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Efficacy of 3 Different Steroid Treatments for Sudden Sensorineural Hearing Loss: A Prospective, Randomized Trial

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Abstract

Objectives. We treated patients with idiopathic sudden sensorineural hearing loss (ISSNHL) with several protocols on an outpatient department (OPD) basis. The study compared the efficacy of 3 different steroid treatments for ISSNHL.

Study Design. A prospective randomized controlled study.

Setting. Tertiary referral center.

Methods. A total of 60 patients diagnosed with ISSNHL were treated through OPD. They were randomly and equally divided into 3 groups based on therapy: oral steroid for 10 days (group I), intratympanic dexamethasone injection (ITDI) 4 times (group II), and both (group III). Pure-tone average (PTA) was measured by taking 4 frequencies (0.5, 1, 2, and 3 kHz). Hearing change was evaluated by comparing pre- and post-treatment PTAs. Recovery rate was assessed by American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) Clinical Practice Guidelines.

Results. The hearing gain was 12.8 ± 15.4 decibels (dB) in group I, 12.1 ± 14.6 dB in group II, and 21.9 ± 26.2 dB in group III. The recovery rate was 60% in groups I and III and 55% in group II. The overall recovery rate was 58.3% (35 of 60 patients). There was no significant difference in hearing gain and recovery rates for the 3 groups. Frequency-specific hearing gain also did not differ significantly among groups.

Conclusion. Three different treatment protocols (oral steroid, ITDI, or the combination) resulted in similar hearing recovery rates. Therefore, OPD-based systemic and/or local steroid therapy can be recommended as an initial treatment in ISSNHL.

Keywords

sudden sensorineural hearing loss, outpatient, treatment, steroid, dexamethasone, hearing

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Idiopathic sudden sensorineural hearing loss (ISSNHL) is commonly defined as a rapid idiopathic hearing decline greater than 30 decibels (dB) in at least 3 consecutive audiometric frequencies that occurs over a period of 3 days or less.[1] The etiologies and pathogenesis of ISSNHL are unclear, although viral, vascular, or immunologic causes are possible. The overall incidence of diagnosed ISSNHL ranges from 5 to 20 per 100,000 persons per year.[2] However, the incidence of diagnosed ISSNHL is doubtless lower than total incidence because the spontaneous recovery rate in patients who did not receive therapy ranges from 32% to 65%.[3-5]

The method of treatment (regimens, either on an inpatient or outpatient basis, including antiviral agents and so on) of ISSNHL varies by otologic center.[6] In the past, generally the recommended treatment for ISSNHL in Korea was systemic steroids with hospitalization. However, this recommendation is now changing to outpatient department (OPD)–based management for cost-effectiveness.

Systemic steroids were effective in treating ISSNHL in a randomized controlled study.[7] However, high-dose administration of systemic steroids can raise risks of important adverse effects, such as avascular necrosis of the femur, endocrine problem, osteoporosis, or weight gain.[8,9] Therefore, more recently, intratympanic steroid injection (ITSI) has come into use frequently by otolaryngologists. Intratympanic steroid injection effectively improves hearing of patients with severe or profound ISSNHL after failure of systemic steroid therapy.[8-10] It has been considered an effective second-line treatment of choice in patients having contraindications to systemic steroid therapy or salvage treatment after systemic steroid therapy. Moreover, several reports introduced ITSI as a first-line treatment combined with systemic steroid therapy with various

