

Original Article

Secondary Hyperbaric Oxygen Therapy for Idiopathic Sudden Sensorineural Hearing Loss in the Subacute and Chronic Phases

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This study investigated the efficacy of hyperbaric oxygen therapy (HBOT) as a secondary treatment for patients with idiopathic sudden sensorineural hearing loss (ISSNHL) in the subacute and chronic phases. Forty-eight ISSNHL patients (HBOT group) who had received primary conventional treatment within 4 weeks after onset and underwent HBOT between 4 and 20 weeks post-onset were retrospectively compared with 44 ISSNHL patients (control group) with primary conventional treatment alone. Mean hearing gain was slight, with gains of 5.2 ± 8.9 dB in the HBOT group and 2.0 ± 7.6 dB in the control group. However, no significant difference was recognized between the two groups. In the HBOT group, no significant difference was observed in hearing gain among patients with HBOT initial time at 4-7, 8-11, 12-15 or 16-20 weeks after onset. Meanwhile, hearing gain was significantly higher in patients with profound hearing loss than in the other patients. We conclude that the effectiveness of secondary HBOT for ISSNHL patients in either subacute or chronic phase remains unproven, and thus, the decision administer HBOT should be made with caution.

Key words: sudden sensorineural hearing loss; idiopathic; hyperbaric oxygen therapy; secondary treatment

Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as a rapid loss of hearing over a period of up to 3 days, and is diagnosed when pure-tone audiometry shows hearing loss (HL) of ≥ 30 dB in three connected frequencies [1]. Therapeutic measures include administration of systemic and intratympanic corticosteroids, antiviral and hemodilution agents, minerals and vitamins. However, effective treatments have yet to be established [2, 3].

In hyperbaric oxygen therapy (HBOT), a patient breathes 100% oxygen at a pressure level higher than 1 atmosphere absolute (ATA) in a mono-place or multi-place chamber. HBOT is thought to have complex effects on immunity, oxygen transport and hemodynamics, resulting in favorable effects by reducing hypoxia and edema and enabling normal host responses to infection and ischemia [4]. Although the true etiology remains uncertain, vascular pathologies have been proposed as causes of HL in ISSNHL. HBOT is administered for ISSNHL to improve circulatory impairments, including ischemia and hypoxia in the inner ear.

HBOT is applied for ISSNHL as a primary or secondary therapy. A primary single treatment of HBOT showed a significant improvement in hearing in comparison to intravenous injections of either buflomedil or pentoxifylline [5, 6]. Addition of primary HBOT therapy to standard pharmacotherapy did not provide any benefit in some reports [7, 8], while addition of primary HBOT resulted in significantly better outcomes than standard pharmacotherapy alone in other reports [9, 10].

Numerous reports have examined HBOT as a

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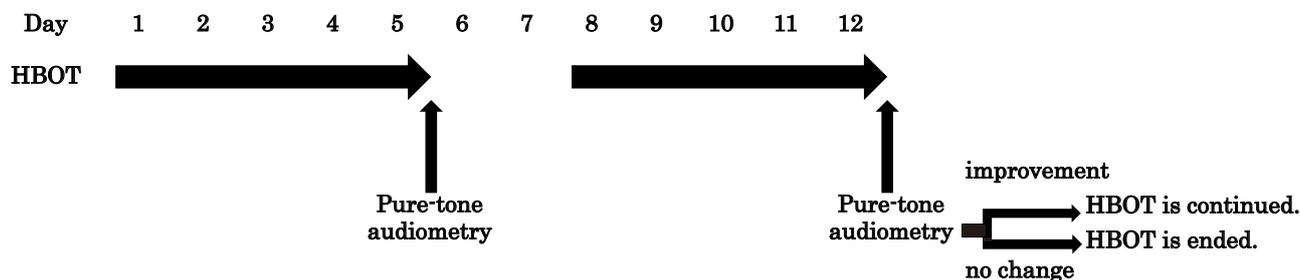


