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Original Article

Intratympanic Injection of Edaravone for Idiopathic Sudden Sensorineural Hearing Loss with Profound Hearing Loss

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BACKGROUND: In Japan, edaravone, a free radical scavenger, is used clinically to reduce neuronal damage after acute cerebral infarction. In this study, a clinical trial has been designed utilizing intratympanic edaravone injection (ITE), which was hypothesized to exhibit high transitivity into the inner ear, with the aim of identifying an improved treatment modality for patients with idiopathic sudden sensorineural hearing loss (ISSHL) presenting with profound hearing loss.

METHODS: Between April 2012 and December 2015, 17 patients with ISSHL, with mean hearing levels equal to or greater than 90 dB HL at the time of the initial visit, were treated with ITE. Fourteen patients with ISSHL under the same conditions were extracted, who received intratympanic steroid injection (ITS) in the department between January 2015 and December 2019 as a historical control. The hearing thresholds were compared between the ITE and ITS groups.

RESULTS: The improvement between the initial and final hearing levels was significantly greater in the ITE group than in the ITS group at 250-1000 Hz. The average hearing improvement was 49.1 (± 21.0) dB in ITE group and 35.2 (± 11.8) dB in ITS group, and the degree of improvement was significantly greater in ITE group. No detectable adverse events associated with ITE were observed in patients' subjective symptoms.

CONCLUSION: The final hearing thresholds of patients treated with ITE were significantly better than those of patients treated with ITS. It has been concluded that ITE treatment may be useful in future clinical studies.

KEYWORDS; Edaravone, intratympanic injection, ISSHL, profound hearing loss

INTRODUCTION

The pathogenesis of idiopathic sudden sensorineural hearing loss (ISSHL) remains unclear, and an effective treatment has not been established.[1] Although systemic corticosteroid therapy is widely used, its efficacy has not been supported by systematic reviews.[2] Especially in patients with profound hearing loss, the outcome of any treatment, including systemic or intratympanic corticosteroids, is markedly poor.[3-5] Therefore, new treatment methods are needed. Kawano et al[6] reported that systemic steroid medication combined with intratympanic steroid injection (ITS) showed additional hearing improvement in patients with profound hearing loss. However, they concluded that the average hearing recovery was approximately 35 dB, and the complete recovery rate was less than 4%, even with additional improvement, indicating that most patients still had moderate to severe hearing loss. In addition, according to the guidelines established by the American Academy of Otolaryngology-Head and Neck Surgery, the recommended treatment protocol for ISSHL involves the administration of systemic corticosteroids as adjunctive therapy within the initial 2-week period following onset. Subsequently, if necessary, ITS is advised as a salvage treatment option during the 2-6 week window post-ISSHL onset.[2] Nevertheless, there is insufficient evidence to support the efficacy of using both systemic corticosteroids and ITS.

Edaravone, a free radical scavenger, has been clinically used to reduce neuronal damage after acute cerebral infarction in Japan.[7] In addition, edaravone has been proven effective in patients with amyotrophic lateral sclerosis (ALS) by significantly reducing

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neurodegeneration associated with oxidative stress in both motor neurons and muscles.[8] Furthermore, edaravone scavenges hydroxyl radicals and inhibits lipid peroxidation and has been shown to be effective in the treatment of a wide range of diseases related to oxidative stress, including ischemic stroke, ALS, Alzheimer's disease, and placental ischemia.[9] In the cochleae, edaravone has been reported to reduce the loss of inner hair cells after transient ischemia in Mongolian gerbils[10] and the loss of outer hair cells after acoustic trauma in guinea pigs.[11] Although the pathophysiology of ISSHL has not yet been identified, ischemia and reperfusion could be possible hypotheses. Furthermore, the pathology of other possible causes such as viral infection and inflammation may be related to oxidative stress. The inner ear is susceptible to ischemic damage because the cochlea is supplied with blood from the labyrinthine artery, which has no collateral blood vessels.[12] Changes in the microcirculation in the cochlea may cause the generation of reactive oxygen species (ROS), which may lead to ISSHL.[13] Therefore, suppressing ROS generation in the cochlea may improve ISSHL.

Between 2004 and 2006, a clinical trial of systemic (intravenous infusion) edaravone treatment for ISSHL patients with profound hearing loss was performed.[14] The treatment results were comparable with those of patients treated with hyperbaric oxygenation therapy; however, most patients had moderate to severe hearing loss.