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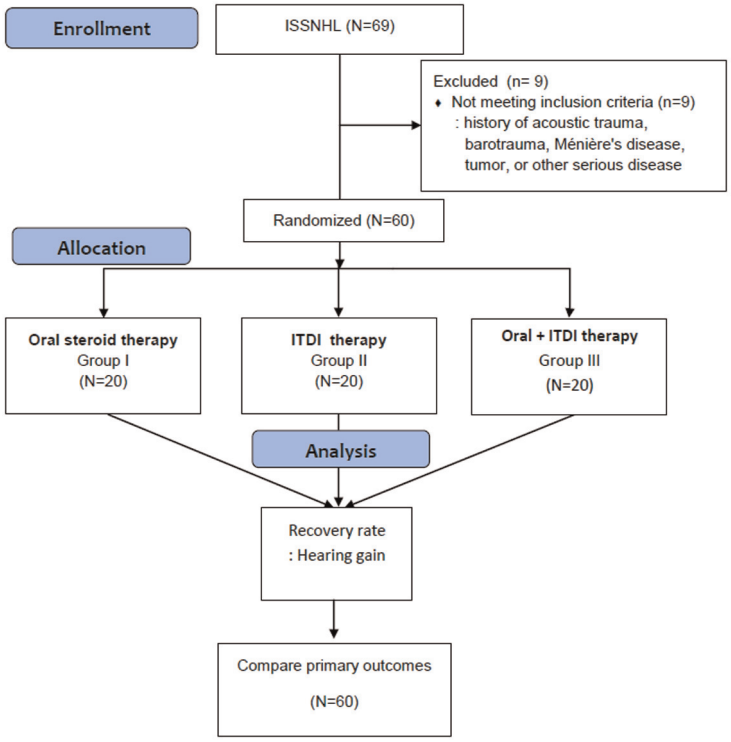

Figure 1. Study flow diagram. ISSNHL, idiopathic sudden sensorineural hearing loss; ITDI, intratympanic dexamethasone injection.

results.[1,11] Intratympanic steroid injection can produce a higher level of drug concentration in the perilymph than oral or intravenous administration and reduce the risks of steroid-related adverse effects.[12] Furthermore, ITSI is an office-based procedure that can be easily applied to patients without the need for hospitalization. The drawbacks to ITSI include transient vertigo, tympanic perforation, and infections such as otitis media or otomycosis. The merits of ITSI compared with conventional treatments are still unclear since several studies have entailed hospitalization, with patient rest being emphasized, or have compared the efficacy of various modalities without mentioning whether the patient was hospitalized.

Therefore, in this prospective randomized clinical study, we treated patients with ISSNHL with several protocols of OPD-based treatments, including steroids. The purpose of this study is to compare the efficacy of 3 different treatment protocols, including steroids, for ISSNHL with regard to hearing gain and recovery rates.

Materials and Methods

Patient Selection and Study Design

This study was performed with a prospective randomized clinical trial design. We enrolled 69 patients diagnosed with ISSNHL through OPD from July 2008 to November 2011. We obtained informed consent from patients after a full explanation of the study and received approval of the Institutional Review Board of Ajou University School of Medicine, Suwon, Republic of Korea. The diagnostic criteria for ISSNHL consisted of acute onset of hearing loss greater than 30 dB in 3 consecutive frequencies occurring within 3 days. We performed routine tests, including history taking, physical examination, pure-tone audiometry, serologic tests, autoimmune tests, and inner ear magnetic resonance imaging. We excluded 9 patients who had a history of acoustic trauma, barotrauma, Ménière's disease, tumor, or other serious disease. The remaining 60 patients were advised to adopt a low-salt diet, cease smoking, and refrain from drinking. The 60 patients were randomly, prospectively, and equally (n = 20 per group) assigned to 3 groups based on the method of steroid administration: oral route (group I), intratympanic dexamethasone injection (ITDI; group II), and oral + ITDI (group III). The method of randomization is a consecutive allocation by visit sequence. The study flow diagram can be seen in **Figure 1**. All treatments took place in the OPD without hospitalization. Group I took prednisolone (Solondo; Yuhan, Seoul, Korea) for 10 days on a schedule (**Figure 2**) consisting of 60 mg/d for 5 days, 40 mg/d for 2 days, 20 mg/d for 2 days, and 10 mg/d for 1 day following the same protocol used in our previous study.[9,10] Group II underwent the ITDI procedure twice a week for 2 weeks, for a total of 4 times. Group III received the ITDI procedure while simultaneously taking oral steroid for 2 weeks. The details of the methods of the 3 different treatments and patient treatment condition were blinded only to outcome assessors to reduce bias.