Figure 1 : HBOT protocol

HBOT was performed every weekday for 2 weeks, with PTA measured once a week. HBOT was continued when any improvement in audiometric thresholds was recognized by the end of 10 sessions.

secondary treatment following an unsuccessful treatment regimen. Lamm et al. [11] analyzed of 2,338 patients with ISSNHL, acoustic trauma, or acute noise-induced HL from 46 previously reported papers, and concluded that HBOT was effective for patients who received the therapy between 2 and 6 weeks after primary conventional therapy. However, patients who received HBOT ≥ 4 weeks after HL onset should be evaluated to determine the effectiveness of for subacute or chronic phases of ISSNHL, as a large proportion of hearing recovery in ISSNHL typically occurs within 1 month after onset [1, 12]. Furthermore, improvements in hearing among patients who received HBOT should be compared with the natural history of ISSNHL, as the possibility of some spontaneous recovery in hearing as late as 4 months post-treatment has been reported [13]. The present study therefore evaluated the efficacy of secondary HBOT in patients who failed to achieve good hearing outcomes from primary standard pharmacotherapy, and to elucidate the point up to which HBOT remains valuable as a treatment for ISSNHL.

Patients, Materials and Methods

Between April 2001 and November 2008, a total of 428 patients with ISSNHL visited the Department of Otolaryngology in Tokyo Medical and Dental University Hospital for treatment and received HBOT at the Hyperbaric Medical Center. Among these 428 patients, we enrolled 48 patients (HBOT group) who underwent HBOT ≥ 4 weeks after onset of ISSNHL without any other treatments. These patients were referred to our hospital for HBOT as a secondary treatment after primary treatment had failed. The time of initiating HBOT ranged from 4 to 20 weeks, with a mean of 7.4 weeks after HL onset (4-7 weeks, $n=29$; 8-11 weeks, $n=13$; 12-15 weeks, $n=4$; 16-20 weeks, $n=2$). The

multi-place chamber (NHC-412-A; Nakamura Tekko-sho, Tokyo, Japan) is pressurized with air to 2.0 ATA, then the patient breathes 100% oxygen through a mask delivery system for 60 min, every weekday for 2 weeks (10 sessions in total) (Fig. 1). A tympanic tube was inserted in some patients or HBOT was cancelled in other patients if any problems including otalgia or otitis media arose. HBOT was continued when any improvement in audiometric thresholds was recognized at the end of the 10 sessions. The number of sessions was thus adjusted for each patient, with a mean of 13.0 sessions (range, 4-43 sessions).

In addition, the study enrolled 44 patients (control group) with ISSNHL who had received treatment of corticosteroids, vitamins and adenosine triphosphate without HBOT in our department within 4 weeks after onset of ISSNHL, but failed to achieve complete hearing recovery, and had received no further treatments after primary therapy. In our primary therapy, corticosteroids were administered as 10 mg/day of intravenous betamethasone followed by tapered doses for 10 days, or 30 mg/day of oral prednisolone followed by tapered doses for 12 days.

All patients met the following inclusion criteria: 1) rapid onset of unilateral sensorineural HL with unknown etiology; 2) pure-tone average (PTA) at onset of HL ≥ 30 dB; 3) PTA in the unaffected contralateral ear < 30 dB; and 4) no finding of vestibular schwannoma on magnetic resonance imaging. Pure-tone audiometry was performed to evaluate HL by obtaining audiometric thresholds, representing the minimum audible sound levels at frequencies of 125, 250, 500, 1000, 2000, 4000 and 8000 Hz. PTA was defined as the average of audiometric thresholds (dB) at frequencies of 250, 500, 1000, 2000 and 4000 Hz. When the patient did not respond to the maximum sound level, 5 dB was added to the level for statistical analysis.

