune, inflammatory, infectious, toxic, traumatic, or neoplastic conditions. Audiometric follow-up, auditory brainstem response test, evaluation for retrocochlear pathology using magnetic resonance imaging when needed is recommended (Stachler 2012).

Standard Management

Various treatments have been proposed for ISSNHL: Steroids, hemodilution, vasodilatation, anticoagulants, antivirals, vasoactive substances, vitamins and hyperbaric oxygen therapy (HBOT) are among these. Although study results are conflicting, systemic steroids are currently the most widely used treatment modality (Wei 2006). The recommended treatment dosage of oral prednisone is 1mg/kg once a day (maximum dose: 60 mg/day) for 4 days, which should be tapered by 10 mg every other day. The total treatment duration is 14 days. The daily maximum dose of dexamethasone is 10 mg , which should also be tapered accordingly (Rauch 2008, Fetterman 1996, Chen 2003, Ghosh 2005). The most frequent adverse effects associated with systemic steroid use are hyperglycemia, weight gain and osteonecrosis (Alexander 2009). Intratympanic corticosteroids may be an alternative in patients who cannot tolerate systemic steroids, or in patients who fail systemic steroid therapy (Yang 2013).

The recently published guideline of The American Academy of Otolaryngology-Head and Neck Surgery Foundation recommends corticosteroids as initial therapy in patients with ISSNHL, and also HBOT as an adjunct to corticosteroids within 3 months of diagnosis of

ISSNHL. The guideline committee recommends against the routine use of antivirals, thrombolytics, vasodilators, vasoactive substances, and antioxidants (Stachler 2012).

Rationale for HBO use

The etiology of SSNHL remains unclear. Vascular occlusion, impairment of labyrinthine blood supply and cochlear hypoxia, viral infections, abnormal cochlear stress response, cochlear membrane damage, labyrinthine membrane breaks, immune system disease, toxins, ototoxic drugs are among several potential pathophysiological mechanisms (Desloovere 2006, Alimoglu 2011).

Because the cochlea is an end organ with no collateral vascularization, direct vascular supply is limited. The cochlea and, particularly the organ of Corti and stria vascularis, therefore, require high oxygen supply due to their high metabolism. Oxygenation of these structures is maintained by the diffusion of oxygen from cochlear capillary networks into the perilymph and cortilymph (Nagahara 1983, Lamm 1988). In case of SSNHL perilymph oxygen tension decreases significantly (Nagahara 1983). Experimental and human studies have shown that hyperbaric oxygenation (HBO) raises the perilymph oxygen pressure up to 9.4 fold, thereby creating very high oxygen concentrations (Lamm 1988). Additional benefits of HBOT in the treatment of ISSNHL include anti-inflammatory effects, which also reduce the unwanted effects of ischemia-reperfusion injury.

Topuz et al. reported a mean 19.3 dB hearing gain in patients with moderate hearing loss and 37.7 dB hearing gain in patients with severe hearing loss (Topuz 2004). Receiving HBOT within two weeks of disease onset was reported as a good prognostic factor. This amount of hearing gain may significantly improve a patient's quality of life.

ISSNHL imposes a heavy social and economic burden on individuals. The hearing-impaired is often socially isolated and may even face unemployment if not treated successfully. The World Health Organization lists hearing loss as the number one disability globally (WHO 2011). Any treatment modality that improves the individual's disability and reduces the cost on society, therefore, is worth considering.

Methods

Formulation of questions and selection of outcomes

We used the Patient, Intervention, Comparison and Outcomes (PICO) format to create the following questions that we believe represent best the clinically relevant questions related with the use of HBOT in ISSNHL:

1. In a patient with acute ISSNHL (treated within the first 2 weeks of disease onset), is HBO therapy alone or combined with medical therapy more effective than medical therapy alone or no therapy for the outcomes of interest?
2. In a patient with chronic ISSNHL (treated after 6 months of disease onset), is HBO therapy alone or combined with medical therapy more effective than medical therapy alone or no therapy for the outcomes of interest?

'No hearing recovery' and 'mean hearing gain over all frequencies' were selected as the critical and important outcomes, respectively.

Literature search

We systematically searched PubMed, EMBASE, Academic Search Complete, CINAHL, MEDLINE, Database of Randomised Trials in Hyperbaric Medicine (DORCTHIM; http://hboevidence.unsw.wikispaces.net), Cochrane Central Register of Controlled Trials, ULAKBIM Turkish National Databases, to identify studies that evaluated the effectiveness of HBOT in patients with ISSNHL. Additionally, the reference lists of review articles and clinical studies identified through the initial search were hand-searched for any potentially relevant studies. Randomized and non-randomized controlled studies that compared the outcome of patients receiving HBOT with or without any medical treatment were retrieved for full text evaluation. The flow diagram for literature search is presented in Figure 1.

