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Research article

Hyperbaric oxygen therapy improves the effects of systemic steroid therapy for sudden sensorineural hearing loss

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ABSTRACT

Objectives: This study aimed to investigate the therapeutic efficacy of combined hyperbaric oxygen therapy (HBOT) and steroid therapy in treating sudden sensorineural hearing loss (SSNHL)
Design: This retrospective analysis included 505 patients diagnosed with SSNHL from August 2017 to July 2022. The patients received either a systemic steroid (SS) alone or SS with HBOT. Hearing improvement was evaluated with pure-tone audiometry (PTA). Among the participants, 102 received SS + HBOT, whereas 403 were treated with SS alone.
Results: The SS + HBOT group demonstrated significantly better improvement in the PTA threshold averaged across four low frequencies (PTA_4) scores (22.7 ± 23.5 vs. 16.2 ± 21.4, $P = 0.007$) and higher response rates ($\geq$15 dB improvement) and significant response ($\geq$25 dB improvement) (61.8 % vs. 44.4 %, $P = 0.002$; and 43.1 % vs. 22.6 %, $P < 0.001$, respectively) than the SS-alone group. HBOT is particularly effective in patients with hearing loss at lower frequencies. Patients treated with HBOT were 2.50 times more likely to achieve substantial hearing improvement. Patients receiving three HBOT sessions or initiating treatment within 11

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days of diagnosis demonstrated optimal outcomes. Greater improvements were observed in patients with initial hearing loss of >50 dB and younger individuals.
Conclusions: HBOT improves the effectiveness of SS treatment in SSNHL, with notable benefits for younger patients and those with an initial hearing loss of >50 dB. HBOT exhibited more pronounced effects at lower frequencies. Initiating HBOT within 11 days of the SSNHL diagnosis is recommended, and a regimen of five sessions is indicated for optimal results.

1. Introduction

Sudden sensorineural hearing loss (SSNHL) is a medical emergency that requires prompt intervention, as delayed diagnosis and treatment cause irreversible and severe consequences [1–3]. SSNHL is characterized by a hearing loss of at least 30 dB across three consecutive frequencies on a standard pure-tone audiogram, occurring over a period of ≤72 h [4–6]. The etiology and optimal treatment strategies for SSNHL remain a matter of debate despite extensive global research. The recovery of hearing thresholds after SSNHL greatly differs. Some patients may experience no recovery, whereas others may have partial or complete restoration of hearing [7].

The precise pathophysiology of SSNHL remains unclear, with proposed mechanisms, consisting of viral infections, vascular insufficiency, immune-mediated disorders, endolymphatic hydrops, and even genetic factors [6]. The treatment options for SSNHL include corticosteroids, vasodilators [8,9], antiviral agents [10,11], and hyperbaric oxygen therapy (HBOT) [12]. Among these, systemic corticosteroids [13–15] are the most predominantly accepted and prevalently used treatment; however, their efficacy continues to be a subject of controversy [16–18].

The hair cells of the inner ear are highly energy-demanding and oxygen-consuming. Increased reactive oxygen species (ROS) levels under hypoxic conditions cause cellular damage, including biomolecular and DNA damage, potentially triggering cell death. Several studies indicate that oxidative stress may play a crucial role in SSNHL development, although the exact mechanisms remain unclear [19]. HBOT, which was first introduced for treating idiopathic SSNHL in the 1960s [20], improves perilymph oxygenation and mitigates inner ear ischemia by delivering oxygen at high pressure. The 2019 updated guidelines for SSNHL recommend HBOT as an initial therapy in combination with steroids within 2 weeks of SSNHL onset or as a salvage therapy option within 1 month [21].

