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Hyperbaric Oxygen Treatments Attenuate the Neutrophil-to-Lymphocyte Ratio in Patients with Idiopathic Sudden Sensorineural Hearing Loss

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Abstract

Objective. Hyperbaric oxygen therapy (HBOT) is a promising treatment in the management of idiopathic sudden sensorineural hearing loss (ISSNHL), but the specific mechanisms of HBOT in ISSNHL are still unclear. The curative effects of HBOT in many diseases are related to the attenuation of inflammatory response. The neutrophil-to-lymphocyte ratio (NLR) is a new inflammatory marker that can be assessed quickly. We investigated the relationship between HBOT and the inflammatory response in ISSNHL using the NLR.

Study Design. Case series with chart review

Setting. Tertiary teaching and research hospital

Subjects and Methods. Between December 2007 and December 2013, 41 ISSNHL patients who underwent HBOT, 45 ISSNHL patients who did not undergo HBOT, and 14 healthy control subjects who underwent HBOT were included in the study. NLRs were assessed at 2 time points: at baseline (pretreatment) and on day 1 after 10 sessions of HBOT (posttreatment). Audiometric testing was performed at the above 2 time points.

Results. The mean post-HBOT NLRs, neutrophil, and white blood cell count values of the ISSNHL patients were significantly lower than their pretreatment values ($P < .001$). Compared with the ISSNHL patients who did not undergo HBOT, the posttreatment NLR levels of the ISSNHL patients who underwent HBOT were much lower ($P = .036$). Higher relative hearing gains were significantly associated with a greater reduction in the NLR after HBOT ($r = -0.885$, $P = .001$).

Conclusions. The beneficial effect of HBOT on ISSNHL may be mediated at least in part by a decrease of inflammation.

Keywords

hyperbaric oxygen therapy (HBOT), idiopathic sudden sensorineural hearing loss (ISSNHL), inflammation, inflammatory marker, neutrophil-to-lymphocyte ratio (NLR)

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as a hearing loss of at least 30 dB HL that occurs in at least 3 consecutive frequencies within 72 hours and has an unknown etiology despite adequate investigations.[1] A number of etiologies resulting in a variety of theories have been proposed, including reduced blood flow in the inner ear, viral infections, and inflammatory processes.[2,3] Each theory is associated with somewhat different treatments, including steroids, antiviral agents, anticoagulants, vasodilators, and hyperbaric oxygen therapy (HBOT).[4]

Although clinical practice guidelines have recommended HBOT for the treatment of ISSNHL,[5] the exact mechanisms of HBOT on ISSNHL are unclear. Some researchers have proposed that HBOT increases the partial pressure of oxygen by increasing the plasma oxygen levels delivered to the inner ear; this hypothesis accounts for the vascular etiological factors in ISSNHL.[6,7] Some researchers have argued that higher HBOT pressure did not seem to result in better hearing recovery in ISSNHL, which implies that other factors in addition to the vascular effects might explain HBOT's results.[8,9]

Recently, hypotheses about the cause of ISSNHL have focused on chronic inflammation.[8,10] The white blood cell (WBC) count and the counts of WBC subtypes are considered classic inflammatory markers.[11] The neutrophil-to-

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lymphocyte ratio (NLR) is a new and quick inflammatory marker that is routinely measured in complete blood count tests without any additional cost. The NLR was reported to be superior to the total leukocyte count as a prognostic indicator of systemic inflammation, such as community-acquired pneumonia, ischemic heart disease, ulcerative colitis, appendicitis and cancer.[12-15]

Recent reports have shown that the NLR was significantly high in ISSNHL patients and that high NLR values were associated with severe hearing loss and poor prognosis.[16-18] However, most studies that have analyzed prognostic factors did not evaluate whether the therapy that was administered to the patients with ISSNHL had an influence on these prognostic factors.