Statistical analysis

We used RevMan (Review Manager, version 5.3) computer program for statistical analysis. Studies identified through the literature search were entered into this program. Heterogeneity between studies was calculated by I^2 statistics. If heterogeneity was substantial (>50%), we used random-effects model to calculate the pooled estimates. The risk ratios and mean differences were calculated in meta-analysis of dichotomous outcomes and continuous outcomes, respectively. If there was only one study, we calculated odds ratio and confidence intervals. Summary of evidence tables were generated by using GRADEpro computer program (GRADEpro, McMaster University, 2014)

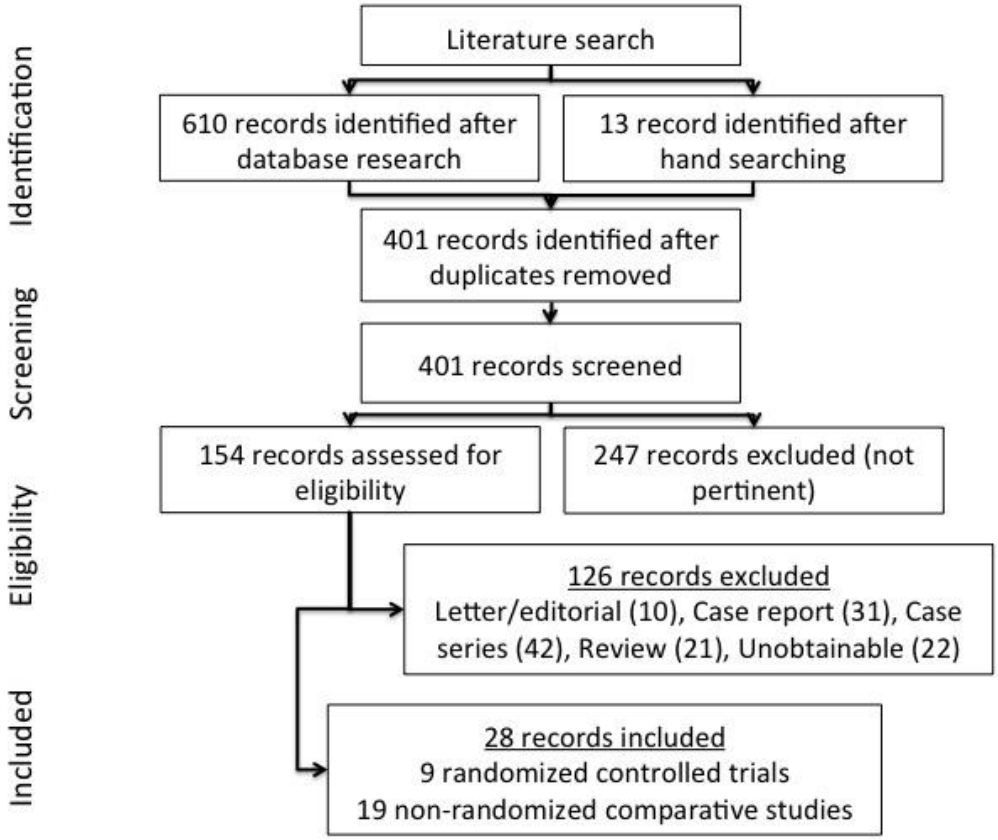

Figure 1. Flow diagram for literature search

Evidence – Based review of HBO use

We identified 9 randomized controlled trials and 19 observational studies. The summaries of these studies were presented on Tables 1 and 2. In the majority of these studies HBOT was used as an adjunct to other medical therapies.

Summary of randomized controlled trials

In 1985, Pilgramm et al. reported the first randomized controlled study on the use of HBOT in patients with acute and chronic ISSNHL. Patients received medical therapy (10% dextran 40, 5% sorbitol, vitamin B, naphtidrofuryl hydrogenelate) with or without HBOT for 10 days. Acute ISSNHL patients receiving HBOT in addition to medical therapy had significantly better outcomes in terms of absolute hearing gain (29.2 ± 14.7 vs. 20.2 ± 11.6).

At the 11th International Congress of Hyperbaric Medicine, Hoffmann et al. presented two randomized controlled trials on the use of HBOT in ISSNHL (Hoffmann 1995a, Hoffmann

1995b). In the first study, they investigated the effectiveness of HBOT in patients with chronic hearing loss (>6 months). In a sham controlled crossover study, patients received either HBOT (n=22) or hyperbaric air (n=22) for 3 weeks (Hoffmann 1995a). Thereafter, the blind was broken and all patients received HBOT for an additional 3 weeks. The average hearing gain in HBOT and hyperbaric air groups was 0 dB and 0.6 dB after initial 3 weeks and 2.5 dB and 0.6 dB after 6 weeks, respectively. The second trial compared the effects of HBOT on patients who failed an initial treatment with medical therapy for 14 days. Twenty patients were randomized into HBOT (n=10) and control groups (n=10). They found higher absolute hearing gains in HBO treated patients (7.5dB vs. -0.7dB) (Hoffmann 1995b). Of note, Hoffman et al. used a lower treatment pressure (1.5 ATA for 45 min.) compared to other clinical trials.

In 1996, Cavallazzi et al. presented the outcome of patients treated with HBOT+medical therapy and medical therapy alone. Medical therapy included citidinephosphocoline, dextran, vitamins, heparin, betamethasone, nicotinic acid, flunarizine, neurotropic and antiviral drugs. Although the number of patients with 50% or more pure tone average (PTA) improvement (18/34 vs. 13/30) was similar in both groups, the number of patients with 25% or more PTA improvement (25/34 vs. 17/30) was significantly higher in patients in the HBO group.