Several studies have revealed that combining HBOT with systemic steroid (SS) treatment for SSNHL is more effective than medical treatment alone [22]. HBOT has been particularly beneficial for patients with severe SSNHL (defined as an initial hearing loss of ≥70 dB) [23,24] and those experiencing hearing loss at lower frequencies [25,26]. However, the optimal HBOT protocol for SSNHL remains unknown. Further research is warranted to identify the ideal number of sessions, pressure settings, timing, and patient characteristics that predict the best outcomes.

This study aimed to investigate the effectiveness of HBOT on SSNHL and analyze HBOT in detail both as a complementary therapy in conjunction with standard medical treatments and in terms of optimizing HBOT protocols.

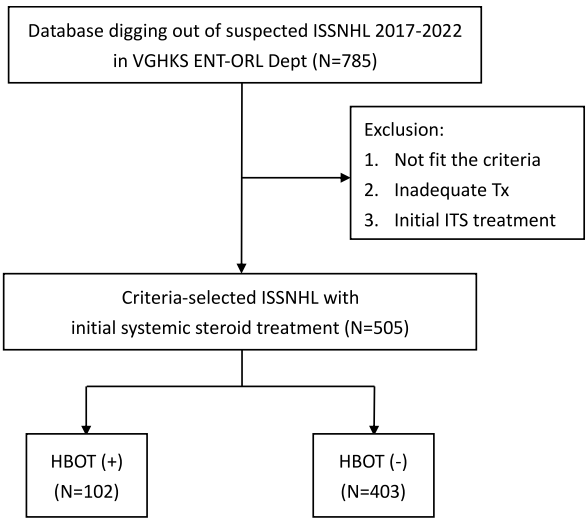

Fig. 1. Flow chart of the study population.

2. Materials and methods

2.1. study design and population

This retrospective study included patients diagnosed with SSNHL at the ENT department and the HBOT center of a tertiary referral hospital from August 2017 to July 2022. SSNHL diagnosis was confirmed through a thorough review of medical records and audiological assessments, including PTA. This study excluded patients who did not meet the SSNHL diagnostic criteria or who received inadequate medical treatment.

2.2. data collection

We obtained and analyzed data on patient demographics (gender and age), underlying diseases, and personal habits (e.g., alcohol consumption, smoking). Information on the affected ear, hearing loss onset, associated symptoms, medical treatment and/or HBOT initiation timing, and number of HBOT sessions were also recorded. The Institutional Review Board and Ethics Committee of the hospital approved this study.

This study initially screened 785 patients who received systemic treatment with or without HBOT. To ensure homogeneity, 66 patients who initially received intratympanic steroids injection (ITS) instead of SS were excluded. Consequently, the final analysis included 505 patients (Fig. 1). Among the participants, 102 received SS + HBOT, whereas 403 were treated with SS alone.

2.3. treatment

2.3.1. Medical treatment

Systemic high-dose corticosteroids (prednisolone or dexamethasone) were initially administered at 1 mg/kg/day for 2 weeks: intravenously during the first week and orally during the second week, followed by a tapering phase. Adjunctive treatments, such as Rheomacrodex, Nicametate, or vitamin B supplements, were provided as needed. ITS was administered either when SS therapy was contraindicated or as salvage treatment if SS did not yield satisfactory results.

2.3.2. HBOT

The HBOT protocol comprised daily 120-min treatments at 2.5 atm absolute (ATA). The latency of HBOT was the number of days between SSNHL diagnosis and HBOT initiation. Patients were referred to the HBOT center upon SSNHL diagnosis, and the benefits, risks, and procedures of HBOT were thoroughly explained before treatment. An initial course of five HBOT sessions was recommended and may be extended based on treatment outcomes.