ITDI Technique

Intratympanic dexamethasone injection in groups II and III was initially conducted immediately at the time of

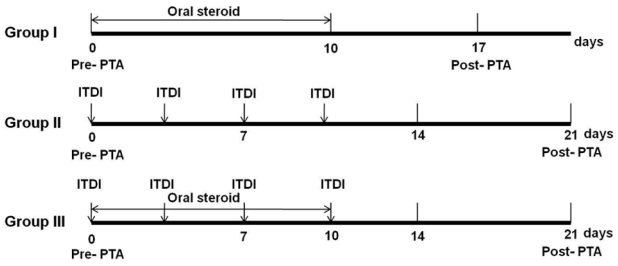

Figure 2. Flow sheet of treatment schedules and hearing evaluation. Group I (oral steroid), group II (ITDI), and group III (oral steroid + ITDI). ITDI, intratympanic dexamethasone injection; PTA, pure-tone audiometry.

enrollment and only in patients with intact eardrums. Local anesthesia was applied into the external auditory canal with a 10% lidocaine pump spray (Xylocaine, 10 mg/dose; AstraZeneca Korea, Seoul, Korea) with the patient in the supine position. We made 2 perforations (1 puncture for ventilation and the other for injection) in the anterosuperior quadrant of eardrums with a 25-gauge needle under microscopic guidance. Dexamethasone (dexamethasone disodium phosphate, 5 mg/mL, 0.3-0.4 mL; Il Sung Pharm, Seoul, Korea) was instilled through the injection site. Any device such as a ventilation tube, microwick, or microcatheter was not used. Each patient was instructed to avoid swallowing, to refrain from head motion during the procedure, and to keep his or her healthy ear pointed down during the 30-minute procedure. The procedure was done twice weekly for 2 consecutive weeks.

Outcome Measures

Pure-tone audiometry was initially performed immediately prior to treatment in all groups and was repeated 17 days later (group I) and 3 weeks later (groups II and III) (**Figure 2**). Pure-tone average (PTA) was calculated by taking 4 frequencies, including 0.5, 1, 2, and 3 kHz. We followed the recommendations of outcomes assessment in the ''Clinical Practice Guideline: Sudden Hearing Loss'' from the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) in 2012 to justify treatment success (**Table 1**).[13] In this guideline, serviceable hearing is defined as PTA $\leq$50 dB and word recognition score (WRS) $\geq$50% according to the American Academy of Otolaryngology—Head and Neck Surgery Foundation Hearing Classification System.

Statistical Analysis

The power and sample size were calculated based on the primary outcome of interest (hearing gain) using 2-sample comparison of means. A sensitivity analysis using our own estimates of hearing gain from our previous data was performed. The sensitivity analysis and power calculation demonstrated that a sample size of 20 patients per arm would give us the ability to detect 10-dB differences in hearing gain. We assumed that a 10-dB difference in PTA indicated significant difference of hearing gain among treatment groups (power = 0.9, α = 0.05). Statistical analyses were done using SPSS, version 18.0 (SPSS, Inc, an IBM Company, Chicago, Illinois). The treatment effects were compared among the 3 groups using the Kruskal-Wallis test, χ^2 test, Fisher exact test, and paired *t* test. Significance was determined at the confidence level of $P < .05$.

Results

Profile of the Patients

Patient characteristics are summarized in **Table 2**. The mean age was 51.3 $\pm$ 14.5 years in group I, 53.3 $\pm$ 15.3 years in group II, and 47.8 $\pm$ 14.2 years in group III. Patients ranged in age from 20 to 83 years (average, 50.8 $\pm$ 14.6 years). The male-to-female ratio was 10:10 in group I, 11:9 in group II, and 10:10 in group III. The overall male-to-female ratio was 31:29 (male, 51.7%; female, 48.3%). The right and left ratio for a diseased site was 8:12 in group I, 10:10 in group II, and 9:11 in group III. One patient each in groups I and II and 2 patients in group III had diabetes

Table 1. Outcome Assessment According to "Clinical Practice Guideline: Sudden Hearing Loss"[13] from the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) in 2012