Both in vitro and in vivo studies have demonstrated that HBOT alleviated inflammatory processes in many diseases, such as chronic wounds, ischemic stroke, traumatic brain injury, acute pancreatitis, and systemic inflammatory response syndrome.[19-23] We hypothesized that HBOT reduces the inflammatory reactions in ISSNHL patients by decreasing the expression of inflammatory markers (WBC count, neutrophils, lymphocytes, the NLR, and C-reactive protein), which may suggest a newly elucidated mechanism of HBOT in ISSNHL. Moreover, we aimed to determine whether the change in the NLR might be a surrogate indicator of the efficacy of HBOT and the prognosis of patients with ISSNHL who undergo HBOT.

Materials and Methods

Patient Selection

A standardized retrospective analysis was performed at the Hyperbaric Oxygen Center of Chinese People's Liberation Army (PLA), the Center of Otolaryngology of the Navy General Hospital of the Chinese PLA, and the Department of Otorhinolaryngology of Tangdu Hospital, Fourth Military Medical University in China between December 2007 and December 2013. Our study was approved by the Ethics Committee of Navy General Hospital and Fourth Military Medical University and was conducted in accordance with the ethical principles described in the Declaration of Helsinki. After the patients were selected, they were contacted through email, phone, or letter, and informed consent was obtained according the requirement of Ethics Committee.

We defined ISSNHL as acute unilateral deafness of more than 30 dB HL hearing loss at 3 consecutive frequencies with an abrupt onset (generally within 3 days).[5] The subjects (group A) in our study included 45 ISSNHL patients who underwent HBOT. The inclusion criteria for group A were as follows: (1) accordance with the diagnostic standard of ISSNHL in our study, (2) presenting within 1 week of symptom onset, (3) no abnormal magnetic resonance imaging (MRI) findings that might explain the hearing loss, and (4) at least 2 pure-tone audiograms and hematologic examinations were available: the first at presentation prior to initiation of therapy and a second after therapy. All patients in group A were treated with HBOT in a hyperbaric chamber, in which they breathed 100% oxygen at a pressure of 2.0 atmospheres absolute (ATA) once a day for 90 minutes in 10 consecutive daily sessions. The exclusion criteria were as follows: acute inflammation, infection, diabetes mellitus, systemic hypertension, hyperlipidemia, acute or chronic renal failure, chronic liver disease, chronic obstructive pulmonary disease, coronary artery disease, connective tissue disease, inflammatory bowel disease, allergic rhinitis, smoking history, and any otologic diseases, such as chronic otitis media, otosclerosis, acoustic trauma history, Meniere disease, and large vestibular aqueduct syndrome. To avoid the influence of steroids on inflammatory markers such as WBC count and the WBC subtypes, ISSNHL patients being treated with steroids were excluded from our study. To avoid the influence of potential confounding factors, such as the use of vasodilators or anticoagulants, ISSNHL patients being treated with vasodilators or anticoagulants were also excluded from our study. Considering the application of neurotrophic drugs under the recommendation of Chinese guidelines[24] and the little effect of neurotrophic drugs on inflammatory markers, ISSNHL patients being treated with neurotrophic drugs (monosialoganglioside or cobamamide) were included.

Group B comprised selected sex- and age-matched ISSNHL subjects who did not receive HBOT and met all the inclusion criteria and exclusion criteria as above.

To distinguish the impact of HBOT itself on the biomarker profile observed in our study, 14 healthy volunteers without hearing loss (group C) were recruited and treated with HBOT (2.0 ATA, 90 minutes $\times$ 10 sessions). None had acute inflammation or otologic diseases based on the above exclusion criteria. Before the study, all subjects in group C underwent a general physical examination, an assessment of laboratory blood parameters, an audiovestibular evaluation, and a cranial MRI.