2.4. Hearing assessment

Hearing assessments were conducted at SSNHL diagnosis and 1 month after medical treatment completion. An improvement in hearing of >15 dB in PTA_4, according to the modified Siegel's criteria, was considered a clinically favorable outcome. Response and significant response were indicated as hearing improvements of >15 dB and >25 dB, respectively. Hearing loss severity was classified using the World Health Organization (WHO) criteria as grades 0 (no impairment, ≤25-dB hearing loss), 1 (slight impairment, 26–40-dB hearing loss), 2 (moderate impairment, 41–60-dB hearing loss), 3 (severe impairment, 61–80-dB hearing loss), and 4 (profound impairment, ≥81-dB hearing loss, including deafness). Grades 1 and 2 were combined into a slight-moderate category as patients with SSNHL had hearing loss of ≥30 dB at diagnosis. The patients were then categorized into three groups: slight-moderate, severe, and profound hearing loss.

Table 1
Patient demography (N = 505).

N (%) Mean ± SD	SS + HBOT N = 102 (20.2 %)	SS N = 403 (79.8 %)	*p*-value
Age, year	51.5 ± 13.3	54.5 ± 14.9	0.064
Sex, male	56 (54.9)	194 (48.1)	0.222
Height	164.2 ± 8.3 (n = 102)	163.1 ± 8.9 (n = 391)	0.259
Weight	65.9 ± 14.0 (n = 102)	65.1 ± 13.9 (n = 390)	0.588
BMI (kg/m2)	24.8 ± 4.2 (n = 491)	24.5 ± 4.0 (n = 64)	0.445
Laterization (Right)	45 (44.1)	195 (48.4)	0.643
Salvage ITS	57 (55.9)	126 (31.3)	<0.001**
Comorbidities	30 (29.4)	98 (24.4)	0.291
Initial severity			
PTA_4 (dB)	53.47 ± 25.69	34.94 ± 27.75	<0.001**
Slight-moderate	24 (23.5)	194 (48.1)	<0.001**
Severe	30 (29.4)	108 (26.8)	0.620
Profound	48 (47.1)	101 (25.1)	0.001**

* P-value<0.05; ** P-value <0.01.

2.5. Statistical analysis

Statistical Package for the Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Categorical variables are reported as frequencies and percentages, whereas continuous variables are presented as means ± standard deviations. The chi-square test was conducted to compare categorical variables, and the Wilcoxon signed-rank test was utilized for paired categorical variables. Differences between continuous variables were evaluated using the independent *t*-test. The paired *t*-test was conducted to compare PTA changes before and after treatment. Statistical significance was set at *P*-values of <0.05. Variables that were significant in the univariate analysis or determined as potential confounders were further investigated using multivariate logistic regression to identify factors related to hearing improvement.

3. Results

3.1. HBOT combined with SS improves the outcome of severe initial hearing loss

Table 1 summarizes the demographic characteristics of the patients. The baseline characteristics were comparable between the groups. However, patients who received SS + HBOT demonstrated more severe initial hearing impairment than those who received SS alone, with a mean initial PTA_4 score of 53.47 ± 25.69 dB versus 34.94 ± 27.75 dB ($P < 0.001$). Patients receiving HBOT exhibited a significant improvement in PTA_4 scores compared to those who did not (22.7 ± 23.5 vs. 16.2 ± 21.4, $P = 0.007$) (Table 2). Notable improvements were observed across all frequencies, except at 4000 and 8000 Hz. The SS + HBOT group demonstrated greater hearing improvements of >15 dB (response) and >25 dB (significant response) compared with the SS-alone group (61.8 % vs. 44.4 %, $P = 0.002$; and 43.1 % vs. 22.6 %, $P < 0.001$).

Hearing improvements, as categorized by the WHO classification, were significant in the SS + HBOT groups, with most *P*-values being <0.001, as determined by the Wilcoxon signed-rank test (Fig. 2).

The bar chart was drafted based on the distribution of patients in different WHO classification severity. Patients classified as mild–moderate increased and as severe and profound decreased in both groups after treatment. The difference was statistically significant ($P < 0.05$). Notably, the mild–moderate group demonstrated a greater increase after SS + HBOT treatment compared to SS alone.

