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# The Optimized Protocol of Hyperbaric Oxygen Therapy For Sudden Sensorineural Hearing Loss

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**Objective:** This study aimed to determine the optimal protocol of hyperbaric oxygen therapy (HBOT) according to various treatment settings for sudden sensorineural hearing loss (SSNHL).

**Methods:** A 112 patients with SSNHL were enrolled in this prospective study. All patients were treated with systemic steroid therapy, intratympanic steroid therapy, and HBOT. According to the pressure and duration of HBOT (10 sessions in total), the patients were divided into three groups: group 1, 2.5 atmospheres absolute (ATA) for 1 h; group 2, 2.5 ATA for 2 h; and group 3, 1.5 ATA for 1 h. The pure-tone average (PTA), word discrimination score (WDS), and mean gain were compared.

**Results:** A total of 105 patients completed the 3-month follow-up, and 6 patients were excluded. Differences among groups were found in PTA, WDS, and mean gain. In the post-hoc analysis, group 3 had significantly lower WDS and mean gain than groups 1 and 2; however, group 2 showed no significant differences from group 1. The proportion of patients with hearing recovery after treatment was significantly higher in group 1 (57.6%) and group 2 (58.8%) than in group 3 (31.3%).

**Conclusions:** When HBOT (10 sessions) was combined with corticosteroids as the initial therapy for SSNHL, a higher pressure (1.5 ATA vs. 2.5 ATA) provided better treatment results; however, increasing the duration (1 h vs. 2 h) under 2.5 ATA did not result in a significant difference. Therefore, HBOT for SSNHL may be performed at 2.5 ATA for 1 h in 10 sessions.

**Key Words:** hyperbaric oxygen therapy, intratympanic injection, sudden sensorineural hearing loss, systemic steroid, treatment.

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## INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is defined as an acute hearing loss of >30 decibels (dB) at three consecutive frequencies, with an abrupt onset (within 3 days).[1,2] The incidence of SSNHL was estimated to range from 5 to 27 per 100,000 people per year.[1,3] Many studies have reported that the spontaneous recovery rate of SSNHL is 32–65%; however, this may be an overestimation.[1,4,5] Considering that the possibility of spontaneous recovery cannot be predicted and the chance for recovery decreases with increasing delay in treatment,[6] patients tend to start treatment early rather than waiting for spontaneous recovery. Although the cause remains unidentified in most cases, various etiologies have been proposed, including vascular compromise, viral infections, immune-mediated factors, and cochlear hydrops.[4] However, as a direct causal link between SSNHL and these etiologies has not been established, and because of the heterogeneity of these etiologies, diverse treatments (e.g., corticosteroids) have been applied, which is why evidence-based treatment are needed. The first clinical practice guideline for sudden HL was published in 2012 and updated in 2019.[1,2] The main treatments in the guideline involved systemic steroid (SS), intratympanic steroid (ITS), and hyperbaric oxygen therapy (HBOT). Corticosteroids administered through the systemic or intratympanic route are commonly used in SSNHL, based on the results of many clinical studies.[1,7]

HBOT, a noninvasive treatment involving the inhalation of 100% oxygen at a pressure of >1 atmosphere absolute (ATA), has been used as a treatment for carbon monoxide poisoning, decompression sickness, and arterial gas embolization.[8,9] Since its first use for SSNHL in the late 1970s, HBOT has been typically used mainly as an adjunctive treatment.[10] HBOT increases the oxygen tension in the blood and, subsequently, via diffusion, delivers an increased pressure of oxygen to inner ear structures, which may be beneficial because hypoxia in the inner ear is a characteristic feature of SSNHL.[11,12] However, in 2014, a survey in the United Kingdom showed that 96% of clinicians were not using HBOT, whereas 99% were using immediate SS in patients with SSNHL.[13] Nevertheless, although HBOT is not as widely used as corticosteroids for the treatment of SSNHL, its effectiveness has been reported in several randomized controlled trials

