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Prognostic factors for hearing outcomes in patients that undergo adjuvant hyperbaric oxygen therapy for sudden sensorineural hearing loss

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Abstract

Introduction: The aim of this study is to explore the potential factors in hearing outcomes and verify the role of oxidant-antioxidant equilibrium on the prognosis of sudden sensorineural hearing loss (SSNHL) treated with hyperbaric oxygen therapy (HBOT).

Methods: Ninety-two patients who were diagnosed with SSNHL between January 2018 and December 2019 in our hearing clinic center were included in this study. All patients were treated with intravenous dexamethasone, and 72 cases were treated with additional HBOT for 10 consecutive days. Peripheral blood was collected prior to any treatment to determine the blood cell count and hemoglobin (HGB), hematocrit (HCT), and superoxide dismutase (SOD) levels. Pure tone audiometry was measured before and after treatment. Complete and overall recovery rate was evaluated. Multivariate logistic analysis was used to identify prognostic factors.

Results: The rate of overall recovery was significantly higher in the patient with combined therapy compared to patients treated with steroids only (51.4% vs 25.0%, $p = .036$). The levels of HGB, HCT, and SOD were much higher in the patients with better hearing outcomes ($p = .027$, .033, and .011, respectively). Multivariate logistic analysis demonstrated that patients with higher initial hearing thresholds, or hearing loss at overall frequency, were more prone to have poor hearing gains after HBOT.

Conclusion: HBOT is effective as an early adjuvant therapy for SSNHL. Hearing loss at low frequency, low initial hearing thresholds, as well as high HBG, HCT, and SOD levels are positive prognostic factors for SSNHL patients treated with HBOT.

KEYWORDS
antioxidant, hearing outcome, hyperbaric oxygen therapy, prognosis, sudden sensorineural hearing loss

Zirong Huo and Xuefeng Cheng contributed equally to this work.

1 | INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is a hearing impairment of unknown etiology. SSNHL is defined as hearing loss of more than 30 dB in three consecutive frequencies that occurs within 72 h.[1] The incidence of SSNHL ranges from 5 to 20 cases per 100,000 people per year, and most frequently affects patients between 30 and 60 years of age.[2] Although the pathogenic causes are far from understood, the most common etiologies mentioned in reported studies are viral infections, vascular disorders, and autoimmune factors.

Hyperbaric oxygen therapy (HBOT) consists of breathing 100% oxygen in a chamber specifically adapted to have a pressure of approximately 2.5 atmospheres absolute (ata). HBOT, in combination with steroid therapy, has been recognized as a primary treatment, for SSNHL within 2 weeks of onset or as a salvage therapy within 1 month of onset.[3] The cochlea demands a high level of oxygen but has a relatively limited vascular supply[4]; thus, oxygen shortage is one of the proposed causes of SSNHL. The benefits of HBOT in SSNHL are associated with improvements in microcirculation and facilitation of oxygen diffusion from blood capillaries to the inner ear.[5] An increase in partial oxygen pressure in the cochlear tissue and a reduction in tissue hypoxia and edema have been observed after HBOT. Moreover, one of the potential causes of SSNHL, chronic inflammation, is not decreased by HBOT.[6] Previous studies have reported that the neutrophil-to-lymphocyte ratio (NLR) is a novel and effective marker for systemic inflammation in illnesses such as ischemic heart disease, ulcerative colitis, and cancer.[7,8] It has also been reported that HBOT has antibacterial effects via oxygen radicals, as well as promotes angiogenesis and tissue regeneration.[9] Elevated O_2 partial pressure is one of the major therapeutic mechanisms of HBOT but also has side effects by reason of the formation of reactive oxygen species (ROS) due to incomplete oxygen reduction in the oxidative chain.[10] The antioxidant defense mechanism comprises antioxidant enzymes, such as superoxide dismutase (SOD), and non-enzymatic antioxidants, such as glutathione (GSH), which are responsible for ROS scavenging and are thus regarded as indicators of oxidative stress.[11]

The aim of this study was to determine the potential factors involved in the therapeutic effect of HBOT in SSNHL from the perspective of oxidative stress and systemic inflammation. The activity of the key antioxidant enzyme SOD, the levels of hemoglobin (HGB) and hematocrit (HCT), and inflammatory markers, such as the number of white blood cells (WBC) and the NLR, were assessed in SSNHL patients with different hearing outcomes after HBOT.