Type	Hearing Recovery
I. Complete recovery	Return to within 10 dB HL of the unaffected ear[a] and recovery of WRS to within 5% to 10% of the unaffected ear[a]
II. Partial recovery	Defined in 2 ways (clinically meaningful recovery/not meaningful recovery) based on whether or not the degree of initial hearing loss after the event of ISSNHL rendered the ear nonserviceable[b]
III. No recovery	Anything less than 10 dB HL improvement

Abbreviations: HL, hearing level; ISSNHL, idiopathic sudden sensorineural hearing loss; PTA, average of pure-tone hearing threshold by air conduction at 0.5, 1, 2, and 3 kHz; WRS, word recognition score.

[a]Unless a pre-event asymmetry of hearing was known or suspected, the unaffected ear should be used as the standard against which recovery should be compared.

[b]PTA >50 dB or WRS <50% (based on the AAO-HNS definition).

Table 2. Comparisons of Patient Profile among Groups

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	*P* Value
Age, y[a]	51.3 ± 14.5	53.3 ± 15.3	47.8 ± 14.2	.465
Sex, male:female[b]	10:10	11:9	10:10	.935
Site, right:left[b]	8:12	10:10	9:11	.622
DM[b]	1	2	1	.765
Pre-PTA, dB[c]	57.8 ± 28.5	58.9 ± 31.2	56.8 ± 28.3	.995
Duration from onset to treatment, d[c]	5.4 ± 3.1	10.1 ± 8.1	9.6 ± 7.5	.326

Group I, oral steroid therapy; group II, intratympanic dexamethasone injection; group III, both. Abbreviations: DM, the number of patients who have diabetes mellitus; pre-PTA, pretreatment pure-tone audiometry.
[a]Data were analyzed by analysis of variance test for continuous variables.
[b]Data were analyzed by χ^2 for categorical variables.
[c]Data were analyzed by Kruskal-Wallis test for continuous variables.

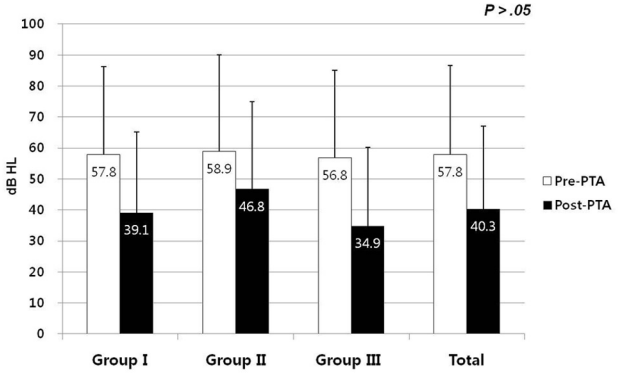

Figure 3. Comparison of pre-PTA and post-PTA in each group ($P < .05$). All groups had similar initial PTAs and revealed no statistically significant difference in post-PTA ($P > .05$). dB, decibel; HL, hearing level; PTA, pure-tone average.

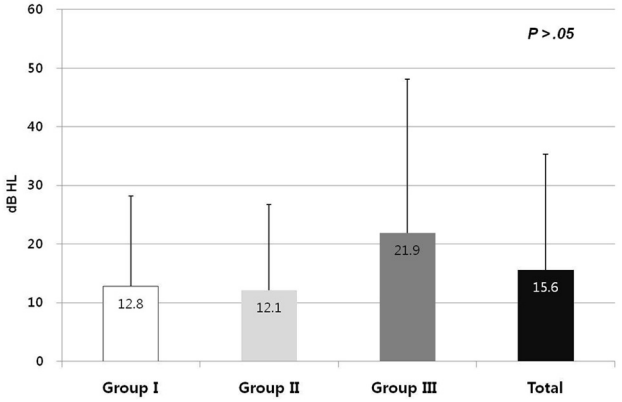

Figure 4. Comparison of hearing gains among 3 groups and overall hearing gain using the Kruskal-Wallis test ($P > .05$). dB, decibel; HL, hearing level.

mellitus. Pre-PTAs and duration from onset to treatment did not significantly differ among all groups.