Audiometric Assessment

Pure-tone audiometry was conducted in sound-treated facilities using a GSI-61 audiometer and standard TDH-39 supra-aural earphones in accordance with ISO 8253-1 (International Organization for Standardization, 1989). Masking was used when indicated. The audiometer was calibrated according to ISO 389-1 (International Organization for Standardization, 1998). A qualified audiologist performed the testing and otoscopic examinations. The audiometric evaluation included pure-tone audiometry to determine the air- and bone-conduction thresholds on the affected and contralateral sides. The pure-tone average (PTA) was calculated from the bone conduction results at 0.25, 0.5, 1, 2, 4, and 8 kHz (6 PTAs). The pattern of the initial audiogram was categorized into 1 of 5 types[25]: (1) low frequency, ascending, greater than 30 dB HL between the poorer low-frequency thresholds and the higher frequencies; (2) mid frequency, U-shaped, greater than 30 dB HL difference between the poorest thresholds in the mid frequencies and those at the higher and lower frequencies; (3) high frequency, descending, greater than 30 dB HL difference between the mean thresholds at 0.5 and 1 kHz and the mean thresholds at 4 and 8 kHz; (4) flat, less than 30 dB HL

Table 1. Demographic and Laboratory Data of the Groups.[a]

Parameter	Group A	Group B	Group C	*P*
Age, y	42.54 ± 14.67	47.24 ± 13.96	42.14 ± 13.97	.249
Sex, female/male, n	23/18	25/20	6/8	.680
Body mass index, kg/m^2	22.62 ± 2.85	21.90 ± 3.14	21.93 ± 2.43	.493
Hemoglobin B, 10^3/u	136.46 ± 18.18	132.07 ± 22.17	129.43 ± 17.23	.427
White blood cell count, 10^3/u	7.33 ± 1.97	8.53 ± 2.39	5.29 ± 1.52	<.001
Neutrophil, 10^3/u	5.74 ± 1.40	6.13 ± 1.44	3.82 ± 1.06	<.001
Lymphocyte, 10^3/u	2.22 ± 0.78	2.21 ± 0.55	1.82 ± 0.49	.114
Neutrophil-to-lymphocyte ratio	3.04 ± 1.14	3.22 ± 1.52	2.14 ± 0.49	<.001
Monocyte, 10^3/u	0.48 ± 0.34	0.45 ± 0.25	0.35 ± 0.26	.360
Platelet, 10^3/u	221.80 ± 49.83	216.18 ± 69.73	199.50 ± 59.53	.701
C-reactive protein, mg/dL	2.49 ± 2.34	4.72 ± 4.39	2.87 ± 2.33	.557
Fibrinogen, g/L	3.07 ± 0.82	2.74 ± 1.05	2.17 ± 0.76	.007

[a]Data are mean ± SD values. Group A, idiopathic sudden sensorineural hearing loss (ISSNHL) with hyperbaric oxygen therapy (HBOT); group B, ISSNHL without HBOT, group C, healthy controls with HBOT.

difference between the mean 0.25- and 0.5-kHz thresholds, the mean 1- and 2-kHz thresholds, and the mean 4- and 8-kHz thresholds; and (5) total deafness, hearing loss of 100 dB or more at 0.5, 1, 2, and 4 kHz. Hearing gain was expressed as the absolute hearing gain (Δ6PTA; dB values) compared with the initial PTA minus the dB values from the final PTA. If a negative value was calculated, the hearing gain was set to zero. To calculate the relative hearing gain, the absolute ΔPTA gain was divided by the initial PTA. To calculate the relative hearing gain in relation to the contralateral ear, the ΔPTA was divided by the initial PTA minus the PTA on the contralateral side.

Biochemical and Hematological Analyses

Biochemical analysis and hemograms were evaluated using peripheral venous blood samples obtained at admission and posttherapy. Blood samples were collected in tubes containing calcium EDTA. A blood cell counter (model XT 2000i; Sysmex, Kobe, Japan) was used for measurements. All samples were run in duplicate. The NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count in peripheral blood.