2 | MATERIALS AND METHODS

2.1 | Patient selection

A standardized retrospective study was performed in a tertiary hospital in accordance with the ethical principles described in the Declaration of Helsinki and approved by the ethics committee of Shanghai Ninth People's Hospital, Affiliated to Shanghai Jiaotong University School of Medicine (approval no. SH9H-2020-T35-3). The informed consents were written by the individual participants.

The inclusion criteria were adult patients diagnosed as unilateral SSNHL with normal contralateral hearing in our department between January 2018 and December 2019. Exclusion criteria were as follows: (1) patients presented more than 1 week after onset; (2) patients had Meniere's disease, inner ear trauma, retrocochlear disease, skull base tumors, abnormal magnetic resonance imaging (MRI) findings, bilateral hearing loss, or any other specific etiology for sudden hearing loss; (3) patients had any other conditions characterized by a proven disruption of the oxidant–antioxidant equilibrium, such as acute inflammation, diabetes mellitus, hyperlipidemia, infection, chronic obstructive pulmonary disease, or chronic abnormalities of liver or kidney, and allergic rhinitis; (4) patients had a history of smoking; (5) patients who took antioxidant products prior to or during therapy.

2.2 | Treatment strategies

A total of 92 patients were included in this retrospective study, according to the above criteria. All patients were treated with the standard SSNHL treatment protocol used in the hospital, including intravenous dexamethasone (10 mg/day) for seven consecutive days. Of these patients, 72 patients were treated with intravenous steroids simultaneously combined with HBOT. HBOT was administered once daily, for 10 consecutive days, in a hyperbaric chamber (Moon Pharm System, Yantai, China, YC32150) with 100% oxygen intake at a pressure of 0.22 MPa. The sessions lasted 60 min and included a 5-min period of rest.

2.3 | Audiometric assessment

All patients were evaluated with pure tone audiometry (PTA), measured at six different frequencies (250, 500, 1 k, 2 k, 4 k, and 8 k Hz), before and 2 weeks after treatment. Mild, moderate, severe, and profound hearing losses were defined as >25 dB and ≤ 45 dB, >45 and ≤70 dB, >70 and ≤90 dB, and > 90 dB, respectively. The PTA frequencies-threshold were grouped as low frequency (250, 500, 1 k Hz), high frequency (4 k, 8 k Hz), and overall frequency (250, 500,

TABLE 1 Outcome evaluation of sudden sensorineural hearing loss

Complete recovery	Final average hearing threshold better than 25 dB
Partial recovery	More than 15 dB hearing gain and final average hearing threshold between 25 and 45 dB
Slight recovery	Final hearing level over 45 dB with hearing gain more than 15 dB
No recovery	Hearing gain less than 15 dB

Note: Average hearing threshold: average PTA measured at six different frequencies (250, 500, 1, 2, 4, and 8 kHz).

1 k, 2 k, 4 k, 8 k Hz). Hearing improvement was evaluated 2 weeks after treatment, according to Siegel's criteria (shown in Table 1).[12]

2.4 | Biochemical and hematological analysis

Peripheral venous blood samples from patients were obtained at admission and placed in tubes containing calcium ethylene diamine tetraacetic acid (EDTA). A blood counter (model XE-5000; Sysmex, Kobe, Japan) was used to measure the samples. The NLR was defined as the ratio of the absolute neutrophil count to the lymphocyte count in peripheral venous blood.

SOD activity was tested as previously described,[13] based on a spectrophotometric measurement of optical density of pyrogallol autoxidation at 420 nm for 3 min at an interval of 30 s with different levels of SOD. One unit of SOD was expressed as 50% inhibition of autoxidation of pyrogallol per minute. Therefore, the SOD concentrations were evaluated by the optical density of the reaction mixture (50 mM of Tris-EDTA buffer [pH 8.2], 0.25 mM of pyrogallol, and blood samples).

2.5 | Statistical analysis

All statistical analyses were performed using SPSS version 24.0. Student *t* tests were used for continuous variables. Chi-square tests or Fisher's exact tests were used for categorical variables. The parameters in peripheral blood which had a significant influence on the effect of treatment, as well as the contributing factors reported in previous studies were included in the multivariate logistic analysis. The $p < .05$ was regarded as statistically significant.