Comparison of Hearing Gain among Groups

Figure 3 depicts the differences between pre- and posttreatment PTAs in each group. In group I, PTAs before and after oral steroid therapy were 57.8 ± 28.5 dB and 39.1 ± 26.1 dB, respectively, and average hearing gain was 12.8 ± 15.4 dB. In group II, PTA was 58.9 ± 31.2 dB before ITDI and 46.8 ± 28.2 dB after ITDI, with hearing gain of 12.1 ± 14.6 dB. In group III, the average hearing gain was the highest among the groups (21.9 ± 26.2 dB), 56.8 ± 28.3 dB and 34.9 ± 25.3 dB in the pre- and postcombination therapies, respectively. Group III's hearing gain was the highest, followed by groups I and II, although these differences were not statistically significant (**Figure 4**).

The frequency-specific hearing gains of the groups are presented in **Figure 5**. Hearing gain was compared again by frequency (low frequency, the average of pure-tone hearing threshold by air conduction at 0.25, 0.5, and 1 kHz; mid-frequency, at 2 and 3 kHz; high frequency, at 4 and 8 kHz) among groups. We observed no significant differences in hearing gain by the 3 classified frequencies (high, mid, and low) among the treatment groups.

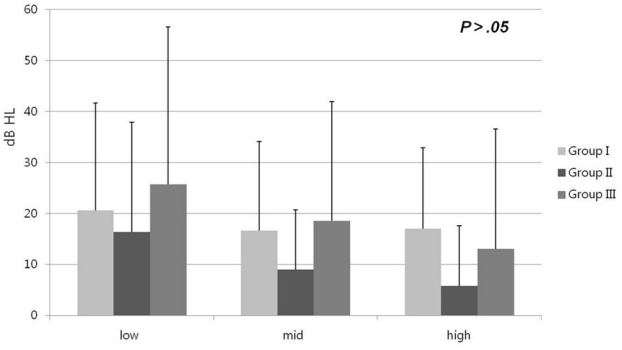

Figure 5. Comparison of hearing gains among the groups according to 3 classified frequencies (low frequency, 0.25, 0.5, and 1 kHz; mid-frequency, 2 and 3 kHz; high frequency, 4 and 8 kHz) using the Kruskal-Wallis test ($P > .05$). dB, decibel; HL, hearing level.

Table 3. Comparison of Recovery Rates among the Groups According to the American Academy of Otolaryngology—Head and Neck Surgery Clinical Practice Guideline

	No. (%)			
Treatment Outcome	Group I	Group II	Group III	*P* Value
Complete recovery	6 (30)	3 (15)	8 (40)	
Partial recovery				
Meaningful	2 (10)	5 (25)	3 (15)	
Not meaningful	4 (20)	3 (15)	1 (5)	
No recovery	8 (40)	9 (45)	8 (40)	.502

There were no significant differences among the groups using the Fisher exact test and χ^2 test ($P > .05$). Group I, oral steroid therapy; group II, intratympanic dexamethasone injection; group III, both.

Comparison of Recovery Rate among Groups

The recovery rates for each group by the AAO-HNS Clinical Practice Guideline are presented in **Table 3**. Attaining PTA $\geq$10 dB and WRS $\geq$10% of hearing gain are defined as hearing recovery. The average recovery rate for all groups was 58.3% (35 of 60 patients). The recovery rates of groups I and III were the same, 60% (12 of 20), exceeding the recovery rate of 55% (11 of 20) in group II. With regard to the proportion including complete recovery and meaningful partial recovery, group III had a 55% recovery rate, whereas both groups I and II were the same at 40% each. However, there were no significant differences statistically among the groups (**Table 3**).