In 1998, Schwab et al. compared HBOT with medical therapy in patients with ISSNHL. The average hearing gain was higher in HBOT group (15.6 dB) than in the medical therapy group (10.7 dB), but the difference was not significant.

In 2001, Fattori et al. published a study on patients treated with either HBOT or buflomedil 200 mg/day for 10 days. Patients in the HBOT group had significantly higher hearing gain than those in the vasodilator therapy group (61.3 ±33.6 vs. 24.0±22.5).

Topuz et al.(2004) reported on the outcome of patients treated with or without HBOT added to medical therapy. Patients with moderate (61-80 dB) and severe (≥81) hearing loss, but not with mild (≤60) hearing loss, who were treated with HBOT added to medical therapy displayed significantly better results than those who received medical therapy alone.

In 2009, Cekin et al. compared the effectiveness of HBOT plus oral prednisolone therapy with oral prednisolone alone. Mean hearing gain was 39.5 dB in the HBO and 44.4 dB in the control group. The hearing outcomes were also similar in both groups in patients older and

younger than 50 years of age. They concluded that HBOT provided no additional benefit over oral prednisolone therapy in patients with ISSNHL.

In 2013, Cvorovic et al. treated patients unresponsive to initial intravenous steroid treatment with either HBOT or intratympanic steroid injections. Effectiveness of both treatments was similar in patients with mild (≤60) and moderate (61-80 dB) hearing loss, but intratympanic steroid therapy was significantly better than HBOT in patients with severe (≥81) hearing loss.

Summary of non-randomized comparative trials

Goto et al. presented one of the earliest comparative studies on the use of HBOT in ISSNHL. Overall they included 91 patients. Patients in group 1 (n=22) received medical treatment alone (vasodilators, steroid hormones and vitamins), those in group 2 (n=49) underwent stellate ganglion block (SGB) plus hyperbaric oxygen therapy (HBO) and those in group 3 (n=20) received medical treatment plus SGB plus HBOT. It is not possible to deduce a net benefit for HBOT in this study because the comparative arms (group2 and 3) both included SGB.

Aslan et al. reported a retrospective study of 50 cases treated either by medical treatment (n=21) comprising betahistine hydrochloride, prednisone, and daily SGB or by HBOT plus the same medical treatment (n=25). They found that HBOT added to the conventional treatment significantly improved the outcome. Of note they also found that patients younger than 50 years of age had significantly higher improvement in hearing as compared with those older than 50 years of age.

Racic et al., in a study on 115 patients, compared the effects of HBOT alone (n=51) with pentoxifylline infusions (n=64). Contrary to current practice, they used a higher pressure (2.8 atm abs) but shorter duration (60 minutes) of HBOT. The benefit was significantly higher for HBOT (Hearing improvement in pure-tone average: 46.4±18.58dB vs. 21.5±13.5dB, $p<0.001$). The rate of patients with complete recovery was also significantly higher in patients treated with HBOT than with pentoxifylline (47.1% vs. 6.2%).

Narozny et al. assessed the effects of HBOT in 52 patients with ISSNHL and compared the results with a historical group of patients (n=81) who received steroids, vasodilators, vitamins, and betaserc. The difference in mean hearing gains was significant in favor of HBOT over the historical group. Additionally, they reported that the presence or absence of tinnitus and/or vestibular symptoms did not influence the treatment outcome for SSNHL.

Satar et al., similarly, used a historical control group involving 17 patients who received medical treatment alone to compare the effects of HBOT added to medical treatment in 37 patients with ISSNHL. Unlike, previously reported observational studies, they did not find any significant difference in hearing gains between the groups.

Desloovere et al. sought to assess the effects of HBOT after failure of conventional therapy for ISSNHL. They retrospectively assessed the outcomes of patients assigned in 3 groups: Group 1 included 100 patients who did not receive any additional treatment following conventional therapy, group 2 and 3 included patients who received HBOT either at 1.5 ATA (n=160) or at 2.5 ATA (n= 56 patients) following failure of conventional therapy. Baseline PTA levels (group 1: 32.5±26.3dB, group 2: 32.3±27.8dB, group 3: 76±27.5dB) significantly differed between groups and, therefore, obviated the possibility to deduce a conclusion from this study.

In 2007, Dundar et al. conducted a retrospective comparative study on a total of 80 patients. All patients received corticosteroids plus vasodilators but those in the study group (n=55) received also HBOT. Outcomes were assessed using the Siegel criteria. Complete recovery rates were significantly higher (38.1% vs. 12%) and no improvement rates lower (12.7% vs. 44%) in patients treated with HBOT. Of note, they also found that tinnitus was a positive prognostic factor.

Fujimara et al., in a study conducted on 130 patients compared the mean percentage hearing gain between patients who received steroids alone (n=63) and those who received steroids plus HBOT (n=67) and found that the recovery rate (59.7% vs. 39.7%; $P < 0.05$), but not the cure or hearing improvement rate, was significantly higher in the HBO group than in the steroid group. Of note, the hearing improvement rates for patients with severe hearing loss (>80dB) was significantly higher in patients in the HBO than in the steroid group ($51.1 \pm 7.0\%$ vs. $27.1 \pm 7.8\%$; $P < 0.05$).