PTA-1 was defined as the PTA of an affected ear

Table I . Profiles of HBOT and control groups

	HBOT group (n=48)	Control group (n=44)	<i>p</i> value
Age (mean ± SD in year)	46.5 ± 13.5	51.8 ± 17.0	0.06 ^a
Sex (male/female in number)	27/21	19/25	0.21 ^b
Dizziness and/or vertigo (in number)	14	16	0.46 ^b
PTA-1 (mean ± SD in dB HL)	63.8 ± 21.9	57.4 ± 23.6	0.07 ^a

HBOT, hyperbaric oxygen therapy; SD, standard deviation; PTA, pure-tone average

^aMann-Whitney U test; ^b χ^2 test

Table II . HBOT initial time and hearing outcome

	HBOT initial time (weeks)				<i>p</i> value
	4-7 (n=29)	8-11 (n=13)	12-15 (n=4)	16-20 (n=2)	
Hearing gain (mean ± SD in dB)	7.8 ± 9.7	1.2 ± 4.8	4.0 ± 6.4	-4.0 ± 8.5	0.06 ^a
Classification of hearing gain					
Good	1	0	0	0	
Fair	8	1	1	0	
No change	20	12	3	2	

HBOT, hyperbaric oxygen therapy; SD, standard deviation

^aKruskal-Wallis test

immediately before HBOT in the HBOT group, or 4 weeks after onset of HL in the control group. Severity of PTA-1 was categorized as mild (PTA-1 <40 dB), moderate (PTA-1 ≥40 dB but <60 dB), severe (PTA-1 ≥60 dB but <90 dB) or profound (PTA-1 ≥90 dB). PTA-2 was defined as the PTA when no apparent change in PTA was recognized >23 weeks after onset of HL. Hearing gain was estimated from the difference between PTA-1 and PTA-2. The degree of hearing gain was classified as "good" (hearing gain ≥30 dB), "fair" (hearing gain <30 dB but ≥10 dB) or "no change" (hearing gain <10 dB). HBOT initiation time was defined as the time between onset of HL and initiation of HBOT.

Analyses of categorical data (sex, presence of dizziness and/or vertigo and classification of hearing gain) were performed using the χ^2 test or Fisher's exact test. Analyses of continuous data (age, PTA-1 and hearing gain) were performed using the Mann-Whitney U test. Comparisons between HBOT initial time and hearing outcome were performed using the Kruskal-Wallis test. Comparisons between severity of PTA-1 and hearing outcome in the HBOT group were performed using the Kruskal-Wallis test with post hoc Tukey-Kramer test. Differences were considered to be significant for values of $p < 0.05$. Statistical analyses

were performed using JMP 7.0.1 statistical software (SAS Institute).

The HBOT has already been established as a standard therapy for patients with ISSNHL. The above procedure was performed after obtaining approval from patients and in accordance with the ethical standards of the Helsinki Declaration.

Results

Patient profiles

Profiles of the HBOT and control groups are summarized in Table I. No significant differences in age, sex, presence of dizziness and/or vertigo at onset of HL or PTA-1 were seen between groups. Severity of PTA-1 in the HBOT and control groups was categorized as mild in 3 and 10 patients, moderate in 22 and 20, severe in 16 and 8 and profound in 7 and 6, respectively.

HBOT initial time and hearing outcome in HBOT group

The relationship between HBOT initial time and hearing outcome is shown in Table II. Mean hearing gain was 7.8 ± 9.7 dB in patients with HBOT initiation time of 4-7 weeks, slightly higher than in the other

Table III. Severity of PTA-1 and hearing outcome in HBOT group

	Severity of PTA-1				<i>p</i> value
	Mild (n=3)	Moderate (n=22)	Severe (n=16)	Profound (n=7)	
Hearing gain (mean ± SD in dB)	2.3 ± 3.5	2.1 ± 5.3	4.4 ± 6.3	18.3 ± 13.2	0.03 ^a
Classification of hearing gain					
Good	0	0	0	1	
Fair	0	3	3	4	
No change	3	19	13	2	

