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HYPERBARIC OXYGEN THERAPY COMBINED WITH STEROID TREATMENT FOR SUDDEN SENSORINEURAL HEARING LOSS: A PROSPECTIVE RANDOMIZED CLINICAL TRIAL

Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

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Abstract

Introduction: The aim of this prospective randomized clinical trial was to compare the therapeutic efficacy of steroid treatment (systemic and intratympanic) versus combined administration of steroids and hyperbaric oxygen therapy (HBOT) as initial treatment in cases of idiopathic sudden sensorineural hearing loss (ISSNHL).

Material and methods: 102 patients with up to a 10-day history of ISSNHL were randomized into two groups and followed prospectively. Group A (52 patients) received prednisolone intravenously followed by methylprednisolone orally and 3 courses of intratympanic injections with dexamethasone, whereas Group B (50 patients) were administered a combination of the aforementioned treatment together with 10 sessions of HBOT. The patients were followed-up with audiograms and pure-tone averages (PTAs) were measured. Hearing change was evaluated by comparing pre- and posttreatment PTAs.

Results: The final mean hearing gain was 21.0 for Group A and 31.1 dB HL for Group B. The 10.1 dB HL difference in favor of Group B was statistically significant (p=0.004). However, when recovery was assessed in terms of Siegel's criteria, no statistically significant difference could be demonstrated. Patients younger than 45 years old achieved better hearing outcomes, and treatment was more effective at low frequencies (0.25 and 0.5 kHz). Combined HBOT and steroid treatment seems to provide greater hearing benefit for patients with severe hearing loss (initial PTA >70 dB HL).

Conclusions: Early application of HBOT combined with systemic and intratympanic steroid administration significantly improved hearing outcomes with an absolute gain in PTA audiometric threshold of 10.1 dB (95% CI 1.5–29.8, p=0.004). Therefore, adding HBOT along with steroids as initial treatment in ISSNHL is recommended. Younger patients with severe hearing loss can be expected to derive most benefit.

Key words: combined therapy • corticotherapy • audiogram • hyperbaric oxygen • idiopathic sudden sensorineural hearing loss • intratympanic steroids

HIPERBARYCZNA TERAPIA TLENOWA POŁĄCZONA Z TERAPIĄ STERYDAMI W LECZENIU NAGŁEGO NIEDOSŁUCHU ODBIORCZEGO: PROSPEKTYWNE, RANDOMIZOWANE BADANIE KLINICZNE

Streszczenie

Wprowadzenie: Celem tego prospektywnego, randomizowanego badania klinicznego było porównanie skuteczności terapii sterydami (podawanymi ogólnoustrojowo i do jamy bębenkowej) i łączonej terapii sterydami i tlenem hiperbarycznym zastosowanych jako początkowe leczenie idiopatycznego nagłego niedosłuchu odbiorczego.

Materiał i metody: 102 pacjentów, u których idiopatyczny nagły niedosłuch odbiorczy wystąpił nie dawniej niż 10 dni wcześniej, zostało losowo podzielonych na dwie grupy i poddanych następnie obserwacji. Grupie A (52 pacjentów) podawano: dożylnie prednizolon, a następnie

doustnie metyloprednizolon i trzy kuracje deksametazonem wstrzykiwanym do jamy bębenkowej. Grupa B (50 pacjentów) otrzymała wyżej opisane leczenie w połączeniu z 10 sesjami tlenoterapii hiperbarycznej. W okresie obserwacji pacjentom wykonano audiogramy i policzono średnie wyniki audiometrii tonalnej (PTA). Celem oceny zmiany słuchu porównano przed- i pooperacyjne wartości PTA.

Wyniki: Ostateczna średnia wartość poprawy słuchu wynosiła w grupie A 21,0, a w grupie B – 31,1 dB HL. Różnica 10,1 dB HL na korzyść grupy B była istotna statystycznie (p=0,004). Jednak gdy do oceny poprawy słuchu zastosowano kryteria Siegela, nie można było wykazać zmiany istotniej statystycznie. Pacjenci młodsi niż 45 lat uzyskiwali lepsze wyniki słuchowe, a leczenie było bardziej skuteczne w zakresie niskich częstotliwości (0,25 kHz i 0,5 kHz). Z kolei połączona terapia tlenem hiperbarycznym i sterydami wydaje się dawać większe korzyści słuchowe pacjentom z niedosłuchem znacznego stopnia (początkowa wartość PTA >70 dB HL).

Wnioski: Wczesne zastosowanie tlenoterapii hiperbarycznej w połączeniu z podaniem sterydów ogólnoustrojowych i do jamy bębenkowej poprawia wyniki słuchowe, bezwzględny wzrost progu słyszenia PTA wynosił 10,1 dB (95%; przedział ufności 1,5–29,8; p=0,004). Dlatego zalecane jest stosowanie tlenoterapii hiperbarycznej równocześnie ze sterydami jako wstępne leczenie w nagłym idiopatycznym niedosłuchu odbiorczym. U młodszych pacjentów z niedosłuchem stopnia znacznego można się spodziewać największych korzyści.

Słowa kluczowe: terapia kombinowana • kortykoterapia • audiogram • tlen hiperbaryczny • nagły idiopatyczny niedosłuch odbiorczy • podanie sterydów do jamy bębenkowej

Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as greater than 30 dB of sensorineural hearing loss (for at least 3 consecutive audiometric frequencies) which occurs with sudden onset (within 3 days) [1]. ISSNHL affects 5–27 per 100,000 people on average per year, and approximately 66,000 new cases are diagnosed annually in the United States, a figure doubtlessly lower than the actual impact due to a spontaneous recovery rate of 32–65% and no official record of untreated patients [2,3]. It presents as rapid, unilateral hearing loss that is often accompanied by vertigo in 30–40% of cases, with up to 90% of patients also complaining of tinnitus [4,5].

Controversy over its pathophysiology has remained for more than 60 years in the literature, and has included viral infection, intralabyrinthine membrane rupture, immunologic disease, and impairment of inner ear blood supply, but generally suggesting diminished inner ear oxygen concentration and microcirculatory disturbance [7–11]. Prompt recognition and imaging facilitates timely intervention which may improve hearing recovery and patient quality of life (QoL) [6].