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation (SD), and categorical variables are expressed as percentages. The Kolmogorov–Smirnov test was used to evaluate the distribution of variables. Student *t* test (the independent-sample *t* test) was used for continuous variables with normal distribution, and the Mann–Whitney *U* test was used for continuous variables without normal distribution. The χ^2 test was used for categorical variables. Pearson and Spearman correlation analyses were used to assess the relationships. All used a *P* value of .05 as a threshold for significance. All statistical analyses were performed using SPSS software (SPSS for Windows, version 17.0; SPSS, Inc, Chicago, Illinois).

Results

One hundred patients, including 41 ISSNHL patients who underwent HBOT (group A), 45 ISSNHL patients who did not undergo HBOT (group B), and 14 non-ISSNHL subjects who underwent HBOT (group C) were included and constituted this study's database. Patient characteristics and laboratory data are provided in **Table 1**, and the audiometric data for the ISSNHL patients are provided in **Table 2**. As **Table 1** shows, the groups were similar in terms of age, sex, and body mass index ($P > .05$). No significant difference was found in the hemoglobin B, lymphocyte, monocyte, platelet, C-reactive protein, and fibrinogen values among the 3 groups. The WBC count and neutrophil levels and the NLR of the ISSNHL patients (group A and group B) were much higher than those of the non-ISSNHL subjects (group C), but there was no significant difference between group A and group B. The clinical characteristics of ISSNHL that are reported to affect ISSNHL outcomes were further analyzed.[24] As **Table 2** shows, the audiovestibular evaluation in 86 ISSNHL patients who did or did not undergo HBOT was evaluated at the inception of our study. The hearing loss was unilateral in 86 cases, and there was no side predominance. When group A was compared with group B, the interval between onset and therapy, the audiogram pattern, additional symptoms (tinnitus or vertigo), and initial hearing loss (6 PTA) were not significantly different between the 2 groups.

Groups A and C underwent 10 consecutive HBOT sessions, and the hematologic analyses on day 11 (the day after the 10 HBOT sessions were completed) were available for all patients. The mean ± SD WBC count before treatment was 7.33 ± 1.97 for group A, 8.53 ± 2.39 for group B, and 5.29 ± 1.52 for group C. The posttreatment WBC levels decreased by 21% in group A ($P < .001$) and 30% in group B ($P < .001$; **Table 3**). However, no significant differences in posttreatment WBC level were observed between group A and group B ($P > .05$). The pretreatment neutrophil

Table 2. Baseline Clinical and Audiometric Parameters of ISSNHL Patients.[a]

Parameter	Group A	Group B	P
Affected side, left/right, n	26/15	25/20	.514
Interval onset to therapy, d	4.00 ± 1.75	4.53 ± 1.62	.145
Audiogram pattern, n/%			.326
Low frequency	11/26.8	6/13.3	
Mid frequency	7/17.1	7/15.6	
High frequency	6/14.6	11/24.2	
Flat	10/24.4	13/28.9	
Total deafness	7/17.1	8/17.8	
Tinnitus, additionally, n/%	30/73.2	36/80	.610
Vertigo, additionally, n/%	8/19.5	7/15.6	.778
Hearing loss, initial (6PTA), dB	48.19 ± 29.4	48.86 ± 27.9	.910

[a]Data are mean ± SD values. Group A: idiopathic sudden sensorineural hearing loss (ISSNHL) with hyperbaric oxygen therapy (HBOT); Group B: ISSNHL without HBOT; Group C: healthy controls with HBOT.

counts for group A, group B, and group C were 5.74 ± 1.40, 6.13 ± 1.44, and 3.82 ± 1.06, respectively. The mean neutrophil levels after treatment were significantly lower in group A and group B compared with the pretreatment levels ($P < .05$; **Table 3**). The posttreatment neutrophil counts showed no significant differences between group A and group B ($P = .058$; **Table 3**). For group A, the pretreatment NLR value was 3.04 ± 1.14, and the posttreatment value was 1.99 ± 0.43 ($P < .001$). For group B, the pretreatment NLR value was 3.21 ± 1.52, and the posttreatment value was 2.43 ± 0.55 ($P < .001$). In addition, there was a significant difference in the NLR between group A and group B after treatment ($P = .036$; **Figure 1**). For group C, the WBC, neutrophil, and NLR values before and after HBOT did not differ significantly ($P > .05$).