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(RCTs). The 2019 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guideline suggests that HBOT can be provided as either initial or salvage treatment when combined with steroid therapy.[1] However, previous studies mainly had a retrospective design, lacked a control group, used HBOT without concurrent or prior medical therapy, and used diverse HBOT protocols. Therefore, the 2019 guideline could not definitively suggest an appropriate standardized HBOT protocol. Although the protocol (pressure, time, and length of treatment) of HBOT varied across studies, most studies used a maximum oxygen pressure of 1.5–2.5 ATA and conducted 10–25 sessions in total.[14] A recent systematic review involving three RCTs proposed the following HBOT protocol for the management of SSNHL: a pressure of at least 2.0 ATA for 900 min, divided into 10 sessions of 90 min each or 15 sessions of 60 min each.[15–18] However, the pressure, frequency, and total time of HBOT remain variable among different studies. Therefore, the optimal HBOT protocol needs to be determined through comparisons in a well-designed investigation. The present study aimed to compare the treatment effectiveness of HBOT according to pressure and duration and to establish a standardized HBOT protocol for SSNHL.

## MATERIALS AND METHODS

### *Study Patients and Design*

This prospective RCT enrolled 112 patients with severe to profound SSNHL who visited the Department of Otorhinolaryngology-Head and Neck Surgery, Pusan National University Hospital of Busan, Republic of Korea, between January 2017 and December 2020. All patients underwent routine tests, including complete clinical history taking, physical examination, magnetic resonance imaging, serologic analysis, complete blood count tests, electrolyte measurement, blood glucose level measurement, autoimmune tests, and viral marker tests, to confirm the etiology of SSNHL. Patient data including age, sex, side of the disease, delay before therapy, audiologic results, and accompanying symptoms (e.g., tinnitus and vertigo) were collected. The inclusion criteria were unilateral SSNHL and a pure-tone average (PTA) (based on the four-tone average at 0.5, 1, 2, and 4 kHz) of >70 dB HL. The exclusion criteria were as follows: (1) trauma (head trauma, noise trauma, or barotrauma), ototoxic drugs (e.g., aminoglycosides, cisplatin, loop diuretics, or quinine), radiation exposure, infection (herpes, human immune deficiency virus, hepatitis, otitis media, or meningitis), retrocochlear disease, and autoimmune HL as potential causes of SSNHL; (2) severe disease (renal, hepatic, or respiratory), emphysema, severe heart failure, history of myocardial infarction within the previous 4 weeks, and pregnancy or child-bearing potential; (3) any pretreatment or ongoing treatment for SSNHL; (4) age <18 or >65 years; and (5) delayed presentation (14 days after onset). Written informed consent was obtained from all patients before starting the study. The study was approved by the institutional ethics review board of Pusan National University Hospital (ethics committee decision no. 2012-016-098).

Seven patients were excluded because of vascular anomaly, viral infections, and Ménière's disease. Finally, 105 patients were randomly and prospectively allocated to one of three groups. Randomization was performed using consecutive allocation according to the visit sequence. All patients underwent audiologic examinations, including PTA and word discrimination score (WDS) tests. PTA and WDS were evaluated on the day of the initial treatment (pretreatment PTA and WDS) and 3 months after the initial treatment. Thresholds that could not be measured because of device limitations were set at 120 dB HL. Patients who did not return for the 3-month follow-up examination were also excluded from the final analysis.

All patients were treated with SS, ITS, and HBOT. The common SS regimen was as follows: oral methylprednisolone was administered at 0.8 mg/kg/day for 7 days, which was tapered for 5 days. For ITS treatment, 0.4–0.8 ml dexamethasone (dexamethasone phosphate; Jeil Pharmaceutical Co. Ltd., Republic of Korea) at a dose of 4 mg/ml was injected into the middle ear space. The patients were asked to remain in this position without swallowing for 20 min. ITS treatment was performed once a day for a total of eight sessions. HBOT involving exposure to 100% oxygen in a hyperbaric chamber was administered for 10 consecutive days, and air-break was not performed. According to the setting of HBOT, the patients were classified into three groups: group 1, 2.5 ATA for 1 h; group 2, 2.5 ATA for 2 h; and group 3, 1.5 ATA for 1 h. If they felt discomfort in the ear, the patients were instructed to swallow to balance the middle ear pressure.