3 | RESULTS

Ninety-two patients diagnosed with SSNHL (44 males and 48 females), ranging in age from 28 to 80 (54.2 ± 12.4) years, were included in this study. Of these, 72 patients were treated with a combination of intravenous dexamethasone and HBOT (IV + HBOT) within 1 week after onset. The other 20 patients were treated with intravenous steroids (IV) only. Detailed characteristics of patients at diagnosis are shown in

TABLE 2 The epidemiological and audiometric information of the patients

	IV ($n = 20$)	IV + HBOT ($n = 72$)	*p*-value
Gender			
Male	7 (35.0)	37 (51.4)	.194
Female	13 (65.0)	35 (48.6)	
Age	52.8 ± 14.1	54.6 ± 12.0	.580
Side			
Right	13 (65.0)	33 (45.8)	.129
Left	7 (35.0)	39 (54.2)	
Type of hearing loss			
Low frequency	5 (25.0)	15 (20.8)	.119
High frequency	6 (30.0)	9 (12.5)	
Overall frequency	9 (45.0)	48 (66.7)	
Level of hearing loss			
Mild	4 (20.0)	9 (12.5)	.727
Moderate	4 (20.0)	15 (20.8)	
Severe	8 (40.0)	26 (36.1)	
Profound	4 (20.0)	22 (30.6)	
Vertigo	7 (35.0)	22 (30.6)	.705
Tinnitus	15 (75.0)	49 (68.1)	.550
Hypertension	9 (45.0)	18 (25.0)	.082
Therapeutic effect			
No recovery	15 (75.0)	35 (48.6)	.028*
Slight recovery	3 (15.0)	11 (15.3)	
Partial recovery	0	7 (9.7)	
Complete recovery	2 (10.0)	19 (26.4)	

Note: The values are expressed as means ± SDs of the means or as numbers and their percentages in the brackets.
Abbreviations: HBOT, hyperbaric oxygen therapy; IV, intravenous steroid; IV + HBOT, intravenous steroid combined with hyperbaric oxygen therapy.
*$p < .05$.

Table 2. Twenty patients (21.7%) were diagnosed with SSHNL at low frequency, 15 (16.3%) at high frequency, and 57 (62.0%) at overall frequency. Thirteen (14.1%), 19 (20.6%), 34 (37.0%), and 26 (28.3%) patients had mild, moderate, severe, and profound hearing loss, respectively. No significant differences in demographic, symptoms, or audiometric characteristics were found between the IV + HBOT and IV groups.

Therapeutic effect was evaluated by PTA 2 weeks after treatment, according to Siegel's criteria. Forty-two patients (45.7%) had a hearing gain of more than 15 dB, among which 21 (22.8%) completely recovered. Patients in the IV + HBOT group had significantly better hearing improvement than those in the IV group (Table 2).

The association between therapeutic effect and the frequency/level of hearing loss at diagnosis was then evaluated in the IV

TABLE 3 The association between therapeutic effect of IV + HBOT and initial hearing loss at diagnosis

	Complete recovery ($n = 19$)	Partial recovery ($n = 7$)	Slight recovery ($n = 11$)	No recovery ($n = 35$)	*p*-value	Combined recovery ($n = 37$)	No recover ($n = 35$)	*p*-value
Type of hearing loss								
Low frequency	7 (36.9)	3 (42.9)	2 (18.2)	3 (8.6)	.081	12 (32.4)	3 (8.6)	
High frequency	2 (10.5)	1 (14.2)	3 (27.3)	3 (8.6)		6 (16.2)	3 (8.6)	.012*
Overall frequency	10 (52.6)	3 (42.9)	6 (54.5)	29 (82.8)		19 (51.4)	29 (82.8)	
Level of hearing loss								
Mild	4 (21.1)	2 (28.6)	1 (9.1)	2 (5.7)	.1	7 (18.9)	2 (5.7)	
Moderate	7 (36.8)	2 (28.6)	3 (27.3)	3 (8.6)	11	12 (32.5)	3 (8.6)	.007*
Severe	5 (26.3)	2 (28.6)	4 (36.3)	15 (42.9)		11 (29.7)	15 (42.9)	
Profound	3 (15.8)	1 (14.2)	3 (27.3)	15 (42.8)		7 (18.9)	15 (42.8)	

Note: The values are expressed as numbers and their percentages in the brackets.
Abbreviations: HBOT, hyperbaric oxygen therapy; IV, intravenous steroid; IV + HBOT, intravenous steroid combined with hyperbaric hyperbaric oxygen therapy.
*$p < .05$.