PTA, pure-tone average; SD, standard deviation

^aKruskal-Wallis test**Table IV.** Overall hearing outcome

	HBOT group (n=48)	Control group (n=44)	<i>p</i> value
Hearing gain (mean ± SD in dB)	5.2 ± 8.9	2.0 ± 7.6	0.09 ^a
Classification of hearing gain			0.28 ^b
Good	1	0	
Fair	10	5	
No change	37	39	

HBOT, hyperbaric oxygen therapy; SD, standard deviation

^aMann-Whitney U test; ^bFisher's exact test

groups (8-11 weeks, 1.2 ± 4.8 dB; 12-15 weeks, 4.0 ± 6.4 dB; 16-20 weeks, -4.0 ± 8.5 dB). The number of patients categorized as showing "good" or "fair" hearing gain was 9 with HBOT initial time of 4-7 weeks, but 1 at 8-11 weeks, 1 at 12-15 weeks and 0 at 16-20 weeks. One patient with "good" hearing gain started HBOT at 5 weeks after onset of HL. However, no significant difference in mean hearing gain was seen among HBOT initial times (Kruskal-Wallis test, $p=0.06$).

Severity in PTA-1 and hearing outcomes in HBOT group

The relationship between severity in PTA-1 and hearing outcome in the HBOT group is shown in Table III. A significant difference in mean hearing gain was seen between each subgroup (Kruskal-Wallis test, $p=0.03$). Mean hearing gain was 18.3 ± 13.2 dB in patients with profound HL, significantly higher than the 2.3 ± 3.5 dB with mild HL, 2.1 ± 5.3 dB with moderate HL and 4.4 ± 6.3 dB with severe HL (post-hoc by Turkey-Kramer test: $p=0.01$, <0.0001 and 0.0005 , respectively). Five of the 7 patients (71%) with profound HL obtained "good" or "fair" hearing gain, while all patients with mild HL showed "no change".

Overall hearing outcome

Table IV shows overall hearing outcomes. Mean hearing gain was 5.2 ± 8.9 dB in the HBOT group, slightly higher than the 2.0 ± 7.6 dB in the control group. However, no significant difference in hearing gain was seen between the two groups (Mann-Whitney U test, $p=0.09$). According to the hearing gain classification, a "good" hearing gain was obtained in 1 of 48 patients (2%) in the HBOT group, but in no patients from the control group. A "fair" hearing gain was seen in 10 of 48 patients (21%) in the HBOT group and 5 of 44 patients (11%) in the control group, whereas "no change" was seen in 37 of 48 patients (77%) in the HBOT group and 39 of 44 patients (88%) in the control group. However, no significant difference in hearing gain classification was noted between the two groups (Fisher's exact test, $p=0.28$). Severity according to PTA-1 in 5 control patients with "fair" hearing gain was categorized as moderate in 2, severe in 1 and profound in 2. The "fair" hearing gain recognized in the control group was thought to have occurred naturally. No patients in either group showed complete hearing recovery.

When hearing gain was evaluated at each severity of

PTA-1, mean hearing gains in the HBOT and control groups were 2.3 ± 3.5 dB and -1.6 ± 5.7 dB for mild PTA-1, 2.1 ± 5.3 dB and 2.0 ± 7.7 dB for moderate PTA-1, 4.4 ± 6.3 dB and 4.8 ± 7.4 dB for severe PTA-1 and 18.3 ± 13.2 dB and 4.5 ± 9.2 dB for profound PTA-1, respectively. However, no significant difference in hearing gain was seen at each severity of PTA-1 between HBOT and control groups (Mann-Whitney U test, mild PTA-1: $p=0.3$, moderate PTA-1: $p=1.0$, severe PTA-1: $p=0.6$ and profound PTA-1: $p=0.08$, respectively).