In 2009, Yildirim et al. compared the clinical outcomes of patients with ISSNHL who either received medical treatment (n=31) or HBOT plus medical treatment (n=32). Although patients in both groups had improvements in hearing the difference between the two groups was not significant.

Ohno et al., conducted a research on patients who initially failed conservative treatment and who subsequently received either no treatment (n=44) or HBOT alone (n=48). Of note they

used a pressure of 2.0 atm abs and delivered an average of 13 (4-43) sessions per patient. Only patients with profound hearing loss (>89dB, n=7) demonstrated significantly higher hearing gains than controls (18.3±13.2dB).

Liu et al. conducted one of the largest studies on this issue (n= 465). Of the patients included in the final analysis, 76 who received systemic steroid treatment constituted the steroid group , 277 who received systemic steroids and dextran constituted the steroid–dextran group and the remaining 112 patients who were treated with HBO in addition to pharmacologic agents formed the steroid–dextran–hyperbaric oxygen group. The outcomes were assessed by comparing the difference in absolute hearing gains after treatment. Similarly, as Ohno et., the results demonstrated that only patients with profound hearing loss (>91dB, n=126) had significantly better hearing gains as compared with patients who received medical treatment.

By using the Siegel criteria, Alimogle et. al sought to assess the effects of both HBOT alone and HBOT combined to corticosteroids in a total of 219 patients with ISSNHL. They classified patients into four groups according to the therapy they received: Oral steroid, oral steroid + HBOT, intratympanic steroid and HBOT alone. Overall, they found that patients receiving oral steroid + hyperbaric oxygen combination therapy had a higher likelihood of recovery than patients receiving either oral steroids, or hyperbaric oxygen or intratympanic steroids alone.

Suzuki et al. evaluated the efficacy of HBOT administration (n=174) in comparison with intratympanic steroid injection (n=102) in patients with ISSNHL. Both groups received systemic corticosteroids. While they did not find a significant difference in the cure rate, marked-recovery rate, hearing gain, hearing level after treatment, or hearing improvement rate between the two groups; they found that the recovery rate was significantly higher in the IT than in the HBO group (79.4% vs. 68.4%; P= 0 .048). They also performed multiple logistic regression analysis and showed that patients in the IT group were significantly more likely to recover than those in the HBO group (odds ratio: 2.045; 95% confidence interval: 1.097-3.812; P=0 .024).

Uysal et al. conducted a comparative study involving 34 patients in the control arm who received corticosteroid plus vasodilator treatment and 39 patients in the study arm who received the same treatment protocol plus HBOT. They did not find a significant difference in mean hearing gains between the two groups.

Yang et al. compared the effects of HBOT (n=22), intratympanic steroid injection (n=35) and the combination of the two (n=19) in patients with ISSNHL refractory to initial treatment with systemic corticosteroids. While they found significantly larger hearing gains in the intratympanic steroid, HBO, and combined groups compared with the no-treatment group ($p < 0.05$), the combination of HBOT and intratympanic steroid injection did not yield any significant benefit when compared with the intratympanic steroid injection group.

Psillas et al. similarly assessed the efficacy of HBOT as a salvage treatment in patients with ISSNHL. All patients initially failed a treatment protocol involving steroids and vasodilators. While the control group (n=30) did not receive any further treatment, patients in the study group (n=15) received HBOT. On study completion at 3 months, patients in the HBO group had significantly higher mean hearing gains than patients in the control group (12.1±18.4 dB vs. 2.7±3 dB).

Pezzoli et al. also studied the benefits of HBOT as a salvage treatment. Of note they conducted a prospective trial. Overall they enrolled 44 patients who failed to recover after primary treatment with systemic steroids. Of these 23 received HBO and 21 served as control group. They found significantly better improvement in hearing gains in patients treated with HBO than in controls (15.6 dB (SD ± 15.3 vs. 5.0 dB (SD ± 11.4; $p = 0.0133$).

Edizer et al., in a retrospective study of 205 patients, divided the patients into four treatment groups: (i) systemic corticosteroids (SC) only, (ii) SC+low-molecular-weight heparin (LMWH), (iii) SC+ HBO, and (iv) SC+LMWH+HBO and evaluated recovery according to Siegel's criteria. They found that the addition of HBO yielded no treatment advantage over the use of SC alone.

Capuano et al. analyzed the records of a total of 300 patients who were diagnosed with ISSNHL and divided them into 3 groups according to the therapy they received: IVS, HBO and IVS + HBO group. Each group involved 100 patients. They also assessed outcomes according to the time of therapy initiation. Patients in the combined treatment group were significantly more likely to show partial or complete recovery (84% vs. 58%). Importantly they found that the mean hearing gains were significantly higher in patients in whom therapy was started in the first 2 weeks ($p < 0.05$).

To summarize, of the 19 non-randomized comparative studies assessed in this report, eight showed significant benefit in favor of the combination of HBOT and medical treatment over

medical treatment alone. In three other studies, only patients with profound hearing loss who received HBOT demonstrated significantly higher hearing gains as compared with control patients. The clinical relevance of these improvements, however, were not reported. Six of the studies reported no benefit for HBOT over medical treatment alone. Finally, due to methodological flaws, it was not possible to draw a reliable conclusion regarding the effectiveness of HBOT in two of the studies.