In this study, another clinical trial was planned using intratympanic edaravone injection (ITE), which expected high transitivity into the inner ear to seek better treatment methods for patients with ISSHL with profound hearing loss, and compared the therapeutic effects of ITE and ITS treatment to investigate the effects of edaravone for ISSHL patients with ISSHL.

METHODS

Study Design and Materials

This study was conducted according to the principles outlined in the Declaration of Helsinki and was approved by the Ethical Committee of Kitasato University Hospital on November 16, 2011 (registered number C11-691). All the patients provided written informed consent to participate in the study. In addition, this trial was registered in the University Hospital Medical Information Network Clinical Trial Registry under the trial registration numberUMIN000008127.

MAIN POINTS

- We investigated the therapeutic effects of intratympanic edaravone injections in patients with idiopathic sudden sensorineural hearing loss.
- The therapeutic effects of intratympanic edaravone injection and intratympanic steroid injection in patients with idiopathic sudden sensorineural hearing loss were compared.
- The improvement between the initial and final hearing levels was significantly greater in the intratympanic edaravone injection group than that in the intratympanic steroid injection group at 250-1000 Hz.
- No detectable adverse events associated with intratympanic edaravone injection were observed in patients' subjective symptoms.

This study was conducted at the Department of Otorhinolaryngology, Head, and Neck Surgery of Kitasato University Hospital from April 2012 to December 2015. A diagnosis of ISSHL was made based on the following criteria: 1) hearing loss of at least 30 dB in 3 sequential frequencies within 72 h and 2) sensorineural hearing loss of unknown etiology.

The inclusion criteria for this study were as follows: 1) treatment can be started within 3 days from the onset, 2) 20 years old or older, 3) 5 frequencies (from 250 Hz to 4000 Hz) averaged hearing levels equal to or more than 90 dB at the time of initial visit, 4) no severe general complications, pregnancy, or lactation, and 5) no medical history of hypersensitivity to edaravone. Magnetic resonance imaging was performed on all patients to rule out vestibular schwannomas.

Selection of Historical Control

At the end of this study, Kawano et al[6] reported that adding ITS to systemic steroid administration for patients with profound ISSHL resulted in a greater improvement in hearing loss. Therefore, the basic policy was changed to recommend the addition of ITS with systemic steroid administration for patients with profound ISSHL. There is no comparative study on the administration period of ITS, and it differs depending on the facility.[2] At the hospital, it was administered for 3 consecutive days.[15] As these cases were considered suitable for comparison with the treatment effects of ITE, it was decided to retrospectively collect them and use them as historical controls. This observational retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kitasato University Hospital (B22-077, November 14, 2022). The need for informed consent was waived owing to the retrospective nature of the study. The clinical records of the patients who visited the outpatient clinic of the Department of Otorhinolaryngology and Head and Neck Surgery at Kitasato University Hospital between January 2015 and December 2019, and were diagnosed with ISSNH and received the ITS in this department, were examined.

Treatment

The treatment regimens for the 2 groups were similar, except for ITE or ITS, and the presence of oral ubidecarenone (150 mg daily). This consisted of a tapering dose of betamethasone (starting from 8 mg), intravenous prostandin (60 μg daily), peroral adenosine triphosphate disodium hydrate (300 mg daily), and mecobalamin (1.5 mg daily) (Figure 1).

For ITE and ITS, paracentesis was performed in the antroinferior quadrant of tympanic membrane, and injected approximately 0.3-0.5 mL of edaravone injection (1.5 mg/mL, Mitsubishi Tanabe, Japan) or dexamethasone disodium phosphate (3.3 mg/mL, Sandoz, Japan) into tympanic cavity under local anesthesia. Patients were instructed to lie in the supine position with the head tilted 45° to the healthy side and to avoid swallowing or moving for 30 minutes. ITE and ITS were performed for 7 consecutive days and 3 days, respectively.