Discussion

The nature of ISSNHL remains unclear, but vascular insufficiency of the cochlear artery is a popular theory. Yamasoba et al. [14] identified slow blood flow within the vertebrobasilar arteries in some patients with ISSNHL. Capaccio et al. [15] found an association between acquired prothrombotic risk factors and related genetic variants in ISSNHL. These findings support the concept of a vascular pathology. In fact, perilymphatic oxygen tension appears to be significantly decreased in patients with ISSNHL [16]. The results of an experimental animal study showed that cochlear hypoxia could be immediately and fully compensated by HBOT, but not by isobaric oxygenation [17].

In most patients with ISSNHL, hearing improves within 1 month after the onset of HL [1, 12]. However, the natural history of ISSNHL can affect the therapeutic evaluation. Slattery et al. [18] reported the possibility of some spontaneous recovery in hearing as late as 4 months after starting treatment. Yeo et al. [12] demonstrated delayed recovery beyond the first month after discharge in 22% of patients. In the present study, 5 patients (11%) in the control group showed a "fair" hearing gain ≥ 4 weeks after onset of HL, supporting those previous reports [12, 18].

The period during which HBOT can be effective as a secondary treatment remains uncertain. Kau et al. [19] examined the efficacy of secondary HBOT in 359 patients with acute and chronic inner ear disorders, including ISSNHL. They divided patients into groups with HL duration < 3 months and ≥ 3 months, and found that HBOT was beneficial only to HL < 3 months after onset. However, this report did not evaluate the efficacy of HBOT for HL in the subacute phase, as HL in the acute and subacute phases was mixed in the group with HL duration < 3 months. Desloovere et al. [20] reported the effectiveness of secondary HBOT at 2.5 ATA for ISSNHL patients who received HBOT within

3 months after onset, with a decrease in hearing gain with increasing time delay. However, that study also did not specifically analyze patients with subacute ISSNHL. The present study compared the HBOT group with the control group at ≥ 4 weeks after onset. A slightly higher mean hearing gain was obtained in the HBOT group than in the control group. The rate of patients with a "good" or "fair" hearing gain was higher in the HBOT group (23%) than in the control group (11%). However, no significant differences in hearing gain or hearing classification were apparent between the two groups. Findings regarding overall hearing outcome suggested that the effectiveness of secondary HBOT for patients with subacute or chronic ISSNHL remains unproven.

Earlier treatment with HBOT results in better hearing outcomes [11, 20, 21]. In the present study, patients with HBOT initiation time of 4-7 weeks obtained slightly better hearing outcomes than other patients in the HBOT group. Furthermore, only patients with "good" hearing gain were started on HBOT at 5 weeks after onset of HL. However, no significant differences were found in mean hearing gain among each HBOT initial time in the HBOT group.

The association between initial hearing level and prognosis of hearing remains contentious [9, 22, 23]. Fetterman et al. [22] reported that the severity of HL was hard to recover. On the other hand, Topuz et al. [9] reported HBOT as more effective in more severe HL. In the present study, patients with profound HL showed significantly better hearing outcomes than other patients in the HBOT group. Actually, nearly 70% of all patients with profound HL obtained "good" or "fair" hearing gain.

The current statistical findings regarding overall hearing outcome indicate the effectiveness of HBOT for patients with subacute or chronic ISSNHL remains unproven. Furthermore, some patients have also shown worsening of hearing after HBOT [7]. A recent systematic review of randomized controlled trials showed that HBOT improved hearing, but the clinical significance of the level of improvement is unclear [24]. Routine application of HBOT to patients with ISSNHL was not justified according to that review. Taken together, secondary HBOT should only be carefully administered for patients with ISSNHL after unsuccessful conventional treatment.

Strict estimation of the efficacy of HBOT for ISSNHL might be difficult, as the pathological condition of ISSNHL in enrolled patients is potentially heterogenous and the number of HBOT sessions varies widely between patients. To address this problem, a

prospective study of a large number of patients is needed.

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