### *Outcome Assessment*

The treatment outcomes were defined according to the hearing gain between the pretreatment PTA and WDS and the final PTA and WDS. The mean gain was calculated as the difference between the final and initial PTA. Complete recovery (CR) was defined as a return of the PTA to within 10 dB HL of that of the unaffected ear and recovery of WDS to within 5–10% of that of the unaffected ear. Partial recovery (PR) was defined as a final hearing threshold of <50 dB HL and a WDS of >50%, which represent serviceable hearing according to the AAO-HNS Foundation Hearing Classification System. Slight improvement (SI) was defined as an improvement of >10 dB. Any <10 dB improvement in PTA was classified as no improvement. We also compared the sum of CR and PR, as well as the sum of CR, PR, and SI, among groups.

### *Data Analysis*

Continuous variables are presented as mean ± standard deviation, and categorical variables are expressed as a number with percentage. Levene's test was used to evaluate the distribution of the variables. Because the sample size of each group was large enough, we assumed a parametric distribution. Continuous measurements were made using the analysis of variance and Jonckheere–Terpstra tests. Categorical measures were analyzed using $\chi^2$ and Fisher's exact tests. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using Statistical Package for the Social Sciences (version 28.0.1.0; SPSS Inc., Chicago, IL, USA).

## RESULTS

After excluding 7 patients who met the exclusion criteria, 105 patients were included and randomly allocated into the three groups with 35 patients each. Six patients were further excluded because of loss to follow-up or incomplete treatment. Finally, 99 patients (33 in group 1, 34 in group 2, and 32 in group 3) completed this study and were analyzed. No statistically significant differences were found among the three groups in baseline demographic characteristics such as age, sex, side, delay before therapy, tinnitus, vertigo, diabetes mellitus, and initial hearing level (initial PTA, WDS, unaffected-side

TABLE I.
Patient Demographics, Clinical Characteristics, and Initial Hearing Levels.

| Characteristics | Group 1 ($n = 33$) | Group 2 ($n = 34$) | Group 3 ($n = 32$) | $p$ value |
|---|---|---|---|---|
| Age, years | 54.1 ± 15.0 | 52.9 ± 13.0 | 55.1 ± 13.4 | 0.809 |
| Male:female ratio | 15:18 | 17:17 | 17:15 | 0.824 |
| Right:center ratio | 15:18 | 15:19 | 19:13 | 0.395 |
| Delay before therapy, days | 3.45 ± 2.02 | 4.71 ± 3.74 | 5.38 ± 4.21 | 0.079 |
| Tinnitus | 26 (78.8%) | 27 (79.4%) | 22 (68.8%) | 0.531 |
| Hypertension | 6 (18.2%) | 5(14.7%) | 6 (18.8%) | 0.894 |
| Vertigo | 12 (36.4%) | 10 (29.4%) | 15 (46.9%) | 0.338 |
| DM | 7 (21.2%) | 6 (17.6%) | 10 (31.3%) | 0.131 |
| Initial PTA, dB | 98.76 ± 15.31 | 93.32 ± 15.30 | 95.56 ± 18.59 | 0.401 |
| Unaffected side PTA, dB | 15.88 ± 12.03 | 15.21 ± 7.95 | 19.56 ± 12.86 | 0.239 |
| Initial WDS, % | 6.06 ± 14.7 | 7.76 ± 19.0 | 10.5 ± 21.9 | 0.630 |
| Unaffected side WDS, % | 92.2 ± 6.7 | 93.5 ± 7.6 | 91.3 ± 5.4 | 0.395 |

*Note*: Values are presented as means ± SD or numbers (%).
DM = diabetes mellitus; PTA = pure-tone average (average of 0.5, 1, 2, and 4 kHz); WDS = word discrimination score.

PTA, and unaffected-side WDS) (Table I). Although adverse effects of SS or ITS were not reported, adverse events after HBOT were confirmed in 8 of 105 patients (4 in group 1, 2 each in groups 2 and 3), with no statistical significance. Middle ear effusion was the most common adverse event (three patients) among the eight patients, followed by otalgia (two patients), claustrophobia (two patients), and hemotympanum (one patient). Patients with claustrophobia were excluded from the study; however, the others had mild symptoms and improved.