Prognosis for recovery depends on a number of factors, including patient age, presence of vertigo at onset, degree of hearing loss, audiometric configuration, and time between onset of hearing loss and treatment [4,12]. Although treatment of ISSNHL varies among otologic centers, systemic administration of steroids orally or intravenously (i.v.) has been considered as treatment of choice for many years with recovery rates of 49–79% [13]. On the other hand, a meta-analysis and review by Conlin and Parnes in 2007 concluded that there was no statistically significant evidence that corticosteroid treatment was better than placebo [14].

Potential side-effects and contraindications of systemic steroids (peptic ulcer, glaucoma, uncontrolled diabetes mellitus, hypertension, etc.) have motivated alternative administration directly into the cochlea. Since 1996, several studies have shown that intratympanic (IT) injection of dexamethasone delivers a higher concentration of medication into the perilymph via absorption through the round window membrane [15,16]. IT delivery has been shown to effectively improve hearing, not only in severe cases where there are contraindications to systemic steroid or are refractory to it, but also as a first-line treatment by itself or combined with systemic steroid therapy, although results have varied [17–24]. Maximal delivery of corticosteroid to the inner ear using both systemic and intratympanic routes optimizes the potential for hearing recovery by achieving rescue of intracochlear spiral ganglion neurites and/or hair cells [16,21–23].

In addition, another treatment modality has attracted interest among clinicians over the last two decades. Hyperbaric oxygen therapy (HBOT) is the therapeutic administration of 100% oxygen, after placing the patient in an airtight vessel and increasing the pressure to greater than one atmosphere absolute (1 ATA). Intracochlear structures, particularly the organ of Corti, require a high oxygen supply due to high metabolism although there is a paucity of direct vascularity. Unfortunately, perilymph oxygen tension is decreased significantly in patients with ISSNHL. The predicted mechanism of HBOT action is to increase the partial pressure of oxygen in the blood in order to generate an extremely high arterial–perilymphatic oxygen concentration difference, which leads through diffusion to a rise in the partial pressure of oxygen in the inner ear fluids [25]. Increased perilymph oxygenation improves erythrocyte elasticity and hemorheology, lowers blood viscosity, and improves microcirculation. HBOT thereby increases cell metabolism in the inner ear, despite low blood supply, reducing potential harm. Furthermore, to restore the intra-organ damage, HBOT speeds up the healing process and promotes the development of new blood vessels by increasing collagenogenesis with proliferation of fibroblasts [25–27].

According to encouraging data, hyperbaric oxygen treatment in a chamber has potential benefits at an early stage of symptom onset (within 1 month, and especially within the first 2 weeks) in young patients with moderate to severe hearing loss. A synergistic effect of steroids and HBOT has been proposed in order to explain gain in threshold [26–33]. In 2012, the Cochrane Database Systematic Review of RCTs concluded that the additional application of HBOT significantly improved hearing in cases of acute ISSNHL [34]. However, there is still the need for an evidence-based optimization of the form, dosage, and duration of the treatment protocol. The purpose of this prospective randomized multicentered clinical trial was to compare the therapeutic efficacy of steroid treatment (systemic combined with intratympanic) versus combined administration of steroids and HBOT as a primary treatment in cases of ISSNHL.

Material and methods

Study design and patient selection

This study was performed with a prospective randomized clinical trial design. We screened 131 patients diagnosed with ISSNHL through the emergencies of Konstantopouleio General Hospital, Ippokrateio University Hospital, and Attiko University Hospital of Athens who were admitted to the Department of Otorhinolaryngology of Konstantopouleio General Hospital from March 2015 to January 2018. Candidates assessed for eligibility were adults aged 18–75 years old, either male or female, with a minimum of 30 dB HL hearing loss in three consecutive octaves that had occurred within 3 days, with time of onset a maximum of 10 days before admission. The hearing thresholds were calculated at 0.25, 0.5, 1, 2, 4, and 8 kHz. Since according to Goodman's criteria a threshold of up to 25 dB HL is normal, the hearing thresholds of the affected frequencies must have been 55 dB HL or higher (initial PTA ≥55 dB HL). Moreover, the affected ear must have been at least 30 dB HL worse than the contralateral ear for at least one of the affected frequencies. To the best of the participant's knowledge, hearing was symmetric prior to onset of hearing loss.

The exclusion criteria for this study were defined as any recent or chronic otitis, history of otologic surgery, trauma, tinnitus, Meniere's disease in the affected ear, or previous episode of ISSNHL, as well as any other prior treatment for the current episode, any contraindication to the use of systemic steroids (such as uncontrolled diabetes mellitus or hypertension), or to the use of HBOT (such as epileptic seizure history or pneumothorax). Patients with a history of other probable causes of SSNHL, such as syphilis, autoimmune disease, hypothyroidism, or ototoxic drug use, were also excluded.

All patients underwent medical history, physical and laboratory examinations, as well as audiologic evaluations that included tuning fork testing, tympanometry, and pure tone audiometry before initiation of treatment. An Interacoustics AA222 middle ear analyzer was used to perform impedance tests. Only patients with a type A tympanogram according to the Jerger classification were included in the study [35,36]. Patients with conductive or mixed hearing loss were excluded. Our study was carried out in accordance with the recommended HBOT treatment profile by the Undersea and Hyperbaric Medical Society (UHMS) for ISSNHL [25]. Every patient underwent an MRI scan of the internal acoustic canal 30 days after the initiation of treatment to rule out retrocochlear pathology (e.g. vestibular schwannoma) or identify other neurologic conditions [37]. In case such a lesion was identified, the patient was excluded from the study.

Audiometric assessment

All audiometric measurements were performed by audiologically trained staff in a soundproof chamber using a calibrated audiometer (Interacoustics AC5) and headphones (Telephonics TDH-50). Air and bone conduction threshold audiometry as well as masking were performed according to the guidelines of the British Society of Audiology in 5 dB steps [35]. Auditory function was determined by pure tone audiometry with the maximum level of the audiometer set at 100 dB HL and PTAs were calculated using the threshold values at 0.5, 1, 2, and 4 kHz. Pure-tone audiometry was initially performed immediately prior to treatment in all groups, as well as at 3, 5, and 14 days (end of treatment), and 30 and 90 days after initiation of treatment. Audiograms were performed before each injection, and if testing showed complete hearing recovery prior to a scheduled injection, then no further injections were performed.