The multivariate analysis revealed that patients undergoing HBOT were 2.50 times more likely to experience significant hearing improvement (95 % confidence interval [CI]: 1.75–4.56, $P < 0.001$) (Table 3). Among patients receiving HBOT, those with an initial hearing loss of >50 dB experienced more pronounced improvements, whereas older patients and those receiving salvage ITS exhibited poorer prognoses (Table 4).

3.2. Five sessions of HBOT for SSNHL treatment

The association of the number of HBOT sessions with hearing outcomes was evaluated. The reference group involved patients who underwent one or two sessions. Those who received three sessions demonstrated more significant improvement compared to those who had four or more sessions (9 [90.0 %] vs. 47 [51.1 %], $P = 0.019$) (Table 5). No significant differences in hearing improvement were observed between patients receiving <5 or those with >5 HBOT sessions.

3.3. HBOT initiated within 11 days of SSNHL diagnosis

The time from SSNHL diagnosis to HBOT initiation ranged from 1 to 162 days (mean: 11.45 ± 17.8 days). Patients who initiated

Table 2
Improvement in PTA of HBOT.

dB, mean ± SD	SS + HBOT N = 102 (20.2 %)	SS N = 403 (79.8 %)	*p*-value
PTA_4	22.7 ± 23.5	16.2 ± 21.4	0.007**
250 Hz	23.8 ± 25.5	16.3 ± 23.5	0.004**
500 Hz	24.6 ± 25.7	19.3 ± 24.2	0.050[a]
1000 Hz	23.7 ± 23.5	17.4 ± 22.7	0.014[a]
2000 Hz	20.1 ± 21.9	15.3 ± 21.6	0.048[a]
4000 Hz	15.6 ± 20.2	11.6 ± 19.8	0.071
8000 Hz	9.9 ± 16.4	8.6 ± 17.5	0.506
Post-treatment severity			
Slight-moderate	64 (62.7)	287 (71.2)	0.117
Severe	16 (15.7)	65 (16.1)	1.000
Profound	22 (21.6)	51 (12.7)	0.027[a]
Hearing gain>15 dB, N (%)	63 (61.8)	179 (44.4)	0.002**
Hearing gain >25 dB, N (%)	50 (49.0)	112 (27.8)	<0.001**

Hearing gain: dB improvement in PTA after treatment.
[a] P-value<0.05; ** P-value <0.01.

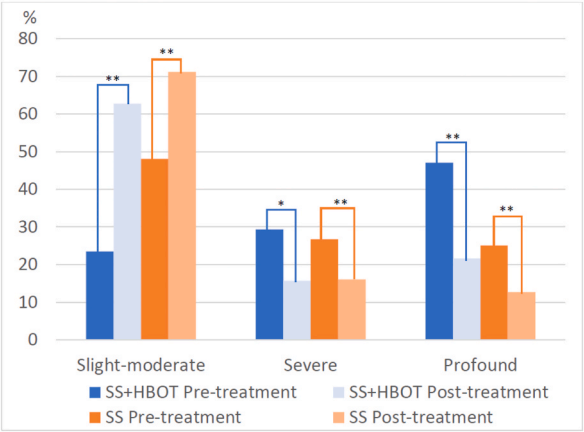

Fig. 2. Distribution of patients' severity before and after treatment.
Notes: * P-value <0.05; ** P-value <0.01.

Table 3
Logistic regression of hearing gain.

	≥25 dB		≥15 dB	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
HBO (+)	2.50 (1.75, 4.56)	<0.001**	1.82 (1.14, 2.92)	0.013[a]
Age, year	0.99 (0.97, 1.00)	0.128	0.98 (0.97, 0.99)	0.007[a]
Sex, male	1.03 (0.69, 1.55)	0.882	0.86 (0.59, 1.26)	0.445
BMI (kg/m2)	0.96 (0.91, 1.01	0.124	0.97 (0.92, 1.02)	0.231
Diabetes mellitus	2.48 (1.44, 4.28)	0.014[a]	1.94 (1.13, 3.34)	0.017[a]
Renal failure	1.34 (0.59, 3.03)	0.489	1.76 (0.75, 4.14)	0.193
Cardiovascular disease	2.44 (0.97, 6.10)	0.057	1.77 (0.70, 4.47)	0.226
Stroke	0.47 (0.20, 1.13)	0.092	0.95 (0.45, 2.00)	0.885

[a] P-value<0.05; ** P-value <0.01.