TABLE 4 The relationship between blood cell counting and therapeutic effect of HBOT

	Complete recovery ($n = 14$)	Partial recovery ($n = 5$)	Slight recovery ($n = 10$)	No recovery ($n = 34$)	*p*-value
WBC (×10^9/L)	8.30 ± 3.09	8.99 ± 1.55	9.25 ± 2.85	9.69 ± 3.69	.705
		8.74 ± 2.75		9.69 ± 3.69	.262
N (×10^9/L)	6.49 ± 2.65	7.78 ± 1.57	7.23 ± 2.80	7.75 ± 3.59	.624
		6.97 ± 2.53		7.75 ± 3.59	.331
L (×10^9/L)	1.52 ± 0.79	0.97 ± 0.35	1.70 ± 0.75	1.53 ± 0.66	.187
		1.49 ± 0.74		1.53 ± 0.66	.820
NLR	4.95 ± 2.48	8.91 ± 3.84	4.96 ± 2.58	6.10 ± 3.59	.165
		5.63 ± 3.07		6.10 ± 3.59	.588
PLT (×10^9/L)	261.64 ± 90.53	242.20 ± 54.31	219.30 ± 44.30	223.53 ± 62.83	.179
		243.69 ± 72.33		223.53 ± 62.83	.241
HGB (g/L)	141.79 ± 16.02	135.82 ± 21.15	146.70 ± 10.09	133.58 ± 15.66	.031*
		142.45 ± 15.17		133.58 ± 15.66	.027*
HCT (%)	40.38 ± 4.32	39.34 ± 4.61	42.60 ± 2.42	38.84 ± 3.85	.051
		40.97 ± 3.90		38.84 ± 3.85	.033*

Note: The values are expressed as means ± SDs of the means.
Abbreviations: HGB, hemoglobin; HBOT, hyperbaric oxygen therapy; HCT, hematocrit; L, lymphocyte; N, neutrophil; NLR, the ratio of neutrophil to lymphocyte; PLT, platelet; WBC, white blood cell.
*$p < .05$.

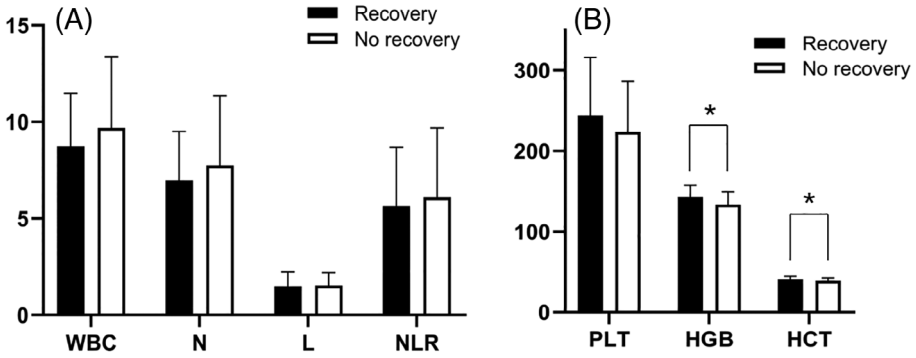

FIGURE 1 The comparison of hearing outcomes between the patients in different oxidant–antioxidant status according to the blood tests. No significant differences were found in the numbers of WBC, N, L, or NRL between patients with or without hearing recovery after treatment with IV=HBOT (Figure 1. (A) Patients with higher levels of HGB and HCT were more likely to have better outcomes after treatment with IV + HBOT, while the number of PLT had no significant influence on the hearing outcomes (B) HCT, hematocrit; HGB, hemoglobin; L, lymphocyte; N, neutrophil; NLR, neutrophil to lymphocyte ratio; PLT, platelets;WBC, white blood cell. *$p < .05$

TABLE 5 Multivariate logistic regression model for hearing recovery after HBOT

Variable	Adjusted OR	Lower 95% CI	Upper 95% CI	*p* value
Age	0.946	0.882	1.014	.116
Type of hearing loss				
Low frequency	1.000 (reference)			
High frequency	0.511	0.063	4.130	.529
Overall frequency	3.388	0.118	96.899	.476
Level of hearing loss				
Mild	1.000 (reference)			
Moderate	0.103	0.008	1.314	.080
Severe	0.067	0.005	0.838	.036*
Profound	1.027	0.077	13.687	.984
Vertigo	0.364	0.059	2.252	.277
Hypertension	0.343	0.028	4.216	.403
HBG	0.977	0.875	1.090	.672
HCT	1.231	0.808	1.876	.333
SOD	1.009	0.979	1.041	.544
NLR	0.843	0.645	1.101	.210

Abbreviations: CI, confidence interval; HCT, hematocrit; HGB, hemoglobin; NLR, the ratio of neutrophil to lymphocyte; OR, odds ratio; SOD, superoxide dimutase.
*$p < .05$.