In the ISSNHL patients, the percentage of NLR decline after treatment (the posttreatment NLR divided by the pretreatment NLR) was much larger in group A than in group B ($P = .002$). Pearson correlation analysis showed a significant negative correlation between the percentage decline of NLR after HBOT and a relative hearing gain in relation to the contralateral ear in group A; in other words, greater hearing improvement was significantly associated with a larger reduction in the NLR after HBOT ($r = -0.885$, $P = .001$; **Figure 2**).

Discussion

Treating ISSNHL still presents a substantial problem for otolaryngologists because of the unexplained etiopathogenesis of the illness. Because steroids are the most widely accepted treatment for ISSNHL, the hypothesis that ISSNHL is an immune-induced disease and inflammation plays an important role in its pathogenesis has been recently highlighted. It has been reported that inflammatory markers such as neutrophil, interleukin 6 (IL-6), and tumor necrosis factor (TNF) levels are elevated in ISSNHL patients, and this increase was found to be associated with the disease's severity and prognosis.[10] Hiramatsu et al[26] found that polymorphisms in the inflammatory factor IL-6 are associated with an increased risk of ISSNHL. However, the detailed mechanism of inflammation in ISSNHL and the mechanism of ISSNHL treatments, such as steroids and HBOT, are still not clear.

Clinical and basic science studies increasingly indicate that HBOT, either alone or as an adjunct treatment, appears to deliver beneficial effects for the treatment of acute inflammation responses or inflammatory processes secondary to ischemia or injury.[19-21] For example, Yu et al[23] reported that HBOT reduces the inflammatory response in acute pancreatitis by inhibiting IL-2, IL-6, TNF-α expression, and NF-κB activation. Wilson et al[27] demonstrated that HBOT alleviated joint inflammation and reduced mechanical hyperalgesia in an animal model of arthritis. HBOT also has been shown to suppress the immune response to antigens, reduce circulating leukocytes, and induce immunologic changes to prolong the survival of an allograft.[28] Surprisingly, studies on HBOT's effect on the inflammatory response during ISSNHL are lacking.

Table 3. Comparison of Laboratory Data in Subjects before and after Treatment.[a]

Parameter		Group A	Group B	Group C
White blood cell count, 10^3/u	Pretreatment	7.33 ± 1.97	8.53 ± 1.12	5.29 ± 1.52
	Posttreatment	5.83 ± 1.12[b]	5.97 ± 1.43[b]	5.78 ± 1.45
Neutrophil, 10^3/u	Pretreatment	5.74 ± 1.40	6.13 ± 1.44	3.82 ± 1.06
	Posttreatment	4.38 ± 1.13[b]	4.90 ± 1.24[b]	4.08 ± 0.93
Lymphocyte, 10^3/u	Pretreatment	2.22 ± 0.78	2.21 ± 0.55	1.82 ± 0.49
	Posttreatment	2.41 ± 1.03	2.60 ± 0.89	1.67 ± 0.58
Neutrophil-to-lymphocyte ratio	Pretreatment	3.04 ± 1.14	3.21 ± 1.52	2.14 ± 0.49
	Posttreatment	1.99 ± 0.43[a]	2.43 ± 0.55[b,c]	2.34 ± 0.69

[a]Data are mean ± SD values. Group A, idiopathic sudden sensorineural hearing loss (ISSNHL) with hyperbaric oxygen therapy (HBOT); group B, ISSNHL without HBOT, Group C, healthy controls with HBOT.
[b]$P < .05$: posttreatment compared with pretreatment.
[c]$P < .05$: group B compared with group A.

