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Comparison of Intratympanic and Systemic Steroid Therapy as Primary Treatments for Idiopathic Sudden Sensorial Hearing Loss

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Abstract

Recently, intratympanic steroid (ITS) therapy has been used as a primary or salvage treatment for idiopathic sudden sensorineural hearing loss (ISSHL). In the present study, we retrospectively compared the efficacies of ITS and systemic steroid (SS) therapies as primary treatments for ISSHL. This study included 112 patients treated for ISSHL at our hospital, of which 44 received ITS therapy and 68 received SS therapy. Regarding patient background characteristics, the mean age (76 vs. 65 years, $p < 0.0001$) and percentage of patients with diabetes mellitus (55 vs. 18%, $p < 0.0001$) were significantly higher in the ITS group than in the SS group, whereas the rate of prior steroid use was lower in the ITS group than in the SS group (9 vs. 31%, $p = 0.0068$). After 3 weeks, the treatment response was cure, marked recovery, recovery, and no change in 11, 9, 8, and 16 patients in the ITS group and 32, 11, 5, and 20 patients in the SS group, respectively. Accordingly, the SS group was found to have a significantly higher cure rate than the ITS group (47 vs. 25%, $p = 0.0191$), with similar findings after propensity score matching (48 vs. 22%, $p = 0.0461$). Therefore, SS therapy is recommended as a primary treatment for ISSHL in patients who are not old or at a high risk of SS therapy-associated complications.

Keywords
- idiopathic sudden sensorineural hearing loss
- intratympanic steroid therapy
- primary treatment

Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) is defined as an unexplained sudden loss of hearing. In 1980, Wilson et al reported systemic adrenocortical steroid therapy as an effective treatment for ISSHL,[1] and since then, it has been commonly used for treating patients with ISSHL worldwide. Recently, intratympanic steroid (ITS) injection therapy has been recognized and selected as a treatment of choice for

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ISSHL; it is performed by injecting steroids into the tympanic cavity of the patients to administer a high concentration of steroids in the inner ear. Notably, ITS therapy is used as a primary or salvage treatment following systemic steroid (SS) therapy. As a primary treatment, ITS therapy is administered as monotherapy or in combination with SS therapy.[2] The effectiveness of ITS monotherapy as a primary treatment has been reported in several randomized controlled trials; to the best of our knowledge, the first study was conducted by Rauch et al who reported that ITS therapy was noninferior to SS therapy.[3–10]

The 2019 Clinical Practice Guideline: Sudden Hearing Loss of the American Academy of Otolaryngology—Head and Neck Surgery Foundation listed ITS as only a primary treatment option.[11] However, in the 2018 Japanese Clinical Practice Guidelines for the Diagnosis and Management of Acute Sensorineural Hearing Loss, ITS was recommended as only a salvage therapy, with a recommendation grade of C1 (i.e., recommended despite having only a weak scientific basis), for primary treatment.[2]

In our department, ITS monotherapy has been used as a primary treatment option for ISSHL since around January 2017. To date, several studies have investigated the effectiveness of this therapy as a primary treatment for ISSHL. However, most of these studies set the threshold for auditory acuity recovery at $\geq$10 to 15 dB, but in actual clinical practice, some patients exhibited poor improvement in subjective symptoms despite showing decent improvement in quantitative analysis. Therefore, in the present study, we retrospectively compared the treatment outcomes of ITS monotherapy with those of SS therapy as primary treatments in patients with ISSHL and investigated the effectiveness of these treatments.

Materials and Methods

Subjects

This study included 225 patients who were diagnosed with ISSHL and were receiving primary treatment on an inpatient or outpatient basis at the Department of Otolaryngology, Japanese Red Cross Okayama Hospital between January 2017 and March 2021. Patients with ISSHL who met the revised diagnostic criteria by the Ministry of Health, Labor, and Welfare Research Group on Intractable Hearing Impairment in 2015 were included in the present study.[2] Patients with other suspected causes, such as Meniere's disease, labyrinthine fistula, acoustic neuroma, and functional deafness, as well as patients with a definite diagnosis (e.g., by imaging) were excluded. Patients with recurrent auditory disturbances, progressive sensorineural hearing loss, or a history of surgery (e.g., surgery for chronic otitis media) were also excluded. This study included 120 patients with primary ISSHL, treatment initiation within 2 weeks of disease onset, contralateral auditory acuity within the age-appropriate range, and a posttreatment follow-up for $\geq$3 weeks or until recovery. Of these, 8 patients who received the combination therapy of ITS and SS were excluded from the study; finally, 112 patients were included in the analysis.