Adverse events

Difficulties with equalizing the middle ear pressure represent the most frequent adverse event observed during the course of HBOT. Nevertheless, the wide variance in the frequency of this complication among studies included in this guideline is interesting. Two of RCTs provide details on adverse events observed during the trials. Cvorovic et al. reported that 12% (3/12) of their patients developed serous otitis media, but did not mention whether these patients were able to complete their treatment or not (Cvorovic 2015). Pilgramm et al. reported that 6.8% (3/44) of the patients who received HBOT developed middle ear barotrauma (Pilgramm 1985). Among the 19 observational studies, 7 reported about the adverse events. While no adverse events were observed in 3 of these studies (Dundar 2007, Psillas 2015, Yang 2013), the remainder provided information on adverse events. One of these studies reported a high prevalence of eustachian tube dysfunction (17/67, 25.4%) in patients undergoing HBOT (Fujimara 2007). Nine of these patients developed otitis media with effusion which required myringotomy in 4 and tympanostomy tube insertion in one case (Fujimara 2007). One other study reported that 12 of the 174 patients (6.9%) who received HBOT underwent myringotomy due to acute otitis media with effusion (Suzuki 2012). Two other studies reported rates of 17.3% (4/23) and 7.6% (3/39) for mild middle ear barotrauma that did not lead to middle ear effusion and hence did not require any further intervention but were managed with topical decongestants (pezzoli 2015, Goto 1979; respectively).

Apart from middle-ear barotrauma, other reported adverse events were quite uncommon. Pilgramm et al. reported that 6.8% (3/44) of the patients failed to complete HBOT due to confinement anxiety and Pezzoli et al. reported a similar condition for a single case. Finally Goto et al. reported one case of convulsion, which did not lead to any serious complication (Goto 1979).

Patient selection for HBO

To determine the quality of evidence prior making any recommendation we systematically reviewed the literature and applied the Grading of Evidence, Assessment, Development and Evaluation (GRADE) approach to the main patient-important outcomes in ISSNHL. The results of statistical analysis were presented on Tables 3&4. We demonstrated that HBOT is beneficial in improving hearing outcomes in patients presenting within the first two weeks of disease onset but not after 6 months (Table 3 &4).

It is generally accepted that early treatment improves the hearing outcome in ISSNHL (Schreiber 2010). This may be generalized to patients receiving HBOT. Some of the studies assessed in the current report provided data on the prognostic impact of timing on the outcomes of ISSNHL in patients treated with HBOT. Hoffman et al. have shown that HBOT did not show any benefit in patients treated after 6 months of disease onset (Hoffman 1995a). Desloovere showed that hearing gain clearly decreased with increasing time delay, Yang et al. found that patients receiving HBOT <7 days as compared to >7 days had significantly better results, Alimoglu et al. As well as Capuano et al. showed that patients who received HBOT in the first two weeks had significantly better outcomes as those treated later. Ohno et al. demonstrated a gradual decrease in hearing gains with time.

While the evidence in not strong, several studies have also shown better results for HBOT in patients with severe and profound hearing loss. Topuz et al. showed that among patients treated with HBOT those with severe hearing loss had the most benefit (Topuz 2004). Additionally, Ohno et al., Fujimara et al. and Liu et al. have reported similar findings in patients with profound hearing loss. This condition merits further research.

Current protocol

HBOT protocols used in the studies reviewed in this report showed a great variation both in terms of treatment pressure, duration and total number of sessions (Table 1, and 2). One of the studies sought to compare the effectiveness of HBOT at 1.5 and 2.5 atm abs in patients with ISSNHL (Desloovere 2006) but the fact that pre-treatment PTA levels among the groups were significantly different (32.3±27.8dB and 76±27.5dB) renders any conclusion obsolete. Several other studies opted to use twice-daily sessions but none provided a comparison of outcome

between once vs. twice-daily sessions. Future studies should focus on comparing the impact of different HBO treatment protocols.

Currently, we recommend the use of HBOT for 90 to 120 minutes at pressures between 2. 0 to 2.5 atm abs once a day for up to 20 treatments in total. A utilization review after 10 sessions through the use of pure tone audiometry is recommended to decide whether to stop or continue HBOT for an additional 10 sessions. A mean hearing gain of more than 10 dB may be used as a criterion for continuing HBOT after the utilization review. Because there is no data to support twice-daily sessions, we recommend against this practice, unless for research purpose. Finally, in view of the results obtained from majority of randomized and non-randomized controlled studies, we recommend the use of HBOT in combination with corticosteroids.

Cost impact

We did not identify any study that investigated the cost effectiveness of HBOT in the treatment of ISSNHL. This is an issue that should be addressed in future studies. Such studies should also consider that the cost of HBOT significantly differs among countries.

Recommendations

We recommend using HBOT combined with medical therapy in patients with acute ISSNHL who presented within 2 weeks of disease onset (Grade B evidence; Level 1 recommendation).

We recommend against the use of HBOT alone or combined with medical therapy in patients with ISSNHL who presented after 6 months of disease onset (Grade C evidence, Level 1 recommendation).