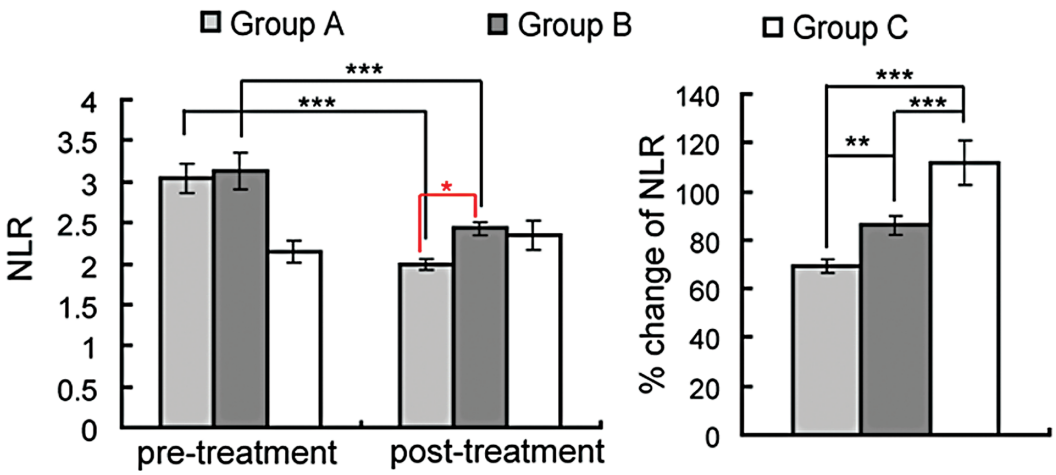

Figure 1. Analysis for pretreatment and posttreatment neutrophil-to-lymphocyte ratios. All values are expressed as mean ± standard error (*$P < .05$; **$P < .01$; ***$P < .001$).

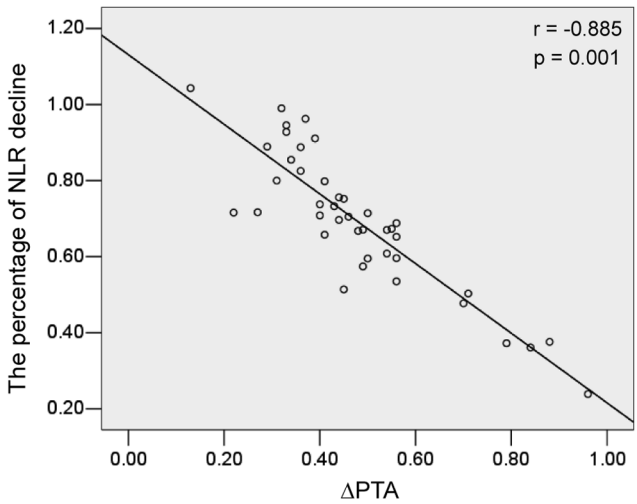

Figure 2. Association of neutrophil-to-lymphocyte ratio (NLR) decline with hearing outcome. Pearson analysis showing the negative correlation between the percentage decline of NLR after hyperbaric oxygen therapy and the relative hearing gain in relation to the contralateral ear in group B (ΔPTA).

The inflammatory response to various physiological stressors is characterized by alterations in circulating WBC counts (for example, increased neutrophil and decreased lymphocyte counts), and the WBC count is often used as an inflammatory marker for assessing the severity of disease pathogenesis.[11] Unlike the total WBC count, the NLR demonstrates the balance of two complementary but paradoxical components of the immune system: neutrophils represent the active nonspecific inflammatory mediator that initiates the first line of defense, whereas lymphocytes represent the regulatory or protective component of inflammation.[12] Although the NLR was initially identified as a prognostic marker in many types of cancer, several recent studies have shown that the change in the NLR after treatment may serve as an indicator of treatment efficacy in patients with cancer.[29,30] For example, Dan et al[31] reported that postoperative NLR changes predict survival in patients with small hepatocellular carcinoma undergoing radiofrequency ablation. Recently, pretreatment NLR values were reported to be significantly higher in ISSNHL patients than in healthy people.[16-18] However, the follow-up of NLR after treatment in ISSNHL has not been performed to date. The most important finding of our study was that the NLRs were significantly lower in patients with ISSNHL who underwent HBOT than in those who did not undergo HBOT, which implies that HBOT may affect the inflammatory response during ISSNHL.