+ HBOT group (Table 3). Patients in the IV + HBOT group were divided into four subgroups as follows: complete recovery, partial recovery, slight recovery, and no recovery. No significant differences were found in the type (hearing loss grouped as low frequency (250, 500, 1 k Hz), high frequency (4 k, 8 k Hz), and overall frequency (250, 500, 1 k, 2 k, 4 k, and 8 k Hz) or level (mild, moderate, severe, and profound hearing loss) of hearing loss among the four groups. However, when the complete, partial, and slight recovery groups were combined into one recovery group and compared with the no recovery group, the patients with hearing loss at low frequency were much more likely to have better hearing gains than those with hearing loss at overall hearing frequencies ($p = .012$). In addition, the milder the hearing loss at diagnosis, the better the improvement in hearing after treatment ($p = .007$).

A total of 81 patients had complete blood cell count tests at diagnosis. Among these patients, 63 were treated with IV + HBOT. Blood cell count, HGB, and HCT were compared between the IV + HBOT subgroups to further explore the prognostic factors associated with HBOT (Table 4). The level of HBG in patients with better hearing gains was significantly higher than in patients with worse hearing outcomes ($p = .031$). The complete, partial, and slight recovery groups were again combined into one recovery group and compared to patients in the no recovery group. Patients with higher levels of HGB (142.45 ± 15.17 vs 133.58 ± 15.66, $p = .027$) and HCT (40.97 ± 3.90

vs 38.84 ± 3.85, $p = .033$) were more likely to have better outcomes after treatment with IV + HBOT (shown in Figure 1). No significant differences were found in the numbers of blood cell between different groups.

In the present study, 72 patients treated with HBOT had blood tests for SOD at diagnosis. The SOD levels were then compared among patients with different hearing gains. The results showed that a higher SOD level may be a positive prognostic factor leading to a better therapeutic effect of HBOT, although the differences were not statistically significant (the SOD levels were 195.74 ± 28.20, 211.88 ± 27.73, 220.86 ± 21.90, and 215.09 ± 18.25 in the no recovery, slight recovery, partial recovery, and complete recovery groups, respectively, $p = .078$). This trend was more obvious when the complete, partial, and slight recovery groups were combined into one recovery group and compared to the no recovery group (212.28 ± 24.36 vs 195.74 ± 28.20, respectively, $p = .011$).

Multivariate logistic regression was conducted to further investigate the potential prognostic factors for patients with SSNHL after HBOT (Table 5). The results showed that the level of hearing loss had a significant influence on SSNHL prognosis after HBOT and that hearing gain was prone to be worse in patients with severe hearing loss at diagnosis ($p = .036$). However, hearing recovery after HBOT was not associated with the type of hearing loss (low frequency, high frequency or overall frequency), or the NLR, HBG, HCT, or SOD levels. Moreover, vertigo or hypertension in patients had no significant influence on the therapeutic result.

4 | DISCUSSION

There is still no consistently accepted approach for routine use of HBOT or clear mechanisms that play a role in the effectiveness of HBOT. The present study showed that HBOT, as an adjuvant therapy, significantly improved the hearing outcomes of patients with SSNHL when used within a week of symptom onset. It was found that low initial hearing threshold and hearing loss at low frequency are protective factors for a better hearing outcome after HBOT. To the best of our knowledge, this is the first study focusing on oxidant–antioxidant equilibrium and SSNHL prognosis after HBOT. The results showed that patients with high levels of SOD, HGB, and HCT are prone to have a better hearing gain after HBOT.

According to clinical guidelines, corticosteroids should be the initial therapy in patients with SSNHL and should be given within 2 weeks of symptom onset. HBOT may be combined with steroid therapy and used as an initial treatment or salvage therapy,[8] particularly in patients with severe to profound hearing loss at baseline. One might postulate that there is a greater elevation in oxidative stress in these patients, which may explain the more successful outcomes when HBOT is added to the treatment regimen. Bennett et al.[5] revealed in a meta-analysis for randomized controlled trials that HBOT improves hearing in patients with SSNHL. Pezzoli et al.[2] showed that untreated patients had a spontaneous mean hearing gain of only 5.0 ± 11.4 dB, while the mean hearing gain was much higher in patients treated with HBOT. In the present study, the overall hearing recovery rate was much higher in the IV + HBOT group than that in the IV group, suggesting that HBOT may have additional therapeutic benefits when it is combined with intravenous steroids. Some researchers are even convinced that early initiation of HBOT is the most important factor in determining outcomes, and recommend initiation of HBOT within 24 or 48 h of hearing loss.[14] Bayoumy et al.[15] reported that the complete and overall recovery rates after HBOT were 29.4% and 44.2% in their meta-analysis review. Likewise, the complete and overall rates in this study were 26.4% and 51.4%, respectively.