Before treatment, the PTA in groups 1, 2, and 3 was 98.76 ± 15.31, 93.32 ± 15.30, and 95.56 ± 18.59 dB HL, respectively (Table I). At 3 months after treatment, the PTA in groups 1, 2, and 3 was 44.97 ± 26.12, 40.79 ± 27.36, and 59.41 ± 26.36 dB HL, respectively, with a significant difference ($p = 0.048$). In the post-hoc analysis, only groups 2 and 3 showed a significant difference (Table II). The WDS after treatment was 72.67E% ± 24.52% in group 1, 76.00% ± 27.92% in group 2, and 53.88% ± 34.29% in group 3, with significance. Significant differences were also observed in mean gain: 53.79 ± 16.03 in group 1, 52.53 ± 18.02 dB in group 2, and 36.50 ± 24.77 dB in group 3. In the post-hoc analysis, groups 1 and 2 had significantly higher WDS and mean gain than group 3; however, there was no significant difference between groups 1 and 2 (Fig. 1, Table II).

Significant differences ($p = 0.016$) in CR were observed in the outcome assessment according to the modified AAO-HNS criteria (Table III). Treatment response rates (CR or PR or SI) did not differ between groups, which were not significantly different between each group, even when comparing the DM and vertigo subgroups (Fig. 2). However, the proportion of patients with hearing recovery (CR or PR) after treatment was 57.6% in group 1, 58.8% in group 2, and 31.1% in group 3, with a significant difference ($p = 0.043$). At the start of treatment, 69% ~ 79% of patients complained of tinnitus in each group, and among these, improvement of subjective tinnitus after treatment was confirmed in 9 patients (34.6%) in group 1, 10 patients (37.0%) in group 2, and 6 patients (27.3%) in group 3, which showed no significant difference between groups.

## DISCUSSION

According to the updated 2019 AAO-HNS guideline, SSNHL is managed mainly with corticosteroids (SS, ITS) and HBOT.[1] At present, corticosteroids are the main treatment for SSNHL, with a mechanism of reducing inflammation and edema through the modification of the inflammatory cell death cascade.[19] Steroids are delivered

TABLE II.
Comparison of Pure-Tone Average, Word Discrimination Score, and Mean Hearing Gain After Treatment Among Groups.

| | 3 months after onset | | | | †$p$ value (Post-hoc analysis) | | |
|---|---|---|---|---|---|---|---|
| | G1 2.5ATA 1 h | G2 2.5ATA 2 h | G3 1.5ATA 1 h | $p$ Value (*Z score) | G1 versus G2 | G1 versus G3 | G2 versus G3 |
| PTA | 45.0 ± 26.1 | 40.8 ± 27.4 | 59.4 ± 26.4 | 0.048 (+1.964) | 0.797 | 0.079 | 0.015‡ |
| WDS | 72.7 ± 24.5 | 76.0 ± 27.9 | 53.9 ± 34.3 | 0.034 (−2.125) | 0.937 | 0.041‡ | 0.017‡ |
| Mean gain | 53.8 ± 16.0 | 52.5 ± 18.0 | 36.5 ± 24.8 | 0.002 (−3.050) | 0.964 | 0.002‡ | 0.004‡ |

*Standardized Jonckheere-Terpstra (J-T) statistics (Z scores) depicting strength and direction of associations among individual each group. Positive values signify that the values predominantly increase as went from group 1 to 3. Negative values indicate that the values predominantly decrease as went from group 1 to 3.
†Post hoc analysis was conducted with Turkey HSD for variables with Homoscedasticity, and Dunnett T3 for variables with heteroscedasticity.
‡$p < 0.05$.