Table 1. Siegel's criteria of hearing recovery

Type	Hearing recovery
I. Complete recovery	Final hearing better than 25 dB
II. Partial recovery	More than 15 dB gain, final hearing 25–45 dB
III. Slight improvement	More than 15 dB gain, final hearing poorer than 45 dB
IV. No improvement	Less than 15 dB gain, final hearing poorer than 75 dB

The primary end-point of the study was the final mean hearing gain, which was defined as the difference between initial and final PTA at day 90. When comparing final follow-up PTA with initial PTA, any change needed to exceed 10 dB HL in order to be considered significant [38]. Secondary outcome measures included final hearing improvement as evaluated at day 90 using Siegel's criteria and prognostic value of age and severity of initial hearing loss. There are no uniform criteria on hearing recovery assessment [6]. To justify treatment success according to Siegel's criteria (**Table 1**), "complete recovery" was here defined as final hearing better than 25 dB HL; "partial recovery" as more than 15 dB HL hearing gain and final hearing 25–45 dB HL; "slight improvement" as more than 15 dB HL gain and final hearing <45 dB HL; and "no improvement" as less than 15 dB HL gain. "Favorable recovery" was defined as final hearing corresponding to Siegel's criteria I and II with final serviceable hearing.

Treatment protocol

Patients who met inclusion criteria and signed consent to enroll after a full explanation of the study and possible complications, were randomized to 2 groups. The method of randomization involved generating sequential random numbers using computer-based software. Upon admission, the 112 recruited patients received random numbers in a closed envelope. Treating physicians and patients were aware of the allocated arm, unlike the investigators who performed the audiologic assessment and data analysis; the latter were kept blinded until the completion of the statistical analysis.

Group A (systemic and intratympanic steroids)

The patients in this group were hospitalized and treated with i.v. 1 mg/kg of body weight prednisolone/day for 7 days (amp Prezolon 25 mg/ml) with gradual dose tapering. More specifically, they received 3 amp Prezolon on day

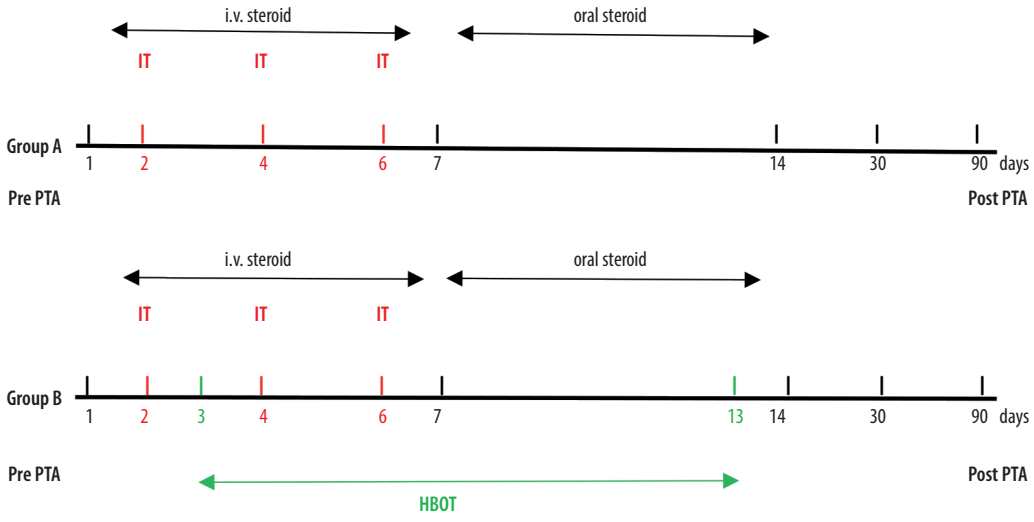

Figure 1. Flowchart of treatment schedules and hearing evaluation. Group A (systemic and intratympanic steroids); Group B (systemic and intratympanic steroids combined with hyperbaric oxygen therapy). IT: intratympanic dexamethasone injection, HBOT: hyperbaric oxygen therapy, PTA: pure-tone audiometry

1 and 2 of their hospitalization; 2 amp Prezolon on day 3 and 4; and 1 amp Prezolon on the 5th, 6th, and 7th day. Subsequently, after discharge tapering followed outside the hospital for another 7 days with oral administration of 32 mg methylprednisolone/day for 4 days followed by 16 mg methylprednisolone/day for another 3 days (tab Medrol 16 mg). The total duration of treatment was therefore 14 days. At the same time, patients underwent 3 IT administration of dexamethasone (amp Dexaton 8 mg/2 ml) on the 2nd, 4th, and 6th day of hospitalization, so that the two medications could synergize. One hour before each injection, every patient received orally 1 tablet that contained 500 mg paracetamol (Depon, Bristol-Myers Squibb) together with 1 tablet that contained 400 mg paracetamol in combination with 10 mg codeine and 50 mg caffeine (Lonarid-N, Boehringer Ingelheim) for purposes of analgesia. Intact tympanic membrane and middle ear status were confirmed by the ENT specialist. While the patient laid in the supine position with the head tilted 45° to the healthy side, a 25-gauge spinal needle was introduced into the posterior–inferior quadrant of the tympanic membrane under microscopic guidance and approximately 0.4 ml of dexamethasone ready solution was slowly instilled into the middle ear. For the next 20 minutes, patients were instructed to remain motionless and avoid swallowing movements, with their head turned to their 'healthy ear' side in order to create the optimal conditions for the solution to fill the round window niche and diffuse into the inner ear. In case complete recovery was confirmed by audiogram, both systemic and intratympanic steroids were discontinued without tapering.

