


# Potential Benefits of Combination Therapy as Primary Treatment for Sudden Sensorineural Hearing Loss

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## Abstract

**Objective.** We analyzed the effectiveness of combination therapy (CT) for idiopathic sudden sensorineural hearing loss (ISSNHL) and the utility of intratympanic dexamethasone injection (ITDI) reapplication as salvage treatment for ISSNHL refractory to CT.

**Study Design.** Case series with chart review.

**Setting.** Academic university hospital.

**Subjects and Methods.** We reviewed 229 patients with ISSNHL and divided these patients into 2 groups according to treatment: systemic steroid therapy (SST) and CT groups. The SST group received prednisolone therapy. The CT group also received ITDI daily. Patients who demonstrated no recovery (<10 dB) after initial treatment were defined as refractory and received salvage ITDI therapy: ITDI reapplication in the CT group and ITDI application in the SST group.

**Results.** Hearing recovery rates were 77.8% (77/99) in the CT group and 60.8% (79/130) in the SST group. The difference was statistically significant ( $P = .011$ ). Initial pure-tone audiometry and vertigo were affective factors on hearing recovery rates in the CT group. After salvage therapy, hearing improvement of 10 dB or greater was noted in 6 of the 22 (27.3%) patients in the CT group and 16 of the 51 (31.4%) patients in the SST group. The difference in efficacy of salvage therapy between the CT and SST groups was simply not significant ( $P = .612$ ).

**Conclusions.** Combination therapy was more effective for ISSNHL in achieving hearing gain than SST alone. Furthermore, ITDI reapplication for ISSNHL refractory to CT was as effective as salvage ITDI for ISSNHL refractory to SST.

## Keywords

sudden hearing loss, intratympanic steroids, combination therapy, salvage therapy

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Idiopathic sudden sensorineural hearing loss (ISSNHL) is an emergency condition and is commonly defined as greater than 30 dB hearing level (HL) in at least 3 audiometric frequencies occurring over 3 days or less. The most common causes of ISSNHL are idiopathic; however, the most prevalent theories are vascular impairment in the inner ear and viral infection.<sup>1,2</sup> The rate of spontaneous recovery from ISSNHL has been reported to be 32% to 65%,<sup>3,4</sup> but various treatment regimens, including corticosteroids (systemic and/or intratympanic), antivirals, vasodilators, osmotic agents, plasma expanders, anticoagulants, and hyperbaric oxygen or carbon dioxide-rich gases, have been used.<sup>5</sup> Among them, steroid therapy is considered the most effective treatment for ISSNHL and is currently the most commonly used method in most centers worldwide.<sup>6,7</sup> In addition, its therapeutic effects appear to provide the greatest recovery in the first 2 weeks, with little benefit after 4 to 6 weeks.<sup>8-10</sup>

Intratympanic steroid injection (ITSI) has been used frequently to treat ISSNHL as a primary or salvage therapy since the trial by Silverstein et al<sup>11</sup> in 1996. This technique is an office procedure under local anesthesia, is well tolerated, and can eliminate the adverse effects of systemic steroids. The efficacy of ITSI as a salvage treatment in patients with ISSNHL refractory to systemic steroid therapy has been reported,<sup>12-14</sup> as has its efficacy as a primary treatment in ISSNHL without systemic steroid therapy.<sup>15</sup> Similar to the concepts of systemic steroids for ISSNHL, ITSI aims to reduce inflammation in the inner ear, which may contribute to hearing loss.<sup>16</sup> Parnes et al<sup>9</sup> and Seggas et al<sup>17</sup> demonstrated experimentally the effects of steroid therapy via an intratympanic route on hearing recovery. Seggas et al<sup>17</sup> concluded through a systematic review that ITSI could be effective for patients with ISSNHL who either cannot tolerate or are refractory to systemic steroid therapy. In addition, the clinical practice guidelines for ISSNHL from the American Academy of Otolaryngology—Head and Neck Surgery

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Foundation (AAO-HNSF) in 2012 recommended offering ITSI to patients with incomplete recovery from ISSNHL after systemic steroid therapy.<sup>16</sup>

Recently, combination of systemic steroid therapy and ITSI as an initial treatment for ISSNHL has gained interest. The concept of combination therapy is that maximal delivery of steroid to the inner ear using both systemic and intratympanic routes optimizes the potential for hearing recovery by achieving rescue of intracochlear spiral ganglion neuritis and/or hair cells.<sup>18</sup> Despite this, there have been few clinical reports regarding the effectiveness of combination therapy as an initial treatment for ISSNHL, and hearing recovery rates for these patients after combination therapy have been reported to range from 12% to 92%.<sup>19-23</sup> Thus, the effectiveness of the addition of ITSI to a systemic steroid as an initial treatment is inconclusive, and no study of salvage treatment for patients with ISSNHL refractory to combination therapy has been published.