Initial hearing level has been widely reported as a prognostic factor for hearing recovery in patients with SSNHL no matter the treatment used.[16–18] Most scientists support the idea that a higher initial hearing threshold is an indicator of a poor prognosis in SSNHL patients, and the results of the present study are in line with those of previous studies. This could be explained by the fact that hair cell injury is more extensive in patients with worse initial hearing, and it is difficult to achieve a significant structural and functional recovery with conventional therapies in these patients.[19,20]

It is hypothesized that SSNHL is an immune-induced disease and that inflammation may play an important role. Clinical and basic studies have increasingly indicated that HBOT appears to have beneficial effects for the treatment of acute inflammatory responses or inflammatory processes resulting from ischemia or injury.[14,16] In the present study, WBC, neutrophil, and NLR levels were also assessed. These are often used as inflammatory markers for evaluating the severity of disease pathogenesis.[17] Li et al.[18] reported that higher relative hearing gains are significantly associated with greater reductions in the NLR after HBOT, indicating that HBOT may affect inflammatory markers when used to treat SSHNL, especially in patients with high levels of inflammation. However, no differences in these markers were found in the present study between patients with different hearing outcomes. This difference may be ascribed to the fact that the proportion of patients with different types of hearing loss (low frequency, high frequency or overall frequency) was not the same.

Some other factors may also have an effect on hearing outcomes in SSNHL. Previous studies verified that the presence of metabolic syndrome is a risk factor for the onset of SSNHL and negatively affects SSNHL recovery. In addition, prognosis was much poorer for patients in which treatment was delayed and in patients with diabetes or hyperlipidemia.[19] Other researchers have shown that vertigo or the canal paresis value might also have an influence on hearing recovery.[20,21]

Antioxidant enzymes, such as SOD, are responsible for ROS scavenging in the human body.[11] Oxidative stress may result in increased intensity of lipid peroxidation, resulting in free radical chain reactions, leading to the oxidation of the polyunsaturated fatty acids that form. It has also been reported that HBOT increases the production of oxygen free radicals, which could have both beneficial and adverse effects. Therefore, one of the possible mechanisms of HBOT is the activity of oxidative stress. In this study, the level of HGB, HCT, and SOD was significantly higher after HBOT in patients with better hearing improvements. It suggests that higher HGB, HCT, and SOD might

be a protective factor for hearing recovery, and HBOT may be more efficient when the level of available oxygen transporter is sufficient in blood. A break-down in oxidant-antioxidant equilibrium may be one of the possible etiological factors of SSNHL, and HBOT has the additional therapeutic effect of modulating the equilibrium. In a study by Paprocki et al.,[6] the researchers evaluated blood cell number and SOD level in patients with SSNHL before the first HBOT session, 5 min after the first session, and after the last session. They found that there was a significant decrease in HGB, HCT, and the SOD activity after HBOT compared with activity before treatment, indicating that repeated HBOT stimulation modulated the activity of antioxidant enzymes. Antioxidant enzyme activity after HBOT has also been found in studies conducted in animals.

There were several limitations to this study. First, the present study is a retrospective, nonrandomized design, and the composition of the patients may have an influence on the results; therefore, the conclusions that can be drawn are limited. However, all patients who met the inclusion criteria were given the same treatment. Second, the range of overall hearing recovery rate was relatively wide, which may hinder a comprehensive assessment of the specific effects of HBOT in adequate details. Thirdly, PTA was measured before and 2 weeks after treatment and indicated the recovery rate after treatment. A long-term follow-up prospective cohort study is needed.

In conclusion, the combination of intravenous steroid and HBOT is effective in patients with SSNHL when administered within a week. Initial hearing level is an independent factor for hearing outcome, and patients with a lower hearing threshold are more likely to have better hearing gains. Hearing loss at low frequency as well as high levels of HBG, HCT, and SOD are protective factors for patients with SSNHL treated with HBOT.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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