Discussion

Idiopathic sudden sensorineural hearing loss is one of the most controversial diseases in etiology and treatment. There are widely varied treatment choices for ISSNHL, including steroids, vasodilators, anticoagulants, plasma expanders, and carbogen inhalation.[14] Although controversial, systemic steroid therapy is a mainstay therapy in ISSNHL. One study noted a significantly greater rate of recovery (61%) in patients receiving systemic steroid therapy compared with placebo (32%).[7] In contrast, Cinamon et al[14] reported no significant difference between steroid and placebo. Despite these contradictory findings, high-dose systemic steroid therapy is accepted as the best treatment modality. However, high-dose systemic therapy has systemic side effects such as immune suppression, osteoporosis, avascular necrosis of the femur head, and glucose intolerance. Thus, ITSI was introduced to avoid these systemic side effects. Several studies emphasized the effectiveness of ITSI as a salvage therapy in patients who showed poor response to initial systemic steroid. Ho et al,[8] Choung et al,[9] and Xenellis et al[15] reported successful results with ITSI as a salvage therapy after failure of systemic steroid therapy, although those studies suffered from small sample sizes and outcome ranges within the spontaneous recovery rate. Intratympanic steroid injection has been investigated as a sole initial therapy, and successful outcomes were reported compared with systemic steroid.[1,16,17] However, hearing gain in the ITSI group at high frequencies (4 and 8 kHz) was less than in the oral steroid group in one of these studies.[17] Combination therapy with systemic steroid was the focus of some studies.[1,11,18,19] In one such study, combination therapy led to better hearing improvement (40 dB, 14 of 16 patients) than systemic steroid alone (21 dB, 8 of 18 patients),[1] whereas no significant improvement was mentioned in other studies.[11,18]

In most of these studies, the kind, dose, and concentration of the steroid used in both systemic and local therapies and the treatment schedules differed. Some studies have involved hospitalization for all treatments,[8,11,18,20] whereas hospitalization was not specifically mentioned in other studies.[1,14,21] Whether the treatment is based on outpatient or not varies according to otologic centers and medical situations. Moreover, there are no standard criteria for hearing recovery. This reduces the comparability of these studies drastically.

In this study, we compared treatment outcomes based on the AAO-HNS ''Clinical Practice Guideline: Sudden Hearing Loss.''[13] According to these guidelines, the authors recommend that the unaffected ear should be used as the standard against the affected ear if pre-event asymmetry of hearing was not suspected. Therefore, complete recovery is defined as a return to within 10 dB hearing level (HL) of the unaffected ear and recovery of WRS to within 5% to 10% of the unaffected ear, which means the guideline reflects the possibility of pre-existing hearing loss. Most previous literature used the amount of absolute hearing gain of PTA and/or WRS score in the affected ear, or the absolute thresholds in final hearing were evaluated like Siegel's criteria.[22] Moreover, the guidelines defined partial recovery in 2 ways (meaningful and not meaningful recovery) based on comparing hearing loss with serviceable hearing level. Therefore, the guideline is considered a more practical method than the previous standard. As shown in **Table 3**, of 35 patients, 27 with hearing recovery had a clinically meaningful recovery.

From this study, OPD-based treatment of ISSNHL showed a recovery rate of 58.3% regardless of protocols. This is very similar to the rate of 56.5% (174 of 308 patients) with hospitalized treatments reported in our

previous study,[23] even though we cannot compare the treatment outcomes to each other because of the small sample size of the present study and the different standards for hearing recovery rate. On an outpatient basis, we could not absolutely restrict bed rest and demand a low-salt diet of the patients, which is part of the management regimen in hospitalized ISSNHL patients.

In the present study, group III had a similar pre-PTA level (56.8 dB) to other groups (group I: 57.8 dB, group II: 58.9 dB), and pre-PTAs of all groups were not different statistically (**Figure 3**). Although there was no statistical significance, the highest hearing gain (21.9 dB) was detected in the group III, compared with group I (12.8 dB) and group II (12.1 dB) (**Figure 4**).