Consequently, the objective of the present study was to analyze the effectiveness of combination therapy and the utility of ITSI reapplication as a salvage treatment for ISSNHL refractory to combination therapy.

## Materials and Methods

We assessed the medical records of 275 patients with ISSNHL who visited the Department of Otolaryngology, Konyang University Hospital, Daejeon, Republic of Korea between 2010 and 2014. The study was approved by the Konyang University Hospital Institutional Review Board. All patients underwent neurotologic and otologic tests, including a history, physical examination, pure-tone audiometry, and magnetic resonance imaging (MRI). The inclusion criteria were (1) unexplained unilateral sudden SNHL >30 dB hearing loss for at least 3 serial audiometric frequencies occurring within 3 days or less, (2) time from the onset of hearing loss to treatment of <14 days, (3) no previous treatment, and (4) no history of ear disease or surgery in the affected ear. Exclusion criteria included cases where the patients had a history of fluctuating or bilateral hearing loss, otosclerosis, congenital and genetic hearing loss, previous ear surgery of any kind, retrocochlear lesions, and interval to first treatment of  $\geq 14$  days from onset. In total, 229 patients were assessed for eligibility; the 229 patients were divided into 2 groups according to treatment: systemic steroid therapy (SST) and combined therapy (CT) groups.

### Systemic Steroid Therapy

The SST group took prednisolone (Solondo; Yuhan, Seoul, Korea) for 10 days (5 days of intravenous prednisolone therapy during the hospital stay and 5 days of tapering with oral prednisolone after discharge from the hospital): intravenous prednisolone 1 mg/kg/d for 5 days and oral prednisolone 40 mg/d for 2 days, 20 mg/d for 2 days, and 10 mg/d for 1 day.

### Combination Therapy

The CT group was administered prednisolone using the same method as the SST group and also received the ITDI procedure daily during the hospital stay (5 injections).

## Salvage Therapy

Patients who showed no recovery (<10 dB) at 1 week after initial treatment (17 days after treatment onset) were defined as refractory to the initial treatment and received salvage ITSI therapy (twice per week for 2 weeks): ITSI reapplication in the CT group and ITSI application in the SST group.

### Intratympanic Dexamethasone Injection

Patients were placed in the supine position with their head turned toward their healthy side. After confirming an intact tympanic membrane, local anesthesia was applied to the external auditory canal with a lidocaine 10% pump spray (Xylocaine, 10 mg/dose; AstraZeneca Korea, Seoul, Korea). We made 2 perforations (ventilation and injection) in the anterosuperior quadrant of the eardrum with a 25-gauge spinal needle. Dexamethasone solution (dexamethasone disodium phosphate, 5 mg/mL, 0.3-0.4 mL; Il Sung Pharma, Seoul, Korea) was instilled through the injection site. Each patient was instructed to avoid swallowing, to refrain from head movement during the procedure, and to keep the healthy ear pointed down during the 30-minute procedure.

### Outcome Measures

Pure-tone audiometry was tested on the day of the initial treatment (initial PTA), 1 week after completion of the initial treatment (presalvage PTA, 17 days after treatment onset), and 1 month after the completion of salvage treatment (final PTA, 8 weeks after treatment onset). Pure-tone average (PTA) was calculated from 4 frequencies: 0.5, 1, 2, and 4 kHz. We used the outcomes assessment in the "Clinical Practice Guideline: Sudden Hearing Loss" from the AAO-HNSF from 2012 to determine treatment "success."<sup>16</sup> The hearing outcomes of the salvage treatment were defined according to the hearing gain between presalvage PTA and final PTA. Hearing improvement was defined as  $\geq 10$  dB hearing gain after salvage treatment.

### Statistical Analysis

Data were analyzed using the SPSS software (version 18.0; SPSS, Inc, an IBM Company, Chicago, Illinois). Independent *t* test and  $\chi^2$  test were used for intergroup comparisons of normally distributed parameters, and the hearing gain of each group was analyzed using the paired *t* test. Qualitative data were compared using the  $\chi^2$  and Fisher exact tests. Significance was set at  $P < .05$ .