Assessment of Hearing Function

An audiometer (AA-78; Rion, Tokyo, Japan) was used to conduct the pure-tone audiometry in a soundproof chamber. The primary outcome measure was 5 frequencies (from 250 Hz to 4000 Hz) averaged hearing levels on the final pure-tone audiogram (more than 2 months after the onset). To avoid cross-hearing, sound masking was used for

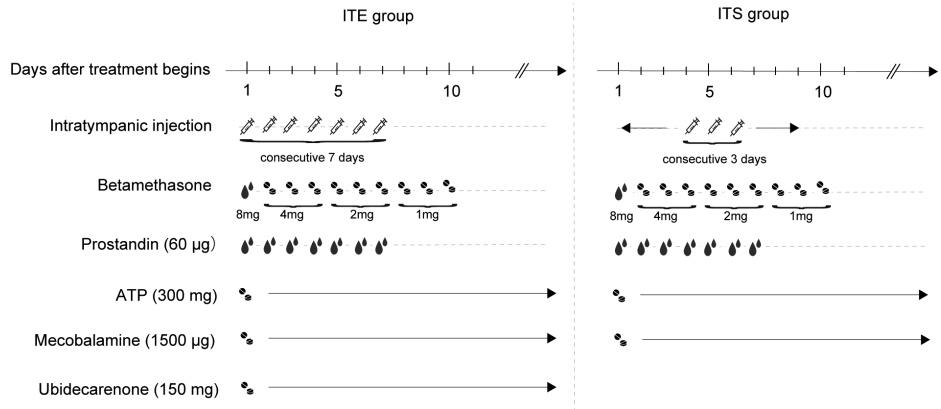

Figure 1. Treatment protocol. The treatment regimens for the 2 groups were similar, except for ITE or ITS and the presence of oral ubidecarenone. Ubidecarenone was administered to the ITE group only. ATP, adenosine triphosphate disodium hydrate; ITE, intratympanic edaravone injection; ITS, intratympanic steroid injection.

the non-test ear, whereas the other ear was tested as required. The secondary outcome measures were hearing recovery (the difference between the initial and final 5 frequency-averaged hearing levels) and incidence of adverse effects.

Statistical Analyses

The normality of all data was evaluated using the Shapiro-Wilk test. To evaluate the differences between groups statistically, univariate analysis using Fisher's exact test or Mann–Whitney *U* test was employed. Statistical analyses were performed using the JMP PRO 17 software (SAS Institute, Cary, NC, USA). For statistical analysis of the hearing evaluation, the hearing thresholds for each frequency and average hearing thresholds were compared between the ITE and ITS groups. Normally distributed data were subjected to an unpaired t-test and non-normally distributed data were subjected to the Mann–Whitney *U* test. Statistical analyses were performed using GraphPad Prism 10 (GraphPad Software Inc., La Jolla, CA, USA). All data are presented as SD, and the significance level was set at $P < .05$.

RESULTS

A total of 17 patients (11 men and 6 women) were treated using the ITE treatment protocol. Average age was 54.9 (± 17.0), average time intervals between the onset and the initial visit was 2.5 (± 0.5) day. Ten patients were affected in the right ear and 7 were affected in the left ear. Ten (59%) patients experienced vertigo or dizziness. The ITS group consisted of 14 patients (5 men and 9 women). Average age was 51.5 (± 13.6), average time intervals between the onset and the initial visit was 1.1 (± 0.9) day. Nine (64%) patients experienced vertigo or dizziness (Table 1). Although pre-treatment hearing thresholds in the affected ears were similar between the 2 groups at all measured frequencies, significant differences were found in some measured frequencies (250 Hz, $P = .007$; 500 Hz, $P = .06$; 1 kHz, $P = .10$; 2 kHz, $P = .03$; 4 kHz, $P = .06$, Figure 2A). In addition, the means of averaged hearing levels at the initial visit was 103.6 (± 7.9) dB in ITE group and 100.7 (± 5.7) dB in ITS group, with no significant difference between the 2 groups ($P = .16$, Mann–Whitney *U* test, Figure 2B). Furthermore, the differences in pre-treatment hearing thresholds between unaffected and healthy ears were investigated. Pre-treatment hearing thresholds in the unaffected ears were similar between the 2 groups at all measured frequencies, and statistical analysis showed no significant differences between the groups (250 Hz, $P = .86$; 500 Hz, $P = .88$; 1 kHz, $P = .55$; 2 kHz, $P = .96$; 4 kHz, $P = .77$; Figure 3A). Furthermore, there was no significant difference in the average hearing threshold on the healthy side at the initial visit between the 2 groups ($P = .74$, Mann–Whitney *U* test, Figure 3B).