Table 4
Factors associated with hearing improvement in HBOT groups (N = 102).

Hearing gains	≥25 dB		≥15 dB	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Initial hearing loss >50 dB	49.06 (5.05, 476.34)	0.001**	27.86 (4.81, 161.37)	<0.001**
Salvage ITS	0.09 (0.03, 0.31)	<0.001**	0.22 (0.07, 0.64)	0.006**
Age, year	0.95 (0.91, 0.99)	0.016[a]	0.97 (0.93, 1.00)	0.124
Sex, male	0.39 (0.13, 1.13)	0.082	0.40 (0.14, 1.12)	0.081
BMI (kg/m2)	1.04 (0.91, 1.18)	0.578	1.08 (0.94, 1.25)	0.251
Diabetes mellitus	4.30 (1.04, 17.7)	0.043	1.54 (0.39, 6.01)	0.538
Renal failure	1.43 (0.17, 11.91)	0.739	4.61 (0.41, 51.85)	0.215
Cardiovascular disease	5.67 (0.01, 3537.41)	0.597	43.6 (0.04, 540.31)	0.550
Stroke	0.69 (0.09, 5.38)	0.720	0.70 (0.10, 5.01)	0.721

[a] P-value<0.05; ** P-value <0.01.

Table 5
Association between HBOT sessions and hearing improvement.

Session number (N)	Hearing improvement, N (%)	*P*-value
3 (10) vs ≥ 4(92)	9 (90.0) vs 47 (51.1)	0.019[a]
≤4 (21) vs > 5 (81)	14 (66.7) vs 42 (51.9)	0.224
≤5 (54) vs > 6 (48)	31 (57.4) vs 25 (52.1)	0.590
≤10 (92) vs > 11(10)	52 (56.5) vs 4 (40.0)	0.319
3-5 (54) vs 6–10 (38)	31 (57.4) vs 21 (55.3)	0.838

Hearing improvement: PTA_4 improve ≥15 dB.
[a] P-value<0.05.

Table 6
Latency in hearing change of SS + HBOT group.

	≤11 days	>12 days	*P*-value
PTA_4 improvement (Hz)	26.41 ± 21.54	15.63 ± 27.88	0.047[a]
Hearing gain>15 dB, N (%)	13 (50)	42 (59.2)	0.491
Hearing gain >25 dB, N (%)	7 (26.9)	26 (36.6)	0.471

[a] P-value<0.05.

HBOT within 11 days of diagnosis demonstrated greater hearing improvements (Table 6). However, no significant differences in the response or significant response rates based on the latency were observed between SSNHL diagnosis and HBOT initiation.