It would be reasonable to consider HBOT as an adjunct to corticosteroids in patients presenting after the first two weeks but not later than one month, particularly, in patients with severe and profound hearing loss (Grade D evidence; Level 3 recommendation).

TABLE 1. Summary of randomized controlled trials

Study	Type and timing of treatment initiation	n of patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, duration, n of sessions)	Results / hearing gains in dB (Unless otherwise stated)	Conclusion/ comment
Pilgramm 1985	Prospective	88	Hearing improvement	Acute hearing loss (<2 weeks) Chronic hearing loss (2 weeks to 1 year)	2.5 atm abs 60 minutes 10 sessions	Acute hearing loss n (Total) = 37 MT (n = 19) vs. MT+HBOT (n = 18) 29.2±14.7dB vs. 20.2±11.6dB ($p<0.05$) Chronic hearing loss n (Total) = 51 MT (n = 25) vs. MT+HBOT (n = 26) 4.2±9.4dB vs. 5.64.2±9.4dB ($p>0.05$) (MT:Dx+Vd.+Vit.)	The difference in pre-treatment mean PTA levels (group 1: 32.5±26.3dB, group 2: 32.3±27.8dB, group 3: 76±27.5dB) obviates the possibility to deduce a conclusion.
Hoffman 1995a	Prospective	44	Hearing improvement	Patients presenting after 6 months of diagnosis	1.5 atm abs 45 minutes 15 sessions	n (Total) = 44 patients Sham (n = 22) vs. HBOT (n = 22) 'Some' hearing improvement: 11/22 vs. 7/22	No significant difference between the groups.
Hoffman 1995b	Prospective	20	Hearing improvement	Patients presenting within 2 weeks of diagnosis	1.5 atm abs 45 minutes 10-20 sessions	n (Total) = 20 patients no treatment (n = 10) vs. HBOT (n = 10) Mean hearing gain: -0.7dB vs. 7.5dB Hearing gain > 10dB: 0/10 vs. 3/10	Favors HBOT.
Cavallazzi 1996	Prospective	32	Hearing improvement	Not available	2.5 atm abs 60 minutes 15 sessions	n (Total) = 62 patients (64 ears) MT (n = 30) vs. MT+HBOT (n = 34) >50% improvement 13/30 vs. 18/34 ($p>0.05$) >25% improvement 17/30 vs. 25/34 ($p<0.05$) (MT: Vd.+Vit.+Dx)	Favors HBOT.
Schwab 1998	Prospective	75	Hearing improvement	Patients presenting within 2 weeks of diagnosis	2.5 atm abs 60 minutes 10 sessions	n (Total) = 57 patients MT (n = 33) vs. HBOT (n = 24) Mean hearing gain: 10.7 dB vs. 15.6dB (MT:HES + Vd.)	No significant difference in hearing gains between the groups.

Fattori 2001	Prospective	50	Hearing improvement	Patients presenting within 48 hours of diagnosis	2.2 atm abs 90 minutes 10 sessions	n (Total) = 50 patients Vd. (n = 20) vs. HBOT (n = 30) Hearing improvement rate: 24.0±22.5% vs. 61.3±33.6% (p=0.005)	Favors HBOT.
Topuz 2004	Prospective	55	Hearing improvement	Patients presenting within 2 weeks of diagnosis	2.5 atm abs 90 minutes 25 sessions (BID in the first 5 days)	n (Total) = 55 patients MT (n = 58) vs. MT+HBOT (n = 34) Mild HL: 22.33±9.31dB vs. 22.53±12.68dB (p=0.758) Moderate HL: 16.18±9.00dB vs. 35.45±22.09dB (p=0.014) Severe HL: 13.00±6.58dB vs. 50.70±21.54dB (p=0.005) (MT: CS+Vd.)	Favors HBOT in moderate and severe hearing loss.
Cekin 2009	Prospective	57	Hearing improvement	Paints presenting within 10 days of diagnosis	2.5 atm abs 90 minutes 10 sessions	n (Total) = 57 patients (59 ears) CS (n = 21) vs. CS+HBOT (n = 38) Complete healing(50dB<): 22 vs.1 Moderate healing (10dB<x<50dB):8 vs. 4 No healing (<10dB): 8 vs.6 (p=0.537)	No significant difference in hearing gains between the groups.
Cvorovic 2013	Prospective	50	Hearing improvement	Patients presenting within 4 weeks of diagnosis	2.0 atm abs 60 minutes 20 sessions	n (Total) = 50 patients IT-CS (n = 25) vs. HBOT (n = 25) Moderate hearing loss (<60dB): 25.4dB vs. 23.3dB (p>0.05) Severe hearing loss (61-80dB): 28.6dB vs. 25.1dB (p>0.05) Profound hearing loss (>81dB): 40.7dB vs. 13.5dB (p<0.05)	IT is better than HBOT in profound hearing loss.