Next, to investigate the therapeutic effects of ITE and ITS on ISSHL, post-treatment hearing thresholds appeared to be better in the ITE group than in the ITS group at almost all frequencies measured, except at 4 kHz, but no significant differences were observed (250 Hz, $P = .16$; 500 Hz, $P = .17$; 1 kHz, $P = .06$; 2 kHz, $P = .23$; 4 kHz, $P = .77$, Figure 4A). The means of averaged final hearing levels was 54.5 (± 27.1) dB in ITE group and 65.5 (± 15.2) dB in ITS group, with no significant difference between the 2 groups ($P = .18$, Unpaired t-test, Figure 4B). In addition, the percentage of cases in which the initial and final hearing levels improved by ≥ 10 dB was 100% (14/14) in the ITS group and 94% (16/17) in the ITE group. According to the criteria for hearing improvement determined by the Sudden Deafness Research Committee of the Japanese Ministry of Health, Labor, and Welfare in 1984 (Supplementary Table 1), the complete recovery rate was 0% (0/14) in the ITS group and 23% (4/13) in the ITE group. The improvement between the initial and final hearing levels was significantly better in the ITE group than in the ITS group at 250-1000 Hz (250 Hz, $P = .02$; 500 Hz, $P = .02$; 1 kHz, $P = .02$; 2 kHz, $P = .08$; 4 kHz, $P = .62$, Figure 5A). The average hearing improvement was 49.1 (± 21.0) dB in ITE group and 35.2 (± 11.8) dB in ITS group, and the degree of improvement was significantly greater in ITE group ($P = .01$, Mann–Whitney *U* test, Figure 5B).

Table 1. Clinicodemographic Patient Characteristics of Intratympanic Edaravone Injection and Intratympanic Steroid Injection Group

	ITE (n = 17)	ITS (n = 14)	*P*
Age (years)	54.9 ± 17.0	51.5 ± 13.6	.41
Affected side (right/left)	9/8	5/9	.47
Sex (male/female)	11/6	8/6	.72
Vertigo (+/–)	10/7	9/5	1.00
Diabetes (+/–)	2/15	3/11	.63
Hearing levels at initial visit (dB)	103.6 ± 7.9	100.7 ± 5.7	.16
Initiation of treatment (days)	2.5 ± 0.5	1.1 ± 0.9	<.001

ITE, intratympanic edaravone injection; ITS, intratympanic steroid injection.

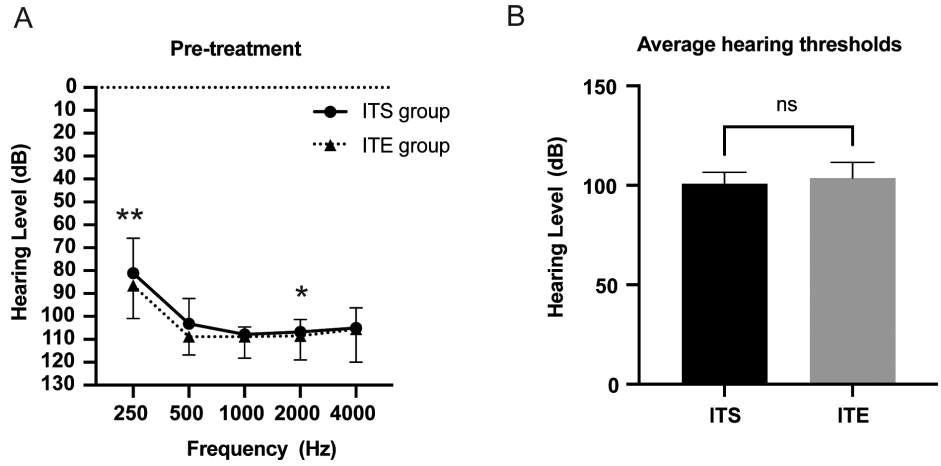

Figure 2. Hearing levels in the ITE and ITS groups at the initial visit. (A) Pretreatment hearing thresholds in the affected ears were similar between the ITE and ITS groups at all measured frequencies. The hearing thresholds in the ITE group were significantly worse than those in the ITS group at 250 Hz and 2000 Hz. All hearing threshold data are presented as mean and SD. (B) Average hearing thresholds at 5 frequencies were not significantly different between the ITE and ITS groups ($P > .05$, Mann–Whitney U test). ITE: intratympanic edaravone injection, ITS: intratympanic steroid injection, *$P < .05$, **$P < .001$.