One of the possible causes may be the high efficacy of combination therapy using both systemic and local administration techniques. An animal study showed that local application of steroid through the round window can result in higher target concentration compared with systemic administration.[12] Systemic steroid via blood vessels and local steroid via diffusion through the round window was supplied to the damaged inner ear. Steroids have an antioxidative effect and prevent apoptosis in hair cells of inner ears. Moreover, mineralocorticoid receptors in inner ears might allow applied steroid to help endolymphatic homeostasis.[24]

In addition, these results might be caused by the group II protocol, in which the concentration of dexamethasone and frequencies of ITDI were insufficient to recover hearing as a sole treatment modality. Battaglia et al[1] reported a prospective, double-blind, placebo-controlled study that consisted of 3 groups: ITDI vs oral steroid vs combination therapy. This study showed hearing gain increasingly, with the combination group > the ITDI group > the oral steroid group. Kakehata et al[16] published results showing that ITDI alone had efficacy similar to systemic steroid alone. Our finding that all groups had similar treatment effects without reference to the modalities of treatment echoes the latter study, although in both studies, the similar treatment effects may be a result of small sample size (**Figure 4**).

Battaglia et al[1] performed ITDI with dexamethasone (12 mg/mL once a week for 3 weeks), a higher dexamethasone concentration than used in the present study (5 mg/mL). In another study,[16] ITDI was performed with a dexamethasone regimen of 4 mg/mL for once a day for 8 days (8 times, consecutive days); this was a more frequent and numerous injection regimen than our study (twice a week for 2 weeks, total 4 times).

In our study, hearing improvements were analyzed according to frequency-specific hearing gain. Groups II and III, which incorporated ITDI treatment, had better hearing gain at low frequencies than at high frequencies. However, there was no statistical difference among groups. Similar patterns in frequency-specific hearing gain were detected in ITDI patients in 2 other studies.[9,11] Although the highest hearing gain occurred in the combination treatment group, the combination therapy cannot be conclusively considered the best treatment modality of ISSNHL because the comparisons of modalities of treatment did not show any statistical significance.

A possible explanation for the different hearing gains in the groups may be different vulnerability of cochlear hair cells. Hair cells in the basal turn showed less resistance to acoustic trauma and ototoxic drugs such as gentamicin than hair cells in the apical turn in an animal study.[25] There may be high levels of intrinsic antioxidant enzymes in the apical turn, unlike in the basal turn.[26] This is consistent with the present finding that hearing gain was better in the lower frequencies than in the high frequencies in groups II and III. This effect may result from higher concentrations of steroid in the apical turn that can be induced by ITDI, rather than by systemic administration.

There are some limitations in this study. Each group may have been so small as to obviate any statistical significance that would be apparent only with higher subject numbers. Furthermore, the study was not a double-blind, placebo-controlled design, like a previous study.[1] However, despite these limitations, a clinically beneficial tendency of the treatment was evident.

Conclusion

Outpatient department–based treatments, including steroids, produce about 58.3% of hearing recovery rates according to the AAO-HNS guideline. Three different treatment protocols (oral steroid, ITDI, and the combination) in this study showed similar hearing recovery rates. Thus, OPD-based systemic and/or local steroid therapy can be suggested as an initial treatment in ISSNHL.

Author Contributions

Hye Jin Lim, drafting the manuscript, data analysis; **Yun Tae Kim**, drafting the manuscript, data analysis; **Seong Jun Choi**, data collection, statistical analysis; **Jong Bin Lee**, data collection, statistical analysis; **Hun Yi Park**, acquisition of data; **Keehyun Park**, review of the manuscript; **Yun-Hoon Choung**, study design, result interpretation, correction of manuscript.

Disclosures

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References

1. Battaglia A, Burchette R, Cueva R. Combination therapy (intratympanic dexamethasone + high-dose prednisone taper) for the treatment of idiopathic sudden sensorineural hearing loss. *Otol Neurotol*. 2008;29:453-460.
2. Byl FM Jr. Sudden hearing loss: eight years' experience and suggested prognostic table. *Laryngoscope*. 1984;94:647-661.
3. Fetterman BL, Saunders JE, Luxford WM. Prognosis and treatment of sudden sensorineural hearing loss. *Am J Otol*. 1996; 17:529-536.
4. Hughes GB, Freedman MA, Haberkamp TJ, Guay ME. Sudden sensorineural hearing loss. *Otolaryngol Clin North Am*. 1996;29:393-405.