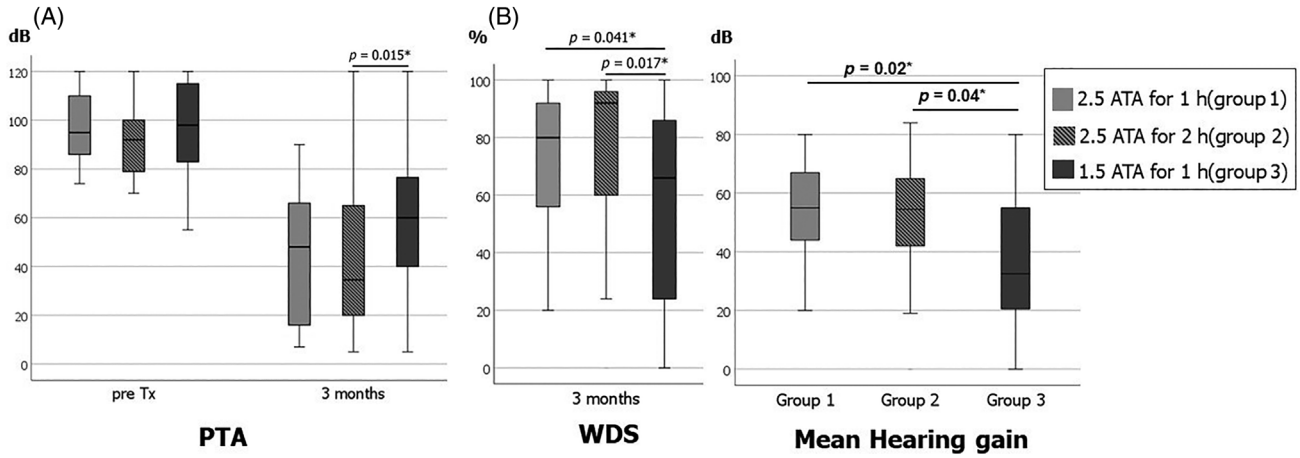


Fig. 1. PTA, WDS, and mean hearing gain in the three groups according to different pressure levels and treatment durations. (A) Comparison of PTA (dB) among groups before treatment and at 3 months after onset. In the box plots, horizontal lines at the top, middle, and bottom of the boxes show the 75th, 50th, and 25th percentiles, respectively. The vertical lines above and below the boxes show the maximum and minimum values, respectively. *$p = 0.015$, group 2 versus. 3. (B) Comparison of WDS at 3 months after onset. *$p = 0.041$, group 1 versus 3; $p = 0.017$, group 2 versus. 3. (C) Comparison of mean hearing gain among groups at 3 months after onset. *$p = 0.02$, group 1 versus 3; $p = 0.04$, group 2 versus 3. ATA = atmospheres absolute; PTA = pure-tone average; WDS = word discrimination score.

to the cochlea in two ways: SS and ITS. Many studies have reported that SS and ITS as initial therapy showed similar therapeutic effects in patients with SSNHL.[20,21] An RCT involving 250 patients compared SS and ITS and demonstrated that hearing did not differ between patients who received prednisone (60 mg/day for 2 weeks) and those who received four doses of intratympanic methylprednisolone (40 mg/ml).[20]

Another treatment option is HBOT, as a method to improve oxygen supply after cochlear damage. The efficacy of HBOT was confirmed in the Cochrane Database of Systematic Reviews in 2012, which showed a significantly increased chance of a 25% improvement in PTA.[14] Several studies and guidelines have shown that HBOT provides an additional effect when used as an adjuvant therapy to steroids rather than as monotherapy for SSNHL.[1,7,22] However, unlike steroid therapy, which has been studied in many ways, investigations on HBOT are still lacking. Animal studies on the role of HBOT in different pathologic settings have shown evidences of positive effects on wound healing, inflammation, neuroprotection, and vascular compromise.[23–25] Especially, in a study on the neuroprotective effect of HBOT on brain injury in transient middle cerebral artery occlusion animal model, in which HBOT was performed for 7, 14, and 21 days at 3 atm for 1 h/day, significant improvement was observed only in the group treated for 14 and 21 days, whereas the group treated for 7 days did not show a difference from the control group.[24] Furthermore, the appropriate pressure level may also be an important consideration. The minimum pressure for eliciting a treatment effect is known to be 1.4 ATA, and the diffusion of oxygen to the tissues is four times on the arterial side and two times on the venous side of the capillary blood circulation at 3 ATA.[26] Therefore, a proper treatment period and pressure beyond a certain level may be required to increase the treatment effect through increased oxygen delivery to the cochlea. The effective therapeutic levels of HBOT pressure exceeded 1.5 ATA in several studies, and HBOT at 2–2.5 ATA is widely used for the treatment of SSNHL.[22] A maximal HBOT pressure of >2.5 ATA did not provide any benefit for hearing recovery.[26]

The treatment strategies for SSNHL have been evolving, and recent attempts involved increasing the effectiveness through various combinations of SS, ITS, and HBOT. Theoretically, the combination of these therapies may have better effects than monotherapy with SS, ITS, or HBOT because each treatment restores cochlear function in different ways and their combinations may optimize the potential for hearing recovery through a synergistic effect.[27] Combined treatment with SS and ITS was attempted to enhance the concentration of steroids in the cochlea. Several studies showed that the combination of SS and ITS had better results than SS alone.[27,28] A systematic review in 2017 suggested that combination