Treatment Plan

In our department, SS therapy is used as the first choice for the primary treatment of ISSHL. For patients with grades 1 to 4 hearing loss, prednisolone was usually administered after hospitalization for 8 days, starting at a dose of 60 mg and gradually decreasing over approximately 5 days (days 1–2: 60 mg; days 3–5: 40 mg), and then switched to oral administration of 10 mg on day 6. In almost all patients, a combination therapy of mecobalamin and adenosine triphosphate disodium hydrate was used. For patients with diabetes, first, the Internal Medicine Department was requested to manage hyperglycemia; subsequently, prednisolone was administered over 9 days, starting at a dose of 60 mg and gradually decreasing to 10 mg. In patients with grade 4 hearing loss, a combination therapy of SS and ITS was used depending on the patient.

ITS monotherapy has been recommended as first-line therapy for older patients and patients with several underlying conditions who are at high risk for complications associated with SS therapy, such as diabetes, psychiatric disorders, and thromboembolism. Although the number of ITS doses and the interval between doses varied slightly as the patient's hearing acuity progressed, two doses were generally administered at approximately 7-day intervals.

In patients with ISSHL who experienced dizziness after hospitalization, SS therapy was administered. However, as mentioned earlier, for patients in whom the risk of complications was judged to be high, ITS therapy was administered together with treatments for dizziness such as fluid replacement and administration of sodium bicarbonate.

Intratympanic Therapy

All patients with ISSHL who did not experience dizziness were treated on an outpatient basis. After achieving tympanic membrane anesthesia by administering liquid anesthetic in the sitting position, the posterior–inferior quadrant of the tympanic membrane was punctured with a 23-G Cathelin needle or mucosal needle, and approximately 0.2 to 0.8 mL of dexamethasone (DEX; 3.3 mg/mL) was injected. Furthermore, immediately after the injection, the patient was transferred to a bed in the lateral recumbent position with the affected ear facing upward for approximately 30 minutes, and during this time, swallowing was prohibited.

Treatment Outcome Determination

Auditory acuity recovery was determined in accordance with the 2012 revised assessment criteria by the Ministry of Health, Labor, and Welfare Research Group on sudden severe hearing loss. In addition, the mean level of improvement in auditory acuity from before to after treatment was recorded for five frequencies. For patients who did not show recovery, the treatment outcome was determined by auditory acuity after $\geq$3 weeks of onset.

Statistical analyses were performed using the Wilcoxon test for continuous variables and Fisher's exact test for nominal variables, and a p-value of <0.05 was considered

statistically significant. Software JMP14 was used for all statistical analyses.

Propensity score matching (PSM) was performed to compare the ITS group and the SS group with matched patient characteristics. Participants' propensity score estimates were determined using logistic regression analysis, considering the presence or absence of intratympanic injection as objective variables and moderator factors as explanatory variables.

A 1:1 pair matching was chosen for the algorithm using the nearest-neighbor matching of the propensity scores of randomly selected patients from the ITS group and the nearest propensity scores of patients from the SS group. The caliper width was 0.2 times the standard deviation of the logit of the propensity score estimate. Substitute sampling was used as the sampling method.

This study was approved by the Ethical Review Board of the Japanese Red Cross Okayama Hospital (approval no. 2021–55).

Results

Patient Background Characteristics

Overall, 112 patients (median age, 68.5 years), including 58 men (52%) and 54 women (48%), were included in this study. The affected sides of the ears were right and left in 50 (45%) and 62 (55%) patients, respectively. The median number of days from disease onset to treatment initiation was 4 days, and the median number of days from treatment initiation to outcome assessment was 34 days. The median auditory acuity at the time of the initial examination was 67 and 20.5 dB on the affected side and healthy sides, respectively. The severity grades of the disease were G1, G2, G3, and G4 in 14 (12%), 31 (28%), 46 (41%), and 21 (19%) patients, respectively. Furthermore, 22 patients (20%) had dizziness, whereas 90 (80%) did not have dizziness. Moreover, 25 patients (22%) had a history of undergoing steroid therapy administered by their previous physician, whereas 87 (78%) did not. Furthermore, 36 patients (32%) had diabetes, and 76 (68%) did not.