Group B (systemic and intratympanic steroids and HBOT)

The patients who were recruited into this group were also hospitalized for 7 days and received the aforementioned (i.v. and IT) steroid treatment in combination with concomitant HBOT. After one day of the 1st IT (3rd day of hospitalization), the enrolled patients underwent daily 90-minute respiration of 100% O_2 at 2.5 ATA for 10 consecutive sessions in the latest generation Haux Starcom 1400/11 multi-room chamber of the Hyperbaric and Diving Medical Center of Athens. The main part of this system consists of a 12-seat chamber, which allows the simultaneous treatment of patients. Its operation is carried out under computer control by an operator outside the chamber. All devices are based on EN ISO 13485: 2016 and approved by the UHMS European Committee. After proper coaching, patients enter the compression chamber, where the surrounding pressure is gradually increased up to 2.5 ATA and the temperature rises 1–2°C; patients are given 100% oxygen through a special nose–mouth mask. Proper Eustachian tube function with ear clearing techniques (Valsalva, swallowing movements, yawning, etc.) are carried out during compression and decompression. Any patient who showed no improvement (≤10 dB) over the 10 courses was considered unlikely to benefit from further treatment [28]. In case complete recovery was confirmed by a pure tone audiogram, treatment was discontinued. The complete flow sheet of treatment schedules and hearing evaluation of the two groups is depicted in **Figure 1**.

Statistical analysis

All statistical analysis was performed using SPSS software package v17.0, while graphs were created in Microsoft Excel (v. 2013). Basic statistics of both groups are given by sample size, median, minimum, and maximum values. In each category, variables were compared with Chi-square test and a Fisher's exact test, whereas the means of metric variables between two groups were compared with an independent sample *t*-test. One-way analysis of variance (ANOVA) was used to determine whether there were significant differences between the means of the two groups, with $p<0.05$ defined as the cut-off for statistical significance. The means of quantitative variables within

the same group at different points in time were compared with paired-sample *t*-tests. Pearson product–moment correlation coefficients were used to measure the linear dependence between two variables. Determining the optimal sample size for a study assures there is an adequate power to detect statistical significance. The power and sample size were calculated based on the primary outcome of interest (hearing gain) using two-sample comparison of means. The power of the statistical test was defined as equal to 90% (power=1–*b*=0.9). The level of statistical significance alpha was defined as equal to 0.05 (*a*=0.05) and pooled standard deviation equal to 15 (σ=15). We assumed that a 10 dB difference in PTA indicated a significant difference of hearing gain among treatment groups (*d*=10) [38]. According to these parameters, the appropriate number of randomized participants needed to give the ability to detect a 10 dB difference in hearing gain was at least 35 patients per group (for a total of 70).

Ethical considerations

This is a clinical study with a randomized controlled two-arm design. Considering the overall audiological burden and devastation of ISSNHL, and its profound impact on QoL, even a small hearing improvement makes corticosteroids and HBOT reasonable options for treating ISSNHL. If there were an additional placebo group, this would subject the allocated patients to care that is outside the accepted standard, raise ethical issues, and diminish group power [6,39]. This study was designed to be adequately powered with the required number of subjects. All patients were counseled on potential side-effects of systemic steroids. The IT technique was explained in detail to all patients, as well as the possible risks, including transient dizziness, otitis media, and residual tympanic membrane perforation. Patients receiving HBOT therapy were informed about the procedure in the compression chamber and possible side-effects, such as mild ear pain or pressure, lightheadedness, barotrauma (middle ear, sinus, lung), and oxygen poisoning, none of which cause harm in the long term. All patients agreed to take part in the study and signed an informed consent form. The study protocol received approval by the Institutional Review Board and Ethical Committee of the Kapodistrian University of Athens under code n.1516018322 and by the local Ethics Committee of Konstantopouleio General Hospital of Nea Ionia-Patisia of Athens under code n.72/6547, and was in accordance with the Helsinki Declaration and its later amendments or comparable ethical standards [40].

Results

Patient profile characteristics

A total number of 131 patients were screened. There were 19 patients excluded for not meeting the eligibility criteria. The remaining 112 patients who consented to participate were randomized and allocated to two groups. There were 10 of the 112 participants who withdrew from the study due to adverse events, withdrawal of consent, loss of contact and follow up, presentation of bilateral symptoms, and detection of vestibular schwannoma in an MRI scan, leaving 102 participants in the per-protocol analysis – 52 patients in Group A and 50 patients in Group B. The study flow diagram is shown in **Figure 2**.

Table 2 summarizes patient demographics and clinical and audiological characteristics. The mean age was 52.9±15.2 years for Group A and 53.8±15.6 years for Group B (range 18–75 years, median 53.4 years). The overall male-to-female ratio was 57: 45 (male 55.9%, female 44.1% participants included in the study). A preponderance towards the left as the disease-affected side was seen in both groups. In total, 87.3% of the enrolled patients presented with tinnitus at the onset of the ISSNHL episode, while 28% experienced vertigo. The mean severity of initial hearing loss was 74.9±18.0 dB HL (range 55–100, median 70.5) and the overall mean delay to initiate treatment was 4.2±3.0 days (range 0–10, median 3.5). According to these characteristics (age, gender, side of ISSHL, initial hearing loss level, dizziness, tinnitus, and time delay) there was no statistically significant difference between the two groups (p>0.05).

Improvement in hearing levels and hearing gain

The mean hearing levels of Groups A and B at initiation (pre PTA), after one month (PTA 1st month), and final mean PTA (PTA 3rd month) posttreatment are shown in **Figure 3**. The final mean post PTAs were 51.4 dB HL for Group A and 46.7 dB HL for Group B. Both groups had similar initial PTAs and had no statistically significant difference in post-PTA (p>0.05). It is important to look at the long-term audiometric follow-up, and even though the majority of patients did not improve completely, final hearing levels were reached by 1 month in 78% of patients and by 3 months in 97% of patients [6].

Figure 4 depicts the mean hearing gain ΔPTA (pre PTA – post PTA final) in each group. In group A the average hearing gain was 21.0±14.5 dB, whereas in Group B there was a significantly greater benefit of 31.1±19.5 dB average hearing gain. That is, the absolute improvement in average pure-tone audiometric threshold was 10.1 dB greater with the combined steroid + HBOT treatment (95% CI 3.3–16.8, p=0.004), and this was statistically significant with an independent sample *t*-test and a one-way analysis ANOVA.