In our study, we found that the posttreatment WBC and neutrophil counts did not differ significantly between the ISSNHL patients who did and did not undergo HBOT. The most likely reason for this result is that some ISSNHL patients can remit spontaneously over a period of time. The spontaneous ISSNHL remission rate has been reported to be 32% to 65%.[1] It is possible that the spontaneous remission is accompanied by a reduced inflammatory reaction during ISSNHL.[2-4] The spontaneous decline in WBC and neutrophil counts may obscure the decrease in the WBC and neutrophils caused by the treatment, leading to the lack of a statistically significant difference between the ISSNHL + HBOT group (group A) and the ISSNHL group (group B). The significant differences in WBC and neutrophil counts observed before and after treatment in both group A and group B also support the above-mentioned hypothesis. A second explanation is that the insufficient number of subjects may have weakened the study's statistical characteristics. In addition, posttreatment WBC counts could be affected by the change in lymphocyte counts, although the increase in lymphocytes after HBOT (in group A) was not significant compared with the increase in ISSNHL patients who did not undergo HBOT (group B; **Table 3**).

In our study, we also observed that HBOT had little influence on WBC count, the WBC subtypes, or the NLR in the healthy controls (group C). Given HBOT's ability to

regulate the inflammatory response during high inflammation states, it is easy to understand why HBOT did not display anti-inflammatory properties in the noninflammatory state and why there was no statistically significant difference in inflammatory markers before and after HBOT in healthy subjects.

The current study has several limitations. First, although we tried to control possible factors that could influence the results, this study included a small number of patients from 2 institutions. Because steroids have been the most widely accepted therapy in ISSNHL, most patients receive steroid therapy after the onset of ISSNHL. However, to avoid the influence of steroids on the inflammatory response, ISSNHL patients who were taking steroids were excluded from our study. Therefore, it was difficult to obtain a large sample based on the standards established in our study. Second, there was unavoidable inherent bias from the retrospective nature of our study. For example, groups A and B were selected from our retrospective data, and the bias introduced by that selection mainly included admission rate bias and prevalence-incidence bias. The former was due to the difference between the study population of ISSNHL patients treated in our department and the actual population of ISSNHL patients. The latter was because the selected patients were often typical cases, and atypical cases with short course were often not selected. For another example, group C was a recruiting separate normal control group and not contiguous with the study population (group A and group B); the selection bias and confounding bias were unavoidable in statistical analysis between group C and group A/group B. For these reasons, new advanced, controlled, and randomized trials should be performed to establish and confirm our results. The third potential limitation is that the serum NLR was not compared with the extent of inflammatory cell infiltration within and around the cochlea. This type of study is hampered by the lack of a reliable animal model of ISSNHL. Fourth, the relationship between serum NLR and the other inflammatory cytokines (IL-6, IL-1β, and TNF-α) that have been proven to be related to ISSNHL has not been clarified. Such correlations should be considered in future analyses.

Conclusions

To our knowledge, this is the first study to investigate the relationship between NLR levels and HBOT efficacy in patients with ISSNHL. Our results suggest that the treatment mechanism of HBOT in ISSNHL involves reducing the inflammatory response.

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Author Contributions

Hang Li, design of the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Daqing Zhao**, acquisition of data, revising article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Mingfang Diao**, acquisition of data, revising article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Chen Yang**, analysis of data, revising article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Yu Zhang**, analysis of data, revising article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Yan Lv**, analysis of data, revising article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Jinjing Zhao**, acquisition of data, revising article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Shuyi Pan**, design of the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work.

Disclosures

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