## Results

Among the 229 patients with ISSNHL, 99 were included in the CT group and 130 in the SST group. Clinical characteristics for each group are summarized in **Table 1**.

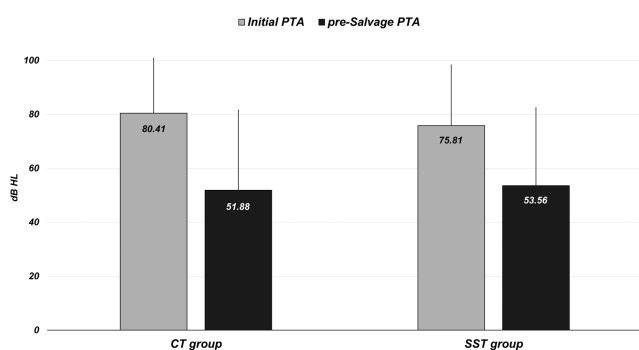
### Hearing Recovery: Combination Therapy vs Systemic Steroid Therapy

**Figure 1** and **Figure 2** show the differences between initial PTA and presalvage PTAs and hearing gain after initial treatment in each group. In the CT group, the mean PTAs

**Table 1.** Clinical Characteristics between CT and SST Groups.

Characteristic	CT Group (n = 99)	SST Group (n = 130)	P Value
Age, mean $\pm$ SD, y	52.82 $\pm$ 17.39	55.46 $\pm$ 15.16	.223
Sex, M:F, No.	55:44	61:69	.203
Time from onset to treatment, mean $\pm$ SD, d	4.14 $\pm$ 2.94	3.72 $\pm$ 3.51	.329
Initial PTA, mean $\pm$ SD, dB HL	80.41 $\pm$ 20.43	75.81 $\pm$ 22.51	.112
Dizziness, No. (%)	30 (30.3)	49 (37.7)	.244
Diabetes, No. (%)	14 (14.1)	31 (21.2)	.117

Abbreviations: CT, combination therapy; dB, decibel; F, female; HL, hearing level; M, male; PTA, pure-tone average; SST, systemic steroid therapy.

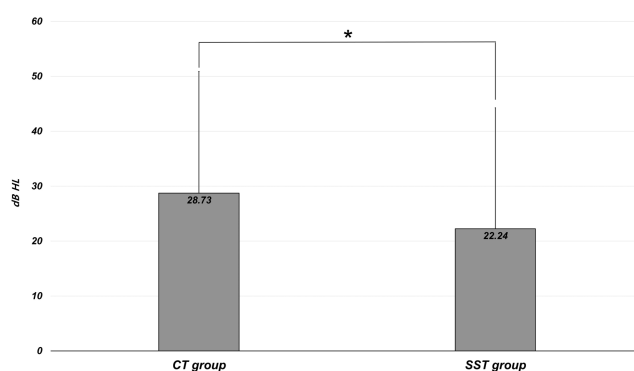


**Figure 1.** Comparison of initial and presalvage PTA between CT and SST groups. CT, combination therapy; dB, decibel; HL, hearing level; PTA, pure-tone average; SST, systemic steroid therapy.

before and after treatment were 80.41  $\pm$  20.43 dB and 51.88  $\pm$  29.67 dB, respectively, and the average hearing gain was 28.73  $\pm$  22.17 dB. In the SST group, the mean PTAs before and after treatment were 75.81  $\pm$  22.51 dB and 53.56  $\pm$  28.88 dB, respectively, and the average hearing gain was 22.24  $\pm$  22.04 dB. The CT group's hearing gains were significantly higher than in the SST group ( $P = .029$ ). The distribution of hearing gain at each frequency after initial treatment is shown in **Figure 3**. The hearing gains at frequencies of 500 Hz and 1.0 kHz were highest. There was a statistically significant difference at 1.0 kHz ( $P < .01$ ).

The hearing recovery rates between the CT and SST groups according to the AAO-HNSF clinical practice guidelines are shown in **Table 2**. The overall rates of hearing recovery in the CT and SST groups were 77.8% (77/99) and 60.8% (79/130), respectively. Regarding the proportion including complete recovery and meaningful partial recovery, the CT group had a 51.5% (51/99) recovery rate, whereas it was 41.5% (54/130) in the SST group. Thus, in patients with ISSNHL, combination therapy was more effective than SST; the difference was statistically significant ( $P = .011$ ).