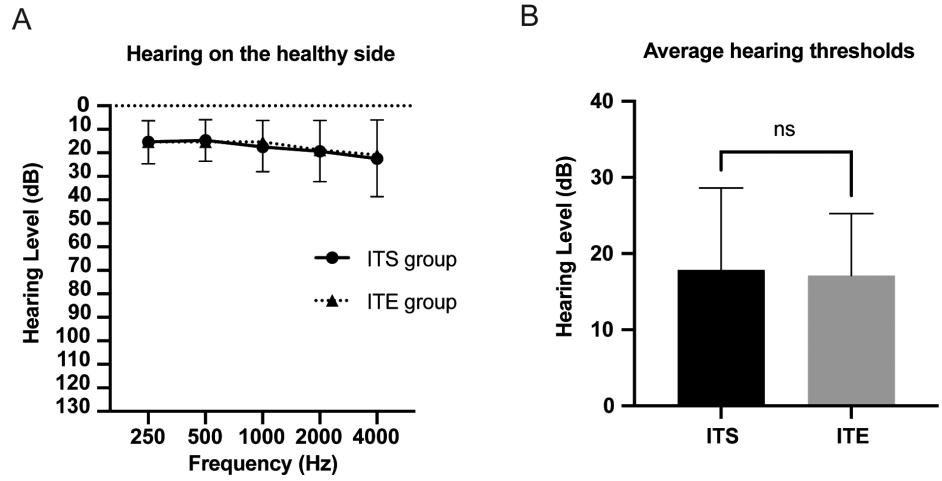

Figure 3. Hearing levels on the healthy side at the initial visit. (A) There was no significant difference in the pretreatment hearing thresholds of the unaffected ear between the ITE and ITS groups at all measured frequencies. All hearing threshold data are presented as mean and SD. (B) Average hearing thresholds at 5 frequencies were not significantly different between the ITE and ITS groups ($P > .05$, Mann–Whitney U test). ITE, intratympanic edaravone injection; ITS, intratympanic steroid injection.

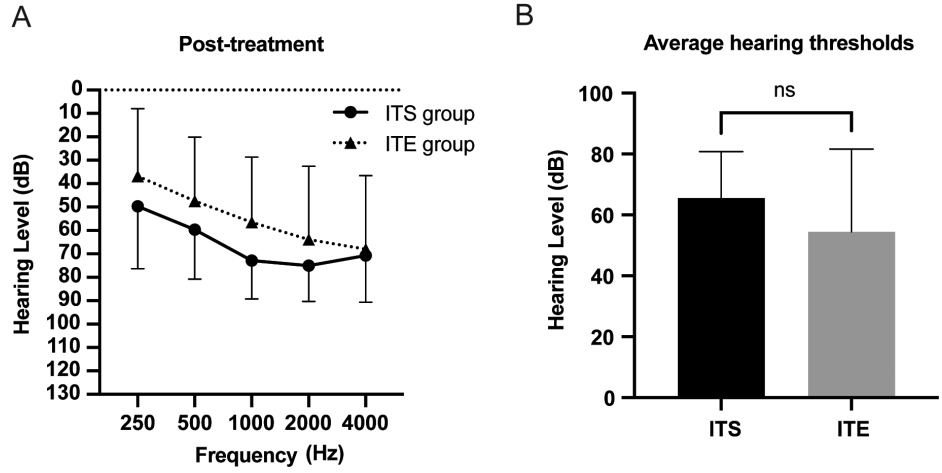

Figure 4. Hearing levels of the ITE and ITS groups after treatment. (A) Post-treatment hearing thresholds were better in the ITE group than in the ITS group at all measured frequencies, but none of the differences were significant. All hearing threshold data were presented as mean and SD. (B) Average hearing thresholds at 5 frequencies were not significantly different between the ITE and ITS groups ($P > .05$, unpaired t-test). ITE, intratympanic edaravone injection; ITS, intratympanic steroid injection.