5. Mattox DE, Simmons FB. Natural history of sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol*. 1977;86:463-480.
6. Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss, I: a systematic review. *Arch Otolaryngol Head Neck Surg*. 2007;133:573-581.
7. Wilson WR, Byl FM, Laird N. The efficacy of steroids in the treatment of idiopathic sudden hearing loss: a double-blind clinical study. *Arch Otolaryngol*. 1980;106:772-776.
8. Ho HG, Lin HC, Shu MT, Yang CC, Tsai HT. Effectiveness of intratympanic dexamethasone injection in sudden-deafness patients as salvage treatment. *Laryngoscope*. 2004;114:1184-1189.
9. Choung YH, Park K, Shin YR, Cho MJ. Intratympanic dexamethasone injection for refractory sudden sensorineural hearing loss. *Laryngoscope*. 2006;116:747-752.
10. Lee JB, Choi SJ, Park K, Park HY, Choo OS, Choung YH. The efficiency of intratympanic dexamethasone injection as a sequential treatment after initial systemic steroid therapy for sudden sensorineural hearing loss. *Eur Arch Otorhinolaryngol*. 2011;268:833-839.
11. Ahn JH, Yoo MH, Yoon TH, Chung JW. Can intratympanic dexamethasone added to systemic steroids improve hearing outcome in patients with sudden deafness? *Laryngoscope*. 2008;118:279-282.
12. Parnes LS, Sun AH, Freeman DJ. Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. *Laryngoscope*. 1999;109:1-17.
13. Stachler RJ, Chandrasekhar SS, Archer SM, et al. Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg*. 2012;146:S1-S35.
14. Cinamon U, Bendet E, Kronenberg J. Steroids, carbogen or placebo for sudden hearing loss: a prospective double-blind study. *Eur Arch Otorhinolaryngol*. 2001;258:477-480.
15. Xenellis J, Papadimitriou N, Nikolopoulos T, et al. Intratympanic steroid treatment in idiopathic sudden sensorineural hearing loss: a control study. *Otolaryngol Head Neck Surg*. 2006;134:940-945.
16. Kakehata S, Sasaki A, Oji K, et al. Comparison of intratympanic and intravenous dexamethasone treatment on sudden sensorineural hearing loss with diabetes. *Otol Neurotol*. 2006;27:604-608.
17. Hong SM, Park CH, Lee JH. Hearing outcomes of daily intratympanic dexamethasone alone as a primary treatment modality for ISSHL. *Otolaryngol Head Neck Surg*. 2009;141:579-583.
18. Lautermann J, Sudhoff H, Junker R. Transtympanic corticoid therapy for acute profound hearing loss. *Eur Arch Otorhinolaryngol*. 2005;262:587-591.
19. Battista RA. Intratympanic dexamethasone for profound idiopathic sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg*. 2005;132:902-905.
20. Arslan N, Oguz H, Demirci M, et al. Combined intratympanic and systemic use of steroids for idiopathic sudden sensorineural hearing loss. *Otol Neurotol*. 2011;32:393-397.
21. Filipo R, Covelli E, Balsamo G, Attanasio G. Intratympanic prednisolone therapy for sudden sensorineural hearing loss: a new protocol. *Acta Otolaryngol*. 2010;130:1209-1213.
22. Siegel LG. The treatment of idiopathic sudden sensorineural hearing loss. *Otolaryngol Clin North Am*. 1975;8:467-473.
23. Oh JH, Park K, Lee SJ, Shin YR, Choung YH. Bilateral versus unilateral sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg*. 2007;136:87-91.
24. Trune DR, Kempton JB, Gross ND. Mineralocorticoid receptor mediates glucocorticoid treatment effects in the autoimmune mouse ear. *Hear Res*. 2006;212:22-32.
25. Choung YH, Taura A, Pak K, Choi SJ, Masuda M, Ryan AF. Generation of highly-reactive oxygen species is closely related to hair cell damage in rat organ of Corti treated with gentamicin. *Neuroscience*. 2009;161:214-226.
26. Sha SH, Taylor R, Forge A, Schacht J. Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals. *Hear Res*. 2001;155:1-8.