The comparison between patients who received ITS monotherapy ($n = 44$) and those who received SS therapy ($n = 68$) is summarized in ►**Table 1**. In the ITS group, 39 patients received treatment on an outpatient basis. The ITS and SS groups did not differ in terms of the affected side, sex, number of days from disease onset to treatment initiation, number of days from treatment initiation to outcome assessment, auditory acuity on the affected side at the initial examination, severity of the disease, or the presence or

Table 1 Patient background characteristics

		ITS group ($n = 44$)	SS group ($n = 68$)	*p*-Value
Age (y)	Median (range)	76 (35–94)	65 (10–84)	<0.0001
Affected side, *n* (%)	Right	18 (41)	32 (47)	0.3571
	Left	26 (59)	36 (53)	
Sex, *n* (%)	Male	21 (48)	37 (54)	0.4893
	Female	23 (52)	31 (46)	
Number of days from onset to the start of treatment (days)	Median (range)	4.5 (1–27)	4 (0–16)	0.2173
Number of days from treatment initiation to outcome assessment (days)	Median (range)	34 (7–411)	33 (4–271)	0.5938
Auditory acuity on the affected side at the initial examination (dB)	Median (range)	68 (28–111)	66 (22–111)	0.2477
Auditory acuity on the healthy side at the initial examination (dB)	Median (range)	27.5 (4–111)	17.5 (3–104)	<0.0001
Severity, *n* (%)	G1	4 (9)	10 (15)	0.5682
	G2	14 (32)	17 (25)	
	G3	16 (36)	30 (44)	
	G4	10 (23)	11 (16)	
Dizziness, *n* (%)	Present	9 (21)	13 (19)	0.8619
	Absent	35 (80)	55 (81)	
History of steroid therapy administered by the previous physician, *n* (%)	Present	4 (9)	21 (31)	0.0068
	Absent	40 (91)	47 (69)	
Diabetes, *n* (%)	Present	24 (55)	12 (18)	<0.0001
	Absent	20 (45)	56 (82)	

Abbreviations: ITS, intratympanic steroid; SS, systemic steroid.
Notes: There was no statistically significant difference in age, auditory acuity on the healthy side at the initial examination, history of steroid therapy administered by the previous physician, or diabetes.

absence of dizziness. Conversely, patients in the ITS group were significantly older than those in the SS group (76 vs. 65 years, $p < 0.0001$), had a higher auditory acuity on the healthy side at the initial examination (27.5 vs. 17.5 dB, $p < 0.0001$), had a lower rate of undergoing prior steroid therapy administered by their previous physician (91 vs. 69%, $p = 0.0068$), and had a higher rate of concurrent diabetes (55 vs. 18%, $p < 0.0001$).

Effects of Intratympanic Injection as a Primary Treatment

As shown in ►**Fig. 1**, the rates of cure, marked recovery, recovery, and no change were 25% ($n = 11$), 20% ($n = 9$), 18% ($n = 8$), and 36% ($n = 16$) in the ITS group and 47% ($n = 32$), 16% ($n = 11$), 7% ($n = 5$), and 29% ($n = 20$) in the SS group, respectively.

Notably, the cure rate differed significantly between the ITS and SS groups (25% [$n = 11$] vs. 47% [$n = 32$], $p = 0.0191$), whereas the rate of marked recovery and greater (cure + marked recovery) did not (45% [$n = 20$] vs. 63% [$n = 43$]). The mean level of auditory acuity improvement for five frequencies from before to after treatment was 17.5 dB in the ITS group and 28 dB in the SS group, indicating a significantly greater improvement in auditory acuity in the SS group ($p = 0.0174$; ►**Table 2**).

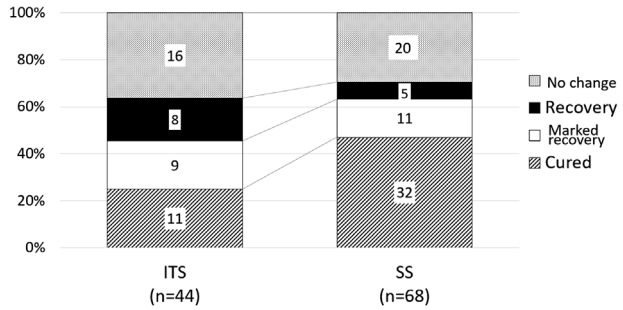

Fig. 1 A comparison of treatment outcomes. The cure rate was significantly higher in the systemic steroid group than in the intratympanic steroid group.