A comparison of the response and the nonresponse subgroups within the CT group is shown in **Table 3**. Patients who showed complete and partial recovery after combination therapy were categorized as the response group. There were 77 (77.8%) patients who responded to combination therapy and 22 (22.2%) patients who did not. Among various affective factors concerning the efficacy of combination



**Figure 2.** Comparison of hearing gains between CT and SST groups. CT, combination therapy; dB, decibel; HL, hearing level; SST, systemic steroid therapy. \* $P < .05$ .

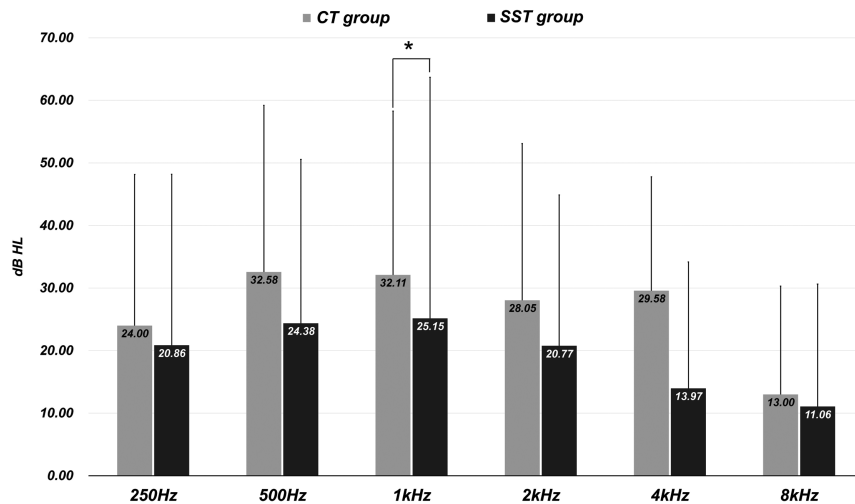
therapy, the differences in the initial PTA between response and nonresponse subgroups were statistically significant ( $P = .044$ ). In addition, 26.0% of the patients in the response subgroup experienced dizziness, whereas 45.5% of those in the nonresponse subgroup did so ( $P = .032$ ).

### Hearing Gain after Salvage Therapy

Patients who showed no recovery (<10 dB) 1 week after initial treatment (17 days after treatment onset) were defined as refractory to the initial treatment and then received salvage therapy. In total, 22 (22.2%) patients in the CT group and 51 (39.2%) in the SST group showed no recovery. Their demographics before salvage treatment are summarized in **Table 4**. The thresholds of initial and presalvage PTA in the refractory CT group were higher than those in the refractory SST group ( $P = .039$  and  $.023$ , respectively).

After salvage therapy, a hearing improvement of 10 dB or greater was noted in 6 of 22 (27.3%) patients in the CT group, with 4 (18.2%) patients improving by more than 15 dB. In the SST group, 16 of 51 (31.4%) patients demonstrated a hearing improvement greater than 10 dB, with 11 (21.6%) patients improving by more than 15 dB. The difference in the efficacy of salvage therapy between the CT and SST groups was not significant (**Table 5**).

Most patients treated with ITSI reapplication tolerated it well. Only 2 (9.1%) transient perforations were noted during the injection procedure, and these had healed spontaneously



**Figure 3.** Comparison of hearing gains between CT and SST groups according to each frequency. CT, combination therapy; dB, decibel; HL, hearing level; SST, systemic steroid therapy. \* $P < .01$ .

**Table 2.** Comparison of Recovery Rates between CT and SST Groups According to the American Academy of Otolaryngology—Head and Neck Surgery Foundation Clinical Practice Guideline.<sup>a</sup>

Treatment Outcome	No. (%)		P Value
	CT Group (n = 99)	SST Group (n = 130)	
Complete recovery	39 (39.4)	32 (24.6)	.011
Partial recovery			
Meaningful	12 (12.1)	22 (16.9)	
Nonmeaningful	26 (26.3)	25 (19.2)	
No recovery	22 (22.2)	51 (39.2)	

Abbreviations: CT, combination therapy; SST, systemic steroid therapy.

<sup>a</sup>There was statistically significant difference of hearing recovery rate between the CT and SST groups using the Fisher exact test and  $\chi^2$  test ( $P = .011$ ).