Table 3 presents the frequency-specific hearing gains of the groups. Hearing gain was compared in terms of three frequency classifications (low frequency: average PTA at 0.25 and 0.5 kHz; mid-frequency: average PTA at 1 and 2 kHz; high frequency: average PTA at 4 and 8 kHz). The data showed no statistically significant differences in hearing gain among the treatment groups in terms of the three classified frequencies. However, the highest arithmetic means and medians can be observed in Group B, in which the efficacy of therapy that included HBOT was better for each of the three frequency ranges. For both groups, the highest hearing benefit can be seen for 0.25–0.5 kHz. In the 1–2 kHz speech range, hearing improvement in both groups was similar to the overall mean hearing gain, while for the high frequencies of 4–8 kHz the therapeutic benefits were the lowest.

Furthermore, in a post hoc subgroup analysis we tested the prognostic value of age and severity of initial hearing loss in terms of final hearing benefit, and the results are shown

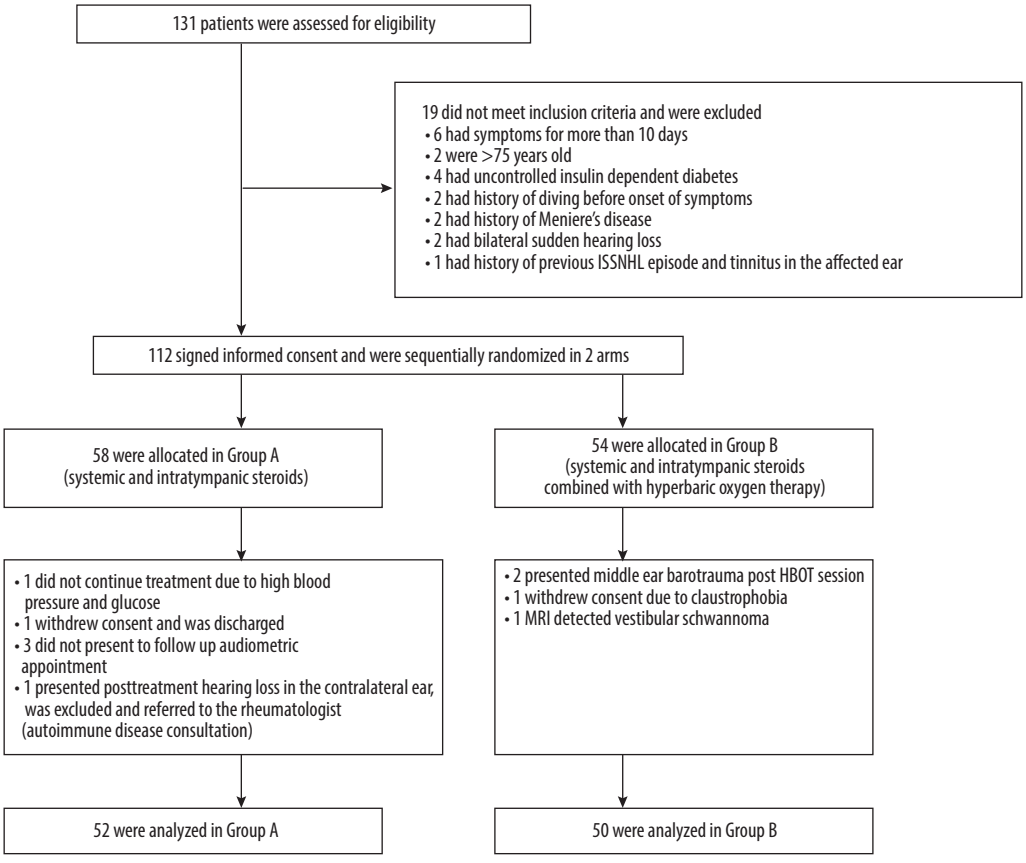

Figure 2. Study flowchart

Table 2. Group comparison of patient profiles

	Group A (SS+IT) (*n*=52)	Group B (SS+IT+HBOT) (*n*=50)	*p*-value
Age (years)* (mean±SD)	52.9±15.2	53.8±15.6	0.34
Gender (male: female)**	25: 27	32: 18	0.91
Ear (right: left)**	24: 28	20: 30	0.65
Initial PTA (dB HL)* (mean±SD)	72.1±18.9	77.7±17.2	0.71
Tinnitus** (%)	86.5 (45)	88 (44)	0.79
Vertigo** (%)	26 (14)	30 (15)	0.23
Time interval from onset to treatment (days)* (mean±SD)	4.44±3.0	4.10±3.07	0.35

Group A (SS: systemic steroids and IT: intratympanic steroids). Group B (SS: systemic steroids and IT: intratympanic steroids combined with HBOT: hyperbaric oxygen therapy). *N*: number of patients. PTA: pure tone average hearing threshold at 0.5, 1, 2, and 4 kHz. SD: standard deviation.

* Analysis of variance test for continuous variables (shown as mean±standard deviation); ** Categorical variables compared with Pearson Chi-square and Fisher's exact test (shown as number of cases and percentage)

in **Figure 5**. Here we divided the population according to the patient's age into two subgroups: ≤45 years old and >45 years old. The mean hearing gain (mean ΔPTA±SD) for Group A was 25.5±16.4 dB HL for the younger group (*n*=15 patients) and 19.2±13.5 dB HL for the older group (*n*=37 patients), while for Group B the comparable figures were 36.7±14.2 dB HL for the younger (*n*=14 patients) and 28.9±20.9 dB HL for the older (*n*=36 patients). When hearing gain for each age group was compared, in both Group A and Group B patients younger than 45 years old had better hearing outcome posttreatment: in Group A, 95% CI −2.53 to 15.16, *p*=0.15 and in Group B, 95% CI −4.55 to 20.01, *p*=0.2, although the difference was not statistically significant.