MT: Medical treatment
CS: Corticosteroid
IV-CS: Intravenous corticosteroid
IT-CS: Intra-tympanic corticosteroid
SGB: Stellate Ganglion Block

Vd: Vasodilator
Vit: Vitamin
Dx: Dextran
LMWD: Low molecular weight dextran
Hs: Hydroxyethyl starch

PTA: Pure tone average
ATA: Atmosphere absolute
HIR: Hearing improvement rate

TABLE 2 Summary of prospective and retrospective non-randomized comparative studies

Study	Type and timing of treatment initiation	n of patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, duration, n of sessions)	Results / hearing gains in dB (Unless otherwise stated)	Conclusion/ comment
Goto 1979	Retrospective	91	Hearing improvement	Sixty-one patients presenting within 2 weeks; 30 after 2 weeks	2.4 ATA 90 minutes 20 sessions	n (Total) = 61 (< 2 weeks) MT (n = 22) : 18dB SGB+ HBOT (n = 19): 32dB MT+ SGB +HBOT (n = 20): 38.1dB (MT: CS+Vd+Vit.)	It is not possible to deduce a net benefit for HBOT because the comparative arms both included treatment with SGB.
Aslan 2002	Retrospective	50	Hearing improvement	Patients presenting within two weeks of diagnosis	2.4 ATA 90 minutes 20 sessions (BID in first 7 days)	MT (n = 25) :20±19.6dB MT+HBOT (n = 25) : 37.9±24.0dB (MT: CS+SGB+Vd)	Favors HBOT.
Racic 2003	Retrospective	115	Hearing improvement	Patients presenting within one week of diagnosis	2.8 ATA 60 minutes 30 sessions (max) (BID)	Vd. (n = 64) : 21.5±13.5dB HBOT (n = 51) : 46.4±18.58dB	Favors HBOT.
Narozny 2004	Retrospective	133	Hearing improvement	Sixteen patients presenting within ten days; 36 after ten days	2.5 ATA 60 minutes 16 ±6 sessions	MT (n = 81) : 14.13±2.05dB MT+HBOT (n = 52) : 27.37±2.56dB (MT: CS + Vit.+Vd.)	Favors HBOT.
Satar 2006	Retrospective	54	Hearing improvement	Patients presenting within five days of diagnosis	2.5 ATA 90 minutes 20 sessions (BID in first 3 days)	MT (n = 17) : 37±18.5dB MT+HBOT (n = 37) : 35.5±19.3dB MT: CS+Vit.	No significant difference in hearing gains between the groups.
Desloovere 2006	Retrospective	316	Hearing improvement	Patients who failed an initial medical therapy presenting within 90 days of diagnosis.	1.5 vs. 2.5 ATA 75 vs. 90 minutes (7-28) vs. (9-32) sessions	MT (n = 100) : 2.6±15dB MT+ HBOT-1.5 ATA (n = 160): 3.1±9dB MT+ HBOT-2.5 atm abs (n = 56): 19.7±23dB (MT: CS+Vd+Hs)	The difference in pre-treatment mean PTA levels (group 1: 32.5±26.3dB, group 2: 32.3±27.8dB, group 3: 76±27.5dB) obviates the possibility to deduce a conclusion.

Dundar 2007	Retrospective	80	Hearing improvement	Patients presenting within one week of diagnosis	2.4 ATA 90 minutes 10-28 sessions	MT (n = 25) : 14.16dB MT+HBOT (n = 55) :40.50dB (MT: CS + Vit.)	Favors HBOT.
Fujimara 2007	Retrospective	130	Hearing improvement	Patients presenting within 30 days of diagnosis	2.5 ATA 60 minutes 10 sessions	CS (n = 63) : 56.0±4.6%CS+HBOT (n = 67) : 64.4±4.2% (HIR [mean ± SEM])	Of the patients treated with HBO, only those with severe hearing loss (>80dB) showed significantly higher HIR than controls.
Yildirim 2009	Retrospective	63	Hearing improvement	Patients presenting within two weeks of diagnosis	2.5 ATA 120 minutes 10-20 sessions (BID in first 3 days)	MT (n = 31) : 14,71±17,79dB MT+HBOT (n = 32) : 19,65±18,58dB MT: CS+Vd.+Vit.+Dx	Although patients in both groups had improvements in hearing the difference between the two groups was not significant.
Ohno 2010	Retrospective	92	Hearing improvement	Patients who failed an initial medical therapy and presenting four weeks after diagnosis.	2.0 ATA 60 minutes 13 (4-43) sessions	CS+Vit.+ATP (n = 44) : 5.2±8.9dB HBOT (n = 48) : 2.0±7.6dB	Of the patients treated with HBO, only those with profound hearing loss (>89dB, n=7) demonstrated significantly higher hearing gains than controls (18.3±13.2dB).
Liu 2011	Retrospective	465	Hearing improvement	Patients presenting within two weeks of diagnosis	2.5 ATA 60 minutes 10-20 sessions	n (Total) = 126 patients with >91dB HL CS (n = 19) : 12.9±3.7dB CS+Dx (n = 61): 15.6±2.7dB CS+Dx + HBOT (n = 46): 24.5±2.7dB	Of the patients treated with HBO, only those with profound hearing loss (>91dB, n=126) had significantly better hearing gains as compared with patients who received medical treatment alone.
Alimoglu 2011	Retrospective	217	Hearing improvement	Patients presenting within 30 days of diagnosis	2.5 ATA 120 minutes 20 sessions (BID in first 3 days)	CS (n = 58) : 22.4dB HBOT (n = 57): 13.6dB CS+HBOT (n = 61) : 27.2dB IT-CS (n = 43) : 14dB	Favors HBOT.
Suzuki 2012	Retrospective	276	Hearing improvement	Patients presenting within 30 days of diagnosis	2.5 ATA 60 minutes 10 sessions	IV-CS+IT-CS (n = 102) : 27.0±22.1dB IV-CS+HBOT (n = 174): 26.2±22.8dB	Similar levels of hearing gain in both groups.