TABLE III.
Assessment of Hearing Recovery According to the Modified American Academy of Otolaryngology-Head and Neck Surgery Criteria Based On the Last Pure-Tone Audiometry At 3 Months After Treatment.

| Modified AAO-HNS criteria | G1 ($n = 33$) | G2 ($n = 34$) | G3 ($n = 32$) | $p$ value |
|---|---|---|---|---|
| Complete recovery* | 12 (36.4%) | 15 (44.1%) | 4 (12.5%) | 0.016 |
| Partial recovery† | 7 (21.2%) | 5 (14.7%) | 6 (18.8%) | 0.784 |
| Slight improvement‡ | 12 (36.4%) | 12 (35.3%) | 15 (46.9%) | 0.572 |
| No improvement§ | 2 (6.1%) | 2 (5.9%) | 7 (21.9%) | 0.083 |
| Complete/partial recovery | 19 (57.6%) | 20 (58.8%) | 10 (31.3%) | 0.043 |
| Complete/partial/slight improvement | 31 (93.9%) | 32 (94.1%) | 25 (78.1%) | 0.083 |

Values are presented as $n$ (%).
*Pure tone average within 10 dB of that of the unaffected ear and word discrimination score within 5 ~ 10% of that of the unaffected ear.
†Pure-tone average ≤ 50 dB HL and word discrimination score ≥50%.
‡More than 10 dB improvement in pure-tone average or more than 10% improvement in word discrimination score.
§Less than 10 dB improvement in pure-tone average.

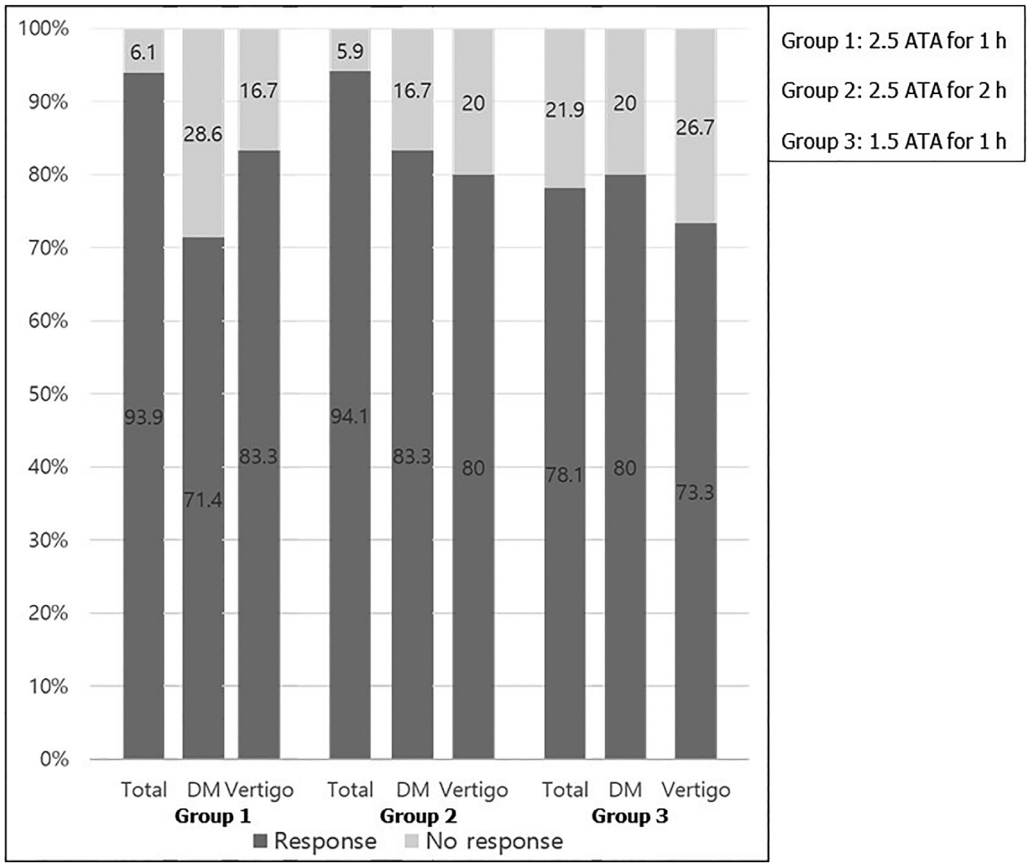


Fig. 2. Treatment response rates between groups, including total and DM/vertigo subgroups. ATA = atmospheres absolute; DM = Diabetes Mellitus.