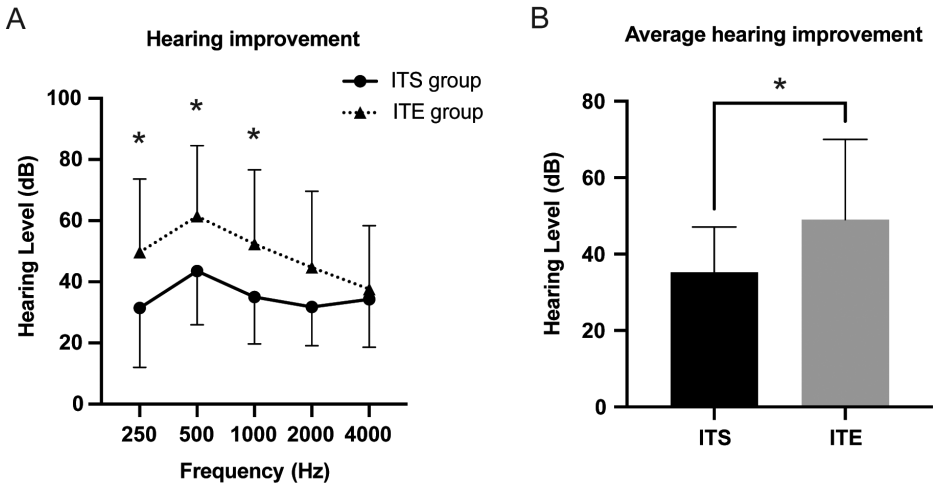

Figure 5. Hearing improvement in the ITE and ITS groups. (A) The improvement between the initial and final hearing levels was significantly better in the ITE group than in the ITS group at 250 to 1000 Hz. All hearing threshold data were presented as mean and SD. (B) The degree of average hearing improvement was significantly greater in the ITE group ($P < .05$, Mann–Whitney *U* test). ITE, intratympanic edaravone injection; ITS, intratympanic steroid injection, *$P < .05$.

No patients had persistent tympanic perforation in either the ITE or ITS group. No adverse events such as ear pain or otorrhea were observed in either group.

DISCUSSION

Although several possible etiologies of ISSHL, such as circulatory disorders and viral infections, have been demonstrated, they have not yet been identified.[1] Recently, oxidative stress and its relationship with diseases have been investigated in many areas. For example, free radicals have been reported to increase during ischemic reperfusion injury, inflammation, cancer, and aging.[16] In otological areas, it has been reported that free radicals increase in the inner ear tissue after acoustic trauma or exposure to inner ear toxic drugs such as amino glucoside and cisplatin.[17,18]

Edaravone is a clinical drug developed as a free-radical scavenger in Japan. Several studies have shown that edaravone has protective effects against inner ear disorders caused by ischemia, ototoxic drugs, and acoustic trauma in animals.[10,11,19,20] Steroid treatment has been shown to play a role in reducing inflammatory biomarkers, such as CRP and Tumor Necrosis Factor alpha in ISSHL.[21] It has been reported that edaravone reduces inflammatory biomarkers in the lung tissue of a mouse model of airway inflammation[22] and in the brain tissue of a mouse model of cerebral infarction.[23] Therefore, edaravone may have an anti-inflammatory effect on ISSHL similar to that of steroids. It was believed that edaravone might achieve better treatment outcomes in patients with ISSHL with profound hearing loss than other conventional treatments. Previously, a clinical trial was performed in which edaravone was administered intravenously as conventional systemic steroid therapy. In that trial, the treatment results in the edaravone group were almost equal to those in the hyperbaric oxygenation therapy group.[14] Although this result indicated that edaravone was comparable to hyperbaric oxygenation therapy, it was considered that their final hearing abilities were insufficient because most patients showed moderate to severe hearing loss. Therefore, this study had been planned to use the ITE. It was reported that the concentration in the perilymph of the scala tympani after ITS was 4.4 to 189.6 times higher than that after intravenous administration.[24] Because edaravone has a smaller molecular weight (MW = 174.20) than steroids,[25] it is expected that the permeability through the round window membrane is higher than that through steroids.[26,27]

In this study, the final hearing improvements in patients treated with ITE were significantly better than those in patients treated with ITS (Figure 5). In addition, patients treated with ITE showed no detectable adverse effects. This clinical study of ITE was a prospective study conducted over a 3-year period from 2012 to 2015, and the research protocol was based on follow-up until 3 months after treatment. Patients who had been treated with ITE were followed up for a minimum of 0.77 years and a maximum of 10.2 years (average 3.7 years). During the follow-up period, a small perforation of the tympanic membrane was observed in one case. No other complications such as delayed or prolonged dizziness, otalgia, or otorrhea were noted. This study was initially conducted as a single-arm, non-randomized, open study with the main objective of investigating the effect on improving hearing and the secondary objective of investigating adverse events.[28] Although the safety of the treatment could be confirmed, it was difficult to determine the effect on hearing improvement because there was not a control group as conducted with prospective study. Therefore, from 2015 to 2019, data was retrospectively collected as the control group that underwent ITS in this department, and compared and examined the treatment effects. It was believed that it would be worthwhile to plan further research using ITE. As the next step, it was planned to conduct a trial using a refined intratympanic injection technique. A randomized controlled trial comparing ITS on a large scale will be conducted.