**Table 3.** Comparison of Demographics between Response and Nonresponse Patients in the CT Group.

Characteristic	Response (n = 77)	Nonresponse (n = 22)	P Value
Age, mean $\pm$ SD, y	50.54 $\pm$ 17.21	60.81 $\pm$ 15.95	.014
Sex, M:F, No.	45:32	10:12	.334
Time from onset to treatment, mean $\pm$ SD, d	3.93 $\pm$ 2.88	4.86 $\pm$ 3.11	.194
Dizziness, No. (%)	20 (26.0)	11 (50.0)	.032
Diabetes, No. (%)	10 (13.0)	4 (18.2)	.377
Initial PTA, mean $\pm$ SD, dB HL	77.98 $\pm$ 19.41	88.92 $\pm$ 22.06	.044
High-tone hearing loss, No. (%)	25 (32.5)	12 (54.5)	.059

Abbreviations: CT, combination therapy; dB, decibel; F, female; HL, hearing level; M, male; PTA, pure-tone average.

within 1 month. Temporary dizziness was noted in 3 (13.6%) patients but resolved spontaneously. No side effects such as dizziness or eardrum perforation were found in the SST group during the course of ITSI and follow-up.

## Discussion

The present findings indicate that the combination of intratympanic and systemic steroids was more effective than

SST alone in patients with ISSNHL (77.8% vs 60.8%). Similar to our findings, a few previous reports have shown the effectiveness of combination therapy as an initial treatment in ISSNHL. Battaglia et al<sup>18,19</sup> performed a multicenter, double-blinded, placebo-controlled, randomized study in 2008 and a prospective, multicentered study in 2014 comparing the effectiveness of combination therapy vs high-dose prednisone alone. They suggested that combination

**Table 4.** Comparison of Demographics between Refractory CT and SST Groups before Salvage Therapy.

Characteristic	CT Group (n = 22)	SST Group (n = 51)	P Value
Age, mean $\pm$ SD, y	60.82 $\pm$ 15.95	58.71 $\pm$ 13.91	.571
Sex, M:F, No.	10:12	24:27	.552
Time from onset to treatment, mean $\pm$ SD, d	4.86 $\pm$ 3.11	4.61 $\pm$ 4.12	.553
Dizziness, No. (%)	10 (45.5)	27 (52.9)	.370
Diabetes, No. (%)	12 (54.5)	30 (58.8)	.466
Initial PTA, mean $\pm$ SD, dB	88.92 $\pm$ 22.06	75.63 $\pm$ 25.84	.039
Presalvage PTA, mean $\pm$ SD, dB	87.67 $\pm$ 22.04	73.06 $\pm$ 25.69	.023

Abbreviations: CT, combination therapy; dB, decibel; F, female; HL, hearing level; M, male; PTA, pure-tone average.

**Table 5.** Response Rates of Salvage Therapy between CT and SST Groups.

Characteristic	CT Group (n = 22), No. (%)	SST Group (n = 51), No. (%)	P Value
PTA improvement $\geq$ 15 dB HL	4 (18.2)	11 (21.6)	.545
PTA improvement $\geq$ 10 dB HL	6 (27.3)	16 (31.4)	.612
PTA deterioration $\geq$ 10 dB HL	0	0	

Abbreviations: CT, combination therapy; dB, decibel; HL, hearing level; PTA, pure-tone average.

therapy offered a higher likelihood of recovery in ISSNHL than systemic steroids alone. In addition, Arastou et al<sup>24</sup> also documented that combination therapy was more effective than systemic steroids alone in patients with ISSNHL with poor-prognosis factors (age  $\geq$ 40 years, hearing loss  $\geq$ 70 dB, or  $\geq$ 2-week delay between the onset of hearing loss and the initiation of therapy). Arslan et al<sup>25</sup> and Koltsidopoulos et al<sup>26</sup> proposed that adding intratympanic methylprednisolone to systemic therapy increased the probability of hearing recovery in patients with ISSNHL.

However, Bae et al,<sup>27</sup> in a study comparing an SST group, an ITSI group, and a CT group in 735 patients with ISSNHL, concluded that there was no significant difference in hearing improvement among the 3 groups (68.7%, 64.9%, and 59.3%, respectively). Lim et al<sup>28</sup> contended that 3 different treatment protocols (oral steroid, ITSI, or the combination) resulted in similar hearing recovery rates. These differences in treatment results in combination therapy may be related to use of different regimens and doses, as well as a differing definition of hearing recovery. Thus, further studies are needed and directed at determining the optimal dosing regimen(s) of combination therapy, while balancing the possible adverse effects.