therapy may provide improved hearing, with an odds ratio of 2.5 and a mean difference of 13 dB.[29] Moreover, studies that used HBOT in combination with SS or ITS have also been published. Because HBOT has a different mechanism of action from steroids, its addition to steroids may enhance the therapeutic effect. Two prospective studies that compared ITS + HBOT and SS + HBOT showed that both combinations provided significant improvements in hearing, with no significant difference between the two treatments.[30,31] Hosokawa et al. reported that the overall hearing recovery rate was significantly higher in patients treated with HBOT + SS (78.3%) than in those treated with SS alone (32.5%) or SS + ITS (48.6%).[32] In 2021, Tong et al. showed in their RCT that 60.6% of patients in the HBOT + SS group achieved >15 dB hearing improvement compared with only 42.9% in the SS group.[33] Recently, combined therapy with SS, ITS, and HBOT has been introduced, and a systematic review of three prospective RCTs with 88 participants showed that the mean hearing gain (mean difference, 10.3 dB) and the odds ratio of hearing recovery (4.3) were higher with the triple combination therapy than with the control therapy.[15–18] Although triple combination therapy has been shown to be sufficiently effective, no standardized HBOT protocol has been established. Considering that HBOT is a costly and time-consuming intervention compared with corticosteroid treatment, it is imperative to identify a protocol that can produce the maximum effect in the shortest time and under minimum pressure. Thereby, this study is meaningful in that the optimal protocol was identified by performing subgroup analyses according to different HBOT settings. In the current study, the 2.5 ATA groups showed better results in WDS and mean gain than the 1.5 ATA group, and the 2.5 ATA groups showed no difference depending on the duration (1 vs. 2 h). Moreover, 57%–58% of patients in the 2.5 ATA groups recovered serviceable hearing (CR or PR), compared with 31.3% in the 1.5 ATA group. Considering our previous study that compared the combination of SS, ITS, and HBOT (2.5 ATA for 1 h, 10 sessions) (CR + PR = 60.7%) with the combination of SS and ITS only (CR + PR = 33.3%), the addition of 1.5 ATA HBOT in the present study showed similar results (CR + PR = 31.3%) to that of the steroid combination without HBOT, which means that adding 1.5 ATA HBOT to steroid combination therapy may not increase the proportion of patients with restored serviceable hearing.[16] These results suggest that 2.5 ATA provides better results than 1.5 ATA regardless of the HBOT duration (1 or 2 h).

This study had limitations. As patients not treated with HBOT were not included, the significance of the addition of HBOT to corticosteroids could not be determined. However, as the effect of HBOT has already been

proven in systematic reviews, guidelines, and our previous study, we did not include a control group without HBOT for conciseness. Furthermore, as patients with SSNHL ≤70 dB were not included in this study, the effect of additional HBOT as the initial therapy for mild to moderate HL is unknown. Because the possibility of hearing recovery in patients with severe to profound SSNHL is likely low, this study focused on identifying the potential optimal treatment for these patients. Also, due to the various etiologies of patients with SSNHL, the patient group is heterogeneous, which may affect the treatment outcome.

## CONCLUSION

When HBOT (10 sessions) was combined with corticosteroids as the initial therapy for SSNHL, a higher pressure (1.5 ATA vs. 2.5 ATA) provided better treatment result; however, increasing the duration (1 h vs. 2 h) did not result in a significant difference. The addition of 1.5 ATA HBOT showed similar results to the treatment without HBOT in our previous study. Therefore, we recommend adding HBOT, performed at 2.5 ATA for 1 h in 10 sessions, to corticosteroids as the initial therapy in patients with SSNHL. Studies on the optimal HBOT protocol in salvage therapy are also needed in the future.

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