The findings of this study offer crucial insights into the management strategies for ISSNHL. However, this study had some limitations. First, the effects of the intratympanic injection techniques must be considered. In this study, approximately 0.3-0.5 mL of edaravone was injected into a tympanic cavity after paracentesis, but the exact volume was not constant and the time holding drug in tympanic cavity was indefinite, especially in the patients who had thin tympanic membrane. Therefore, it was very difficult to inject the liquid into the tympanic cavity, and the actual amount injected might be less than 0.3 mL. In addition, it was reported that round window obstruction caused by adhesion, ossification, or thickened soft tissue was

observed in 10%-30% of Meniere's patients.[27,29,30] Some patients with round window obstruction may have been included in this study. New methods for intratympanic injection, such as gelatin hydrogel[28] and endoscope-assisted intratympanic injection,[31] may become more reliable and effective drug delivery methods for the inner ear. In addition, the combination of edaravone and hyaluronic acid (HA) is expected to improve the therapeutic effects of ITE. Drugs combined with HA are readily transported through the round window membrane and enter the perilymph owing to an increase in osmotic pressure in the round window membrane, modulation of membrane permeability, or prolonged contact owing to the high viscosity of HA.[32] It has been reported that when the treatment effects of the ITS group and the group that combined HA and ITS were compared, the group that combined HA and ITS showed significantly improved hearing loss.[33] Therefore, HA may be an effective drug delivery method to the inner ear.

Second, it must be considered that the ITE and ITS groups differed in terms of whether they were administered oral ubidecarenone. Ubidecarenone (Coenzyme Q10) is a mobile electron carrier in the mitochondria and an endogenous antioxidant that prevents the oxidation of membrane-bound lipid peroxide free radicals. It is used clinically to treat cardiac, neurological, oncologic, and immunological disorders. There are few reports on the effectiveness of treatment for patients with ISSNHL, and there are no reports of significant improvements in auditory outcomes in patients with ISSNHL.[34,35] However, prospective studies with a complete set of conditions are required to confirm the effect of edaravone on auditory function in patients with ISSNHL.

Third, since the number of patients with ISSHL who met the research criteria was 10 per year in the hospital and 30 were expected over the 3-year period from 2012 to 2015, the sample size was set at a maximum of 30. However, only 17 patients received ITE during this period. The limitations of this study are that the sample size was small, and there was no control group, as conducted in a prospective study. As there were 17 participants in the edaravone group, the accuracy of the results was at most 90%, with a margin of error of 10%.[36] The results of this study show the therapeutic superiority of edaravone over intratympanic steroid injections; however, further multicenter studies involving larger populations are needed.

CONCLUSION

We examined the effectiveness of ITE in patients with ISSHL and profound hearing loss. The final hearing thresholds of patients treated with ITE were significantly better than those of patients treated with ITS. It was conclude that treatment with ITE is worth conducting further clinical studies.

Availability of Data and Materials: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethics Committee Approval: This study was approved by Ethics Committee of Kitasato University (approval no.:C11-691; date: November 16, 2011)(approval no.: B22-077; date: November 14, 2022).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.S.; Design – H.S.; Supervision – H.S.; Resources – H.S.; Materials – Y.N.; Data Collection and/or Processing – Y.N.; Analysis and/or Interpretation – Y.N.; Literature Search – T.Y.; Writing – Y.N., T.K.;

Declaration of Interests: The authors have no conflicts of interest to declare.

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Supplementary Table 1. Criteria for hearing improvement determined by Sudden Deafness Research Committee of the Japanese Ministry of Health, Labor and Welfare in 1984

Complete recovery	Recovery of a hearing level within 20 decibels (dB) at all five frequencies tested (0.25, 0.5, 1.0, 2.0 and 4.0 kHz) or recovery to the same level as the opposite side in pure-tone audiometry
Marked recovery	30 dB and over recovery in the mean hearing level at the five frequencies tested
Slight recovery	Recovery of better than 10 dB and less than 30 dB in the mean hearing level at the five frequencies tested
No response	Less recovery than 10 dB in the mean hearing level at the five frequencies tested