4. Discussion

HBOT has exhibited beneficial effects in treating SSNHL when administered as an adjunct to SS treatments. The rationale for HBOT application in treating SSNHL lies in addressing the underlying hypoxia that contributes to cochlear injury. Various etiological factors, including vascular compromise, viral infections, and autoimmune processes, may culminate in reduced oxygen supply to the cochlea, thereby causing damage. HBOT, by improving oxygen delivery to the inner ear, targets this hypoxic state, thereby supporting tissue repair and recovery. Several studies have revealed that HBOT used adjunctively with corticosteroid therapy yields a synergistic therapeutic effect, potentially improving hearing outcomes more than steroids alone [22,25,27]. In addition, repeated HBOT sessions affected the activity of antioxidant enzymes, thereby potentially disrupting redox balance that is frequently altered in SSNHL. Specifically, repeated HBOT modulates the activity of antioxidant enzymes after HBO sessions [28]. The present study indicated that patients treated with a combination of SS and HBOT demonstrated significantly better improvement in PTA_4 compared with those who received SS alone. Notably, the benefits of adding HBOT were more pronounced at lower frequencies. Patients treated with the combination of HBOT and SS achieved a higher absolute hearing gain and more substantial auditory function recovery than those receiving medical treatment alone, consistent with results from previous studies. Dova et al. and Yucel et al. revealed no significant differences in outcomes between combined SS and HBOT compared with medical treatment alone [22,24]. However, Yucel et al. revealed the average hearing improvement after medical treatment alone at 21 dB, which was notably higher than the 16.2 dB gain observed in our study. This discrepancy may be attributed to the inclusion of ITS as an initial treatment in the study of Yucel et al. In contrast, our study excluded patients who initially received ITS to avoid confounding the therapeutic effects of HBOT.

The present study revealed that HBOT caused significantly better hearing improvement (gain) at lower frequencies. The mean improvement at 250, 500, 1,000, and 2000 Hz exceeded 20 dB each. Meanwhile, no significant improvement was observed at 4000 and 8000 Hz after treatment. Chin et al. reported hearing improvement at all frequencies after HBOT, but a greater improvement remains in lower frequencies [29]. The frequency-specific effectiveness of HBOT may be attributed to the cochlea's susceptibility to ischemia and hypoxic changes, as well as its unique anatomical structure. However, a paradox exists the abundant blood flow at the cochlear base does not necessarily correlate with improved recovery. The diverse etiologies of SSNHL further complicate the treatment outcomes. HBOT has consistently exhibited better outcomes at lower frequencies despite these complexities, which aligns with our results. Notably, the patients in our study who received HBOT reported a mean age of 55 years and presented with more severe hearing loss. These factors could potentially impede recovery from hair cell damage. In recent years, N-acetylcysteine has been an effective adjuvant therapy when combined with steroids in treating SSNHL. Previous studies revealed that N-acetylcysteine decreases hair cell death caused by ROS stress [30,31]. A deeper understanding of the complex interactions within the inner ear and a more detailed frequency-specific analysis could help determine patient subgroups that would derive the greatest benefit from HBOT.

Our results indicated that patients with an initial hearing loss of >50 dB experienced better outcomes after HBOT. Rhee et al. revealed that the combination of SSs and HBOT was more effective than SS alone in patients with severe-to-profound hearing loss [32]. Similarly, Ahn et al. demonstrated that HBOT caused a significantly faster improvement in hearing recovery at the initial recovery periods in the severe SSNHL group (60–79 dB of initial PTA) than in the steroid-alone groups, with significant differences especially at low frequencies [27]. Consistent with these results, Chin et al. revealed greater improvement in patients with more severe hearing loss, with an odds ratio of 5.034 for HBOT in improving pure-tone average PTA results [29].

Conversely, a recent study indicated that patients with mild–moderate hearing loss achieved better outcomes than those with severe-to-profound hearing loss [33]. However, this study did not specify a clear hearing loss cutoff level and included a relatively small sample size. Our results align with those of earlier studies that involved a larger sample size and revealed a lower initial hearing loss threshold of 50 dB. Moreover, our multivariate regression analysis provides stronger evidence that the effect of HBOT surpasses other influencing factors.