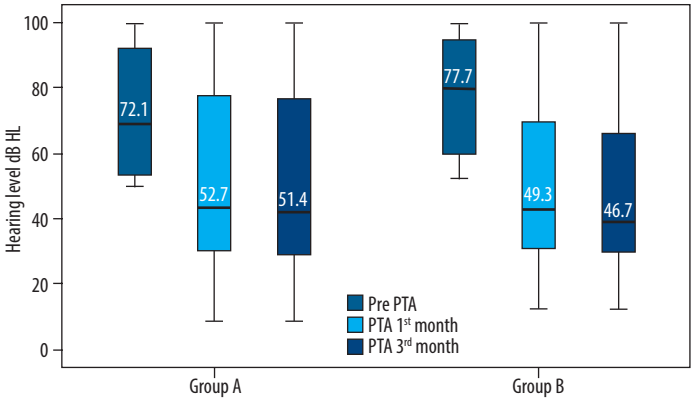

Figure 3. Mean hearing level of ISSNHL patients in each group at initiation, after 1 month, and after 3 months (final post PTA) of treatment. The bars shown mean PTA±SD

Group statistics

	Groups	N	Mean	Std. deviation	Min	Max	Median	Std. error mean
Hearing gain	Group A	52	21.0394	14.54469	.00	60.00	20.0000	2.01699
ΔPTA	Group B	50	31.1300	19.51440	.00	85.00	26.8750	2.75975

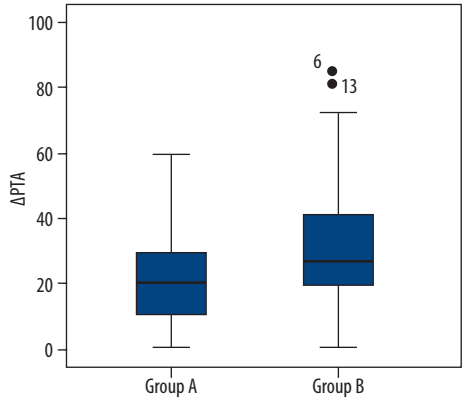

Figure 4. Comparison of hearing gain among the two groups

In a subsequent analysis, the hearing gain was evaluated in terms of severity of the initial hearing loss, and the results are shown in **Figure 6**. Here patients were divided into two groups according to Goodman's criteria: "moderate" loss with pre PTA between 55 and 70 dB HL, and "severe" with pre PTA 70 dB HL or higher. In Group A the mean hearing gain (mean ΔPTA ±SD) was 22.7±11.53 dB HL for the moderate patients (n=26) and 19.4±17.1 dB HL for the severe patients (n=26); in comparison, for Group B the figures were 29.9±10.8 dB HL for the moderate patients (n=21) and 32.0±24.3 dB HL for the severe patients (n=29). Overall, the hearing improvement in Group A was not as good as in Group B (Group A: 95% CI –4.79 to 11.45, p=0.4, and in Group B: 95% CI –13.43 to 9.25, p=0.7). Patients in Group B who had severe hearing loss benefitted most from combined HBOT and steroid treatment. However, there was no statistically significant correlation between the severity of initial hearing loss and mean hearing gain.

Comparison of recovery rates between groups

In our study Siegel's criteria (**Table 1**) were used to assess response to treatment among the two groups, and the recovery rates of Groups A and B are shown in **Table 4**. The percentage of full recovery of hearing in Group B exceeded the full recovery rate in Group A (22% to 15% respectively), although there was a similar rate (56–57%) of overall "favorable" serviceable hearing achieved in both groups. Patients with slight improvement were potential candidates for amplification with a hearing aid. Some 29% of the patients in Group A (nearly 1 in 3) did not respond to treatment with steroids, whereas 16% of the patients in Group B (about 1 in 6) had no improvement when HBOT was added. However, there were no significant statistical differences between the groups (p>0.05). Anything less than a 10 dB HL improvement (the smallest recordable improvement above the range of error for most audiograms) indicates failure to prevent hair cell apoptosis and irreversible damage, perhaps due to a compromised microvascular, oxidative stress or hypoxia, and deregulation of endolymphatic homeostasis. Poorer hearing outcomes after ISSNHL treatment have been correlated with greater age, severity of hearing loss, and vertigo at onset [6,34].

Table 3. Differences in frequency-specific hearing gain between groups

Frequency	Group	Mean	SD	Median	Min	Max	p
0.25–0.5 kHz	A B	23.6 34.1	18.1 23.4	20.2 30.0	0 0	67.5 80.0	0.07
1–2 kHz	A B	21.4 30.8	14.5 19.5	18.0 26.5	-10 -15	52.0 68.5	0.1
4–8 kHz	A B	16.5 25.8	12.3 16.8	15.0 20.0	-20 -18	43.0 54.5	0.3

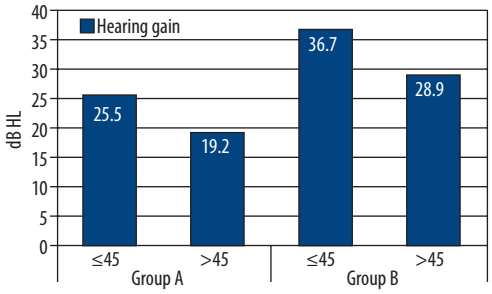

Figure 5. Bar chart of hearing gain depending on age (≤45 and >45 years)

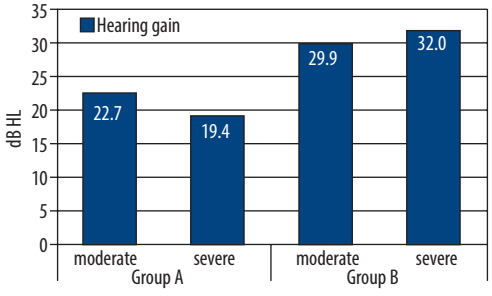

Figure 6. Bar chart of hearing gain depending on the severity of the initial hearing loss (moderate or severe)

Table 4. Recovery statistics for Groups A and B

	Group A (*n*=52)		Group B (*n*=50)	
Complete recovery	8	(15%)	11	(22%)
Partial recovery	22	(42%)	17	(34%)
Slight improvement	7	(13%)	14	(28%)
No improvement	15	(29%)	8	(16%)

Adverse events

There were no significant complications during IT or the follow-up period. Only four patients experienced transient dizziness as a result of caloric stimulation from the injected steroid solution directly after the first injection. The symptoms resolved completely within 15 min and there was no need to discontinue the treatment. The injections that followed caused no further side effect.