Frequency-associated hearing improvement has been reported by some previous studies. Lee et al<sup>29</sup> showed a significant hearing improvement only at a low frequency (0.5 kHz) with intratympanic steroids. Similarly, Ahn et al<sup>13</sup> reported greater hearing improvement only at 250 Hz with combination therapy. In the present study, we also found greater hearing gains at 500 Hz and 1000 Hz. This phenomenon may be explained by Sha et al,<sup>30</sup> who showed that hair cells in the apical turn might have a greater ability to recover. However, Gundogan et al<sup>31</sup> reported that combination therapy

showed greater hearing improvement at all frequencies. However, for patients with ISSNHL who fail to recover spontaneously or after initial treatment, clinicians usually recommend salvage therapy as an option to obtain additional hearing recovery. The most frequently used salvage therapy for refractory ISSNHL has been intratympanic delivery of steroids. Other salvage therapies include oral steroid reapplication, hyperbaric oxygen therapy, and their combined use. Ng et al<sup>32</sup> examined, through a meta-analysis, the efficacy of salvage ITSI in patients who had initial treatment failure with systemic steroids and concluded that additional treatment with ITSI demonstrated a statistically significant reduction in the hearing thresholds compared with controls in patients who had failed initial treatment with systemic steroids. To date, studies for ITSI as a salvage therapy have focused primarily on the selection of the drug (dexamethasone vs methylprednisolone) and the dose and concentration of steroid administered, as well as the timing, frequency, and total number of injections.<sup>17</sup> Yang et al<sup>33</sup> suggested another salvage therapy and compared ITSI, hyperbaric oxygen, and combination treatment in ISSNHL refractory to systemic steroids. They concluded that the addition of hyperbaric oxygen therapy to ITSI resulted in significantly greater hearing gain and rate of good recovery. In the present study, we used ITSI reapplication as a salvage therapy for ISSNHL refractory to combination therapy. Approximately 27% of patients showed hearing improvement of more than 10 dB after ITSI reapplication as a salvage therapy. Thus, salvage therapy may have been as effective as salvage ITSI in the refractory SST group, and there were few side effects of ITSI reapplication. However, we did not randomize the selection of patients and analyzed the data retrospectively. Thus, a randomized prospective study with a larger sample is needed to

further analyze the efficacy of ITSI reapplication as a salvage therapy in ISSNHL refractory to combination therapy.

Many prognostic factors for the initial treatment of ISSNHL have been reported in several studies: age, vertigo, degree and type of hearing loss, and time of initiating treatment.<sup>34-36</sup> However, these factors remain controversial. Sheehy<sup>37</sup> reported that the recovery rate of patients with vertigo was lower than that of patients in the nonvertigo group, whereas Cho and Choi<sup>38</sup> found no significant difference in hearing recovery rates between groups with and without vertigo. In the present study, we analyzed the factors affecting hearing recovery rates of ISSNHL after combination therapy. We found that differences in initial PTA threshold and vertigo significantly affected the hearing recovery rate of patients with ISSNHL.

Intratympanic steroid injection is known as a safe and simple technique. Araújo et al<sup>39</sup> reported minimal side effects such as light vertigo and otalgia, and these complaints were mild and resolved spontaneously soon after the injections. Despite ITSI reapplication, we also observed no serious complications: 2 (9.1%) transient perforations of tympanic membrane in the CT group were seen, and 3 (13.6%) patients in the CT group complained of temporary dizziness, but this improved rapidly. No patient experienced deterioration of hearing. Thus, we consider ITSI reapplication to be a safe and easy-to-perform procedure.

There are some limitations in this study: first, this is a retrospective study. Second, this study has a limitation stemming from its small sample size. Last, other limitations of this study included a different course of steroids used, more frequent ITSI than other reported studies, and treatment within 2 weeks of disease onset. However, despite these limitations, we observed a clinically beneficial result with our treatment methods.

## Conclusion

Combination therapy was a more effective treatment for ISSNHL in terms of achieving hearing recovery than SST alone. Thus, we recommend CT as a first-line therapy in patients with ISSNHL. In addition, we thought that ITSI reapplication as a salvage therapy for ISSNHL refractory to CT was as effective as salvage ITSI for those refractory to SST.

## Author Contributions

**Jong Bin Lee**, data collection and analysis, drafting the manuscript, figure drawing, and final approval; **Seong Jun Choi**, study design, revising the manuscript, final approval, and overall management.

## Disclosures

**Competing interests:** None.

**Sponsorships:** None.

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