The protocols for HBOT significantly differ across institutions, which may contribute to inconsistencies in the reported outcomes for SSNHL. Thus, we analyzed different HBOT protocols and related parameters. Our results indicated that patients who received 3 HBOT sessions demonstrated the highest likelihood of experiencing a hearing improvement of >15 dB. Our analysis revealed similar outcomes for patients receiving 1–5 sessions than those undergoing 6–10 sessions. This finding is consistent with that of Chin et al., who revealed significant improvement in their patients [29]. Additionally, Kim et al. demonstrated that extending the HBOT session duration from 1 hour to 2 hours did not provide additional benefits, although higher pressure levels were related to improved outcomes [34]. Rhee et al. revealed that patients who received >1200 min of HBOT demonstrated a 2.04-fold increase in the likelihood of achieving complete hearing recovery [32]. However, the high degree of subgroup heterogeneity in their study indicates variability in the patient's treatment response. The beneficial effects of HBOT remain evident after the initial sessions despite this variability. In contrast, our study revealed that extended HBOT sessions did not confer additional significant benefits, indicating that the therapeutic efficacy of HBOT in SSNHL may not be dose-dependent. These results indicate that a trial of five HBOT sessions is reasonable. This approach enables shared decision-making, allowing clinicians and patients to tailor the treatment plan to individual needs.

This study demonstrated that initiating HBOT within 11 days after SSNHL diagnosis caused better outcomes, with an approximate 10 dB improvement in PTA_4. The latency from SSNHL diagnosis to HBOT initiation in our cohort ranged from 1 to 162 days, with a mean of 12.34 ± 18.34 days. Tong et al. similarly revealed that HBOT, initiated within 14 days after the symptom onset, significantly improved outcomes [33]. Chin et al. further supported this finding, demonstrating that HBOT that commenced within 12 days of diagnosis exhibited a 6.484-fold greater therapeutic effect [29]. Conversely, Yucel et al. indicated no significant difference in outcomes according to different initiation times, specifically within 1–3 days, 4–10 days, and >10 days [22]. The discrepancy in these results may be attributed to the standard administration of steroid therapy within the first 2 weeks after SSNHL diagnosis. The observed improvements may be caused by the synergistic effect of combining HBOT with SS therapy during this critical period and or spontaneous recovery [7,16]. The effect of the timing and duration of simultaneous HBOT and medical treatment requires further investigation to optimize therapeutic outcomes.

Our study has several limitations. The HBOT regimen was not standardized considering the retrospective analysis, causing variability in the treatment protocols. The multivariate analysis revealed that age, cardiovascular disease, and diabetes mellitus were significant factors associated with hearing outcomes, aside from HBOT. These factors may be potential confounding factors. Propensity score matching or weighted analysis should be conducted in a subsequent study to alleviate the factors and inherent differences between the two groups. Patients who experienced improvement after three HBOT sessions were frequently less motivated to complete the full course of 5 or 10 sessions. Conversely, those who underwent more sessions may indicate a selection bias, as their lack of significant improvement during the initial sessions could influence the results toward less favorable outcomes with extended HBOT. Further prospective studies with a strictly adhered HBOT protocol are warranted to confirm our results.

5. Conclusions

HBOT exhibited a synergistic effect when combined with SS in patients with SSNHL, particularly among younger patients and those with an initial hearing loss of >50 dB. The therapeutic benefits of HBOT were more profound at lower frequencies. Initiating HBOT within 11 days of SSNHL diagnosis was related to improved clinical outcomes. These results indicate that recommending a minimum of five HBOT sessions is a reasonable approach.

CRediT authorship contribution statement

Yu-Ching Chen: Writing – original draft, Visualization, Validation, Investigation, Formal analysis. **Yu-Hsi Liu:** Resources, Data curation. **Bor-Hwang Kang:** Supervision, Resources. **Cai-Sin Yao:** Software, Formal analysis, Data curation. **Yao-Shen Chen:** Supervision. **Wen-Chung Liu:** Writing – review & editing, Validation, Project administration, Methodology, Conceptualization.

Data availability statement

The data that support the findings of this study are available from the Kaohsiung Veterans General Hospital, Taiwan. Restrictions apply to the availability of these data, which were used after ethical approval and under license for this study. Due to the legal restrictions imposed by the government of Taiwan in relation to the "Personal Information Protection Act," data cannot be made publicly available.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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