HBOT is recognized as a safe treatment modality if the pressure is kept lower than 3 ATA in sessions lasting up to 2 h. Middle-ear barotrauma is the most common complication (13%), but in the vast majority of cases resolves with no sequelae. The incidence of middle ear barotrauma can be lowered using slower compression rates, nasal spray decongestants, and coaching in proper ear clearing techniques [41]. In our study middle ear barotrauma presented in two patients after a HBOT session, and these were excluded from the analysis. Due to claustrophobia in the HBOT chamber one patient withdrew consent. The complications did not cause any harm on a longer timeframe.

Discussion

ISSNHL remains one of the most controversial clinical entities in both etiology and treatment. Despite the contradictory findings in numerous studies, steroids are still accepted as the mainstay of therapy. ISSNHL probably involves a decreased blood supply to the cochlea, and subsequent edema likely activates the immune response and inflammation in the inner ear. Steroids have anti-inflammatory and antioxidative effects and improve microvascular circulation, thereby avoiding cochlear ischemia [16]. Moreover, steroids inhibit apoptosis in hair cells, downregulate local proinflammatory cytokines, and help endolymphatic ion homeostasis via mineralocorticoid receptors in the spiral ligament [16,42]. Their ability to arrest an immune reaction in the context of autoimmune disorders probably translates to ISSNHL affecting the inner ear, and provides a major neuroprotective advantage [42]. Administering systemic and IT steroids together can result in a higher target concentration, in this way achieving the maximum therapeutic effect [21,22].

In the present study that involved hospitalization, combined i.v. and IT steroid as an initial treatment resulted in a complete or partial recovery rate of 57%. Outpatient department–based treatment, including combined steroid therapy has a functional hearing success rate of 55–88% in the literature [21–23]. Generally, the benefit to hearing occurs if therapy is started within 7 days, with worthwhile results out to 14 days. Battaglia et al. reported that patients after combined steroid treatment had greater PTA improvement and they recovered their hearing significantly more quickly than other groups [21]. Arslan et al. also suggest that adding intratympanic methylprednisolone to systemic steroid therapy increases the probability of hearing recovery in ISSNHL patients [22]. On the other hand, Baysal et al. and Tsounis et al. concluded that combined treatment did not have additional benefits in improving hearing compared with systemic or intratympanic steroids alone [24,43]. In most studies of this kind, dosage and duration of steroid treatment varies, and the sequence in combined treatment schedules differs, drastically limiting comparability and making it difficult to reach a consensus.

The administration of hyperbaric oxygen in ISSNHL is based on the argument that both hearing loss and tinnitus may result from a hypoxic event in the cochlea, and HBOT may be able to reverse that oxygen deficit [32]. In addition, HBOT has been found to improve hemorrhage, reduce possible swelling, and speed up repair and recovery. Animal studies have shown that inhaling 100% oxygen at 2.5 ATA increases PO2 in the cochlea by more than 450% [44]. Increased oxygenation of tissues – up to 20 times more than normal – increases available energy and enhances repair of damaged cells, while accelerating collagen production and neoangiogenesis [25,27]. HBOT may therefore be an effective treatment approach in ISSNHL, enhancing the function of red blood cells. In the cochlea, it can enhance local tissue and inner hair cell 'detoxification', thereby helping to restore hearing before permanent cellular damage occurs [25]. HBOT also has a vasodilative effect on the organ of Corti and stria

vascularis, countering the compromised vasculature and oxidative stress which are hypothesized to play major roles in sustaining ISSNHL. All these factors might add to the immuno-suppressant effect of steroids [41].

The addition of HBOT to steroid treatment has given different results in the literature. Suzuki et al. retrospectively compared IT plus systemic steroid application in 174 patients with HBOT plus systemic steroid administration in 102 patients. The complete recovery rate was 29.3% and 21.6% respectively, a difference which was not statistically significant [45]. Toroslu et al. analyzed combination therapy protocols in 90 patients divided into four groups: oral steroids, oral steroids and IT, oral steroids and HBOT, and IT alone. The overall complete recovery rate was 32.2%, and there was no statistically significant difference in mean hearing gain between subgroups [46]. The largest systematic review in the Cochrane Database (updated in 2012) showed a significantly better chance of a 25% increase in PTA following HBOT (RR 1.39, 95% CI 1.05–1.84, p=0.02), with an absolute improvement in average PTA of 15.6 dB (95% CI 1.5–29.8, p=0.03) [34]. The UHMS Committee and various otologic centers claim that better hearing is achieved with early intervention with HBOT and concomitant steroid treatment [25,27,29,31,33]. The European Committee on Hyperbaric Medicine (ECHM), based on a thorough review in the context of the 10th European Consensus Conference on Hyperbaric Medicine, recommends HBOT with strong agreement for the indication of sudden deafness [47]. The updated American Academy of Otolaryngology and Head and Neck Surgery (AAOHNS) 2019 Guidelines recommend that clinicians may offer HBOT with promising results if combined with steroid therapy within 2 weeks of onset of ISSNHL [6].

AAOHNS recognizes that outcome assessment criteria still have limitations [6]. As set out in **Table 4**, of 52 patients in Group A and 50 patients in Group B, 37 and 42 patients respectively had a clinically meaningful recovery. HBOT combination therapy provided the best overall response. According to our results, HBOT when combined with i.v. + IT steroid treatment, gives improved hearing in 56–82% of patients, with a complete recovery rate up to 22%. There was an absolute improvement in PTA audiometric threshold which was 10.1 dB greater in Group B patients compared to Group A, and this difference was clinically and statistically significant.

However, the effectiveness of HBOT is time-dependent. Early application of HBOT helps prevent intra-organ damage before it becomes irreversible [33,41]. Recent data suggest that application as early as possible, preferably within 72 h, correlates with better prognosis [6]. In this study the included subjects started treatment within 10 days of hearing loss, excluding patients with delayed treatment. Moreover, according to our protocol, early HBOT application was initiated on the 3rd day of combined steroid treatment (Group B).