Uysal 2013	Retrospective	73	Hearing improvement	Patients presenting within 6 to 16 days of diagnosis	2.5 ATA 150 minutes 20 sessions	MT (n = 34) : 16dB MT+ HBOT (n = 39) : 20.09dB MT: CS+ Vd.	No significant difference in mean hearing gains between the two groups
Yang 2013	Retrospective	103	Hearing improvement	Patients presenting within 4,23 ±3,26 days of diagnosis	2.5 ATA 120 minutes 10 sessions	No treatment (n = 27) : 7.4dB IT-CS (n = 35): 18.87±21.66dB HBOT (n = 22): 17.39±18.2dB IT-CS+HBOT (n = 19): 22.5±18.7dB	The combination of HBOT did not yield any significant benefit over the intratympanic steroid injection group alone.
Psillas 2015	Retrospective	45	Hearing improvement	Patients who failed an initial medical therapy.	2.2 ATA 90 minutes 15 sessions	No treatment (n = 30) : 2.7±3dB HBOT (n = 15): 12.1±18.4dB	Favors HBOT.
Pezzoli 2015	Prospective	44	Hearing improvement	Patients who failed an initial medical therapy and presenting within 30 days of diagnosis.	2.5 ATA 90 minutes 15 sessions	CS (n = 21) : 5±11.4dB CS+HBOT (n = 23) : 15.6±15.3dB	Favors HBOT.
Edizer 2015	Retrospective	205	Hearing improvement	-	2.5 ATA 120 minutes 20 sessions	CS (n = 48) : 35.3 dB CS+HBOT (n = 53): 37.6 dB CS+LMWD (n = 27): 22.2 dB CS+LMWD+ HBOT (n = 77): 26 dB	The addition of HBO yielded no treatment advantage over the use of SC alone
Capuano 2015	Retrospective	300	Hearing improvement	Patients presenting within 90 days of diagnosis	2.5 ATA 90 minutes 16 sessions	IV-CS (n = 100) : 23.76dB HBOT (n = 100): 24.16dB IV-CS+HBOT (n = 100) : 37.90dB	Favors HBOT.
MT: Medical treatment CS: Corticosteroid IV-CS: Intravenous corticosteroid IT-CS: Intra-tympanic corticosteroid SGB: Stellate Ganglion Block			Vd: Vasodilator Vit: Vitamin Dx: Dextran LMWD: Low molecular weight dextran Hs: Hydroxyethyl starch			PTA: Pure tone average ATA: Atmosphere absolute HIR: Hearing improvement rate	

Table 3 Summary of the findings for the main comparison-1

Hyperbaric oxygen therapy with or without any medical treatment compared to medical treatment alone or no treatment for a patient with ISSNHL presenting within 2 weeks of disease onset.

Patient or population: a patient with ISSNHL presenting within 2 weeks of disease onset.
Setting: outpatients
Intervention: hyperbaric oxygen therapy with or without any medical treatment
Comparison: medical treatment alone or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with medical treatment alone or no treatment	Risk with hyperbaric oxygen therapy with or without any medical treatment				
No improvement in hearing assessed with: Pure tone audiometry follow up: range 10 days to 3 months	**Study population**		**RR 0.60** (0.42 to 0.86)	193 (4 RCTs)	⨁⨁⨁◯ MODERATE [1]	
	469 per 1000	**281 per 1000** (197 to 403)				
Mean hearing gain assessed with: Pure tone audiometry Scale from: 0 to 120 follow up: range 10 days to 3 months	The mean hearing gain ranged from **-0.7-44.4** dB	The mean hearing gain in the intervention group was 15.64 dB more (1.45 more to 29.83 more)	-	228 (5 RCTs)	⨁⨁◯◯ LOW [1,2]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. No allocation concealment, unclear randomization method, no blinding of outcome assessors
2. Large confidence interval

Table 4 Summary of the findings for the main comparison-2

Hyperbaric oxygen therapy with or without medical treatment compared to medical treatment alone or no treatment for chronic (>6 months) ISSNHL

Patient or population: chronic (>6 months) ISSNHL

Setting: outpatients

Intervention: hyperbaric oxygen therapy with or without medical treatment

Comparison: medical treatment alone or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with medical treatment alone or no treatment	Risk with hyperbaric oxygen therapy with or without medical treatment				
No improvement in hearing assessed with: Pure tone audiometry	**Study population**		**OR 2.14** (0.63 to 7.30)	44 (1 RCT)	⨁⨁◯◯ LOW [1,2]	
	500 per 1000	**682 per 1000** (387 to 880)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

3. No allocation concealment, unclear randomization method, no blinding of outcome assessors
4. Large confidence interval

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