In an attempt to identify other possible prognostic factors regarding the final hearing gain in ISSNHL, we tested age and severity of initial hearing loss as factors in a subgroup analysis. Patients younger than 45 years showed better response to treatment compared to older patients in both groups, achieving greater hearing gain especially in HBOT group, but with no statistical significance (p>0.05). Recent studies confirm our results and correlate younger age with higher rates of hearing recovery [29,34]. Our data analysis demonstrated no significant predictive value of the severity of initial hearing loss in the effectiveness of treatment in ISSNHL, although there was a slightly higher effect of HBOT combination therapy on ISSNHL patients diagnosed with severe or profound hearing loss (>70 dB). In other studies, initial hearing level has been found to have both stronger and weaker correlations to the final hearing outcome [2,4,34]. A study by Topuz et al. concluded that the HBOT group had a statistically significant greater hearing benefit in comparison to the control group when patient age was <50 and there was a pretreatment level of 61–80 dB or greater [29]. In a systematic review, Eryigit et al. concluded that in severe or profound hearing-impaired ISSNHL patients, the addition of HBOT to conventional treatment modalities significantly improves recovery of hearing level [33]. Our results agree with the current literature that combined HBOT treatment offers the most severely affected ISSNHL patients a better chance of hearing recovery.

Lamm et al. assume that HBOT changes the permeability of the round window membrane, increasing the flux of steroids into the perilymph after IT application and giving higher concentrations of steroid first in the basal turn and then in the apex [32]. Dundar et al. and Topuz et al. found similar results and showed that, if the treatment started within 2 weeks, combined HBOT treatment was statistically more effective at low and mid frequencies for pretreatment levels >60 dB and patient age <50 [48]. In our study, hearing gain was analyzed according to three frequency bands. In terms of means and medians, the HBOT group showed better outcomes in all frequency subgroups. Both Group A and Group B had better hearing gains at low frequencies. The best hearing benefit occurred in Group B in the 0.25–0.5 kHz range, with the difference at the borderline of statistical significance (p = 0.07). A possible explanation for the frequency factor may be the different vulnerability of hair cells. In one animal study, hair cells in the basal turn seemed to show less resistance to acoustic trauma and ototoxic drugs and more vulnerability to free-radical damage than those in the apical turn [49]. Also, unlike the basal turn, there may be higher levels of intrinsic antioxidant enzymes in the apex [23].

When treating ISSNHL with HBOT clinically, several different protocols have been carried out involving different timing and duration. The most frequently used treatment protocol is a 90-minute HBOT session once a day for 10 days at 2.5 ATA, which our Group B patients were also exposed to. In a recent research article there was a notable difference in the therapeutic effect of this HBOT protocol depending on the applied pressure (while maintaining the same number of sessions, periodicity, and exposure times). In the low frequency range 0.25–0.5 kHz, the use of 2.5 ATA pressure was more effective. However, at higher frequencies (1–2 kHz and 4–8 kHz), better hearing gains were obtained at 2.0 ATA pressure [50]. These results support the possibility of optimizing treatments individually, depending on the type and frequency range of hearing impairment (shape of the audiogram) in order to obtain the best therapeutic effect.

Hearing loss dramatically affects QoL for patients and their families and may heavily impair their social life and career (WHO 2010) [51,52]. There is no formal detailed cost analysis for ISSNHL in the literature. With most insurance providers not covering HBOT, hearing aids are the cheapest option, although they cost $1500–3000 per pair (USA) or 1000€ to 2000€ each (in Europe) and require replacement every 3–5 years, without always giving fully functional hearing. HBOT is a time-consuming and rather expensive intervention. A 10-session course at an outpatient facility ranges between $2000 and $5000 in the USA, while typical fees in academic institutions are approximately $600–700 per session [52]. A facility in Australia calculated that the cost of one HBOT session to be around A$304 [33]. For the current study protocol, the authorized cooperation by the committee entailed an expense of 40€ per session, making a total cost of 400€ per patient receiving HBOT. Early application of HBOT enhances the likelihood of recovery to a normal hearing or perhaps to a level having only slight impairment. Such an improvement on an average patient would prevent the need for them to wear hearing aids and learn lip reading, preserving their QoL [52]. Isolation, employment problems, compromised safety, and depression are only some of the profound consequences of permanent hearing loss [51]. We believe that, based on current medical evidence, the use of combined therapy with HBOT significantly improves the patient's hearing and minimizes the psychosocial and financial burden of impairment, outweighing the treatment costs [25].

Limitations

According to Mattox and Simmons (1977), a considerable percentage (32–65%) of patients suffering ISSNHL show spontaneous recovery in the first 2 weeks; there is therefore always the possibility of bias in treating the condition [3]. However, this factor applies to every treatment group. Although treating with HBOT appears to be sensible advice, it is only available in specialized hospitals and medical centers, creating a practical obstacle. The availability of HBOT centers in every region and their capability of accepting this 'new patient flow' is being questioned, as is the cost effectiveness of the treatment. Compared to the cost of hearing aids, and loss of income and QoL, in severe cases of sudden hearing loss HBOT seems a fair expense to incur, although the cost may vary considerably among facilities. Despite these limitations, a clinically beneficial tendency of combined HBOT treatment was evident.

Conclusions

The present study demonstrates that, in ISSNHL patients, there is a better remedial effect from early HBOT when combined with systemic and IT steroid therapy than by relying on steroid treatment alone. Combined therapy resulted in a statistically significant hearing gain of about 10.1 dB in the final PTA compared to using only steroids. Although age and the severity of initial hearing loss are factors of clinical importance, when tested for their predictive value in ISSNHL treatment, our study did not see a significant correlation. The addition of HBOT had a positive impact on all tested frequencies, with maximal remedial benefit at 0.25 and 0.5 kHz. Our results add to the mounting evidence that suggest combination therapy offers ISSNHL patients the best chance of achieving a favorable hearing level.

In conclusion, younger patients with severe hearing loss, who present within 10 days of symptom onset should be considered for combined HBOT and steroid treatment. The conditions under which additional HBOT is used to treat ISSNHL still need to be optimized. Future comprehensive clinical trials are needed to determine which subgroup of patients can be expected to derive maximum gain from HBOT combined treatment, standardize dosages, and optimize treatment sequences in order to establish the most effective approach for each patient.

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Conflict of interest

The authors declare that they have no conflict of interest.

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