Patient Background Characteristics and Treatment Outcomes after PSM

After PSM, there were 27 patients in each group, and the significant differences existing before adjustment among background characteristics (age, auditory acuity of the healthy side at the time of the initial examination, the presence or absence of the history of steroid therapy administered by their previous physician, and the presence or absence of diabetes) were not found after adjustment (►**Table 3**).

Regarding treatment outcomes, the rates of cure, marked recovery, recovery, and no change were 22% ($n = 6$), 30% ($n = 8$), 22% ($n = 6$), and 26% ($n = 7$) in the ITS group and 48% ($n = 13$), 15% ($n = 4$), 4% ($n = 1$), and 33% ($n = 9$) in the SS group, respectively (►**Fig. 2**). The cure rate was significantly higher in the SS group than in the ITS group ($p = 0.0461$; ►**Table 2**), but the rate of marked recovery or greater (cure + marked recovery) did not significantly differ between the two groups ($p = 0.583$). Furthermore, the mean levels of auditory acuity improvement for five frequencies from before to after treatment did not differ significantly between the ITS and SS groups (26 vs. 27 dB, $p = 0.4159$).

Complications in the ITS Group

No serious adverse events were reported in either group. In the ITS group, two patients (5%) had tympanic membrane perforations, and both patients were examined for persistent perforation following treatment. In one patient, the perforation closed spontaneously within 2 months of treatment. In the other patient, a very small perforation remained after 2 months of treatment. Furthermore, the patient experienced some pain during intratympanic injection, but it was temporary. Furthermore, there was no dizziness or infection, such as otitis media.

Discussion

Effects of Intratympanic Steroid Injection

In the present study, ITS monotherapy and SS therapy as primary treatments were compared, and it was found that

Table 2 Comparison of treatment outcomes

		Overall			After propensity score matching		
		ITS group ($n = 44$)	SS group ($n = 68$)	*p*-Value	ITS group ($n = 27$)	SS group ($n = 27$)	*p*-Value
Cure, *n* (%)		11 (25)	32 (47)	0.0191	6 (22)	13 (48)	0.0461
Marked recovery or less, *n* (%)		33 (75)	36 (53)		21 (78)	14 (52)	
Cure + marked recovery, *n* (%)		20 (45)	43 (63)	0.0801	14 (52)	17 (63)	0.583
Recovery + no change, *n* (%)		24 (55)	25 (37)		13 (48)	10 (37)	
The mean level of auditory acuity improvement for five frequencies (dB)	Median	17.5	28	0.0174	26	27	0.4159

Abbreviations: ITS, intratympanic steroid; SS, systemic steroid.
Notes: The cure rate was significantly higher in the systemic steroid group than in the intratympanic steroid group ($p = 0.0191$), with similar findings after propensity score matching ($p = 0.0461$).

Table 3 Patient background characteristics after propensity score matching

		After propensity score matching		
		ITS group ($n = 27$)	SS group ($n = 27$)	*p*-Value
Age (y)	Median (range)	73 (35–93)	71 (48–84)	0.3818
Affected side, *n* (%)	Right	11 (38)	15 (56)	0.2127
	Left	16 (62)	12 (44)	
Sex, *n* (%)	Male	15 (56)	15 (56)	1
	Female	12 (44)	12 (44)	
Number of days from onset to treatment initiation (days)	Median (range)	4 (1–13)	5 (0–10)	0.4734
Number of days from treatment initiation to outcome assessment (days)	Median (range)	35 (7–411)	27 (4–271)	0.2461
Auditory acuity on the affected side at the initial examination (dB)	Median (range)	67 (36–106)	71 (37–111)	0.7098
Auditory acuity on the healthy side at the initial examination (dB)	Median (range)	27 (4–83)	24 (9–104)	0.8557
Severity, *n* (%)	G1	2 (7)	2 (7)	0.9701
	G2	8 (30)	6 (22)	
	G3	12 (44)	14 (52)	
	G4	5 (19)	5 (19)	
Dizziness, *n* (%)	Present	6 (22)	5 (19)	0.7355
	Absent	21 (78)	22 (81)	
History of steroid therapy administered by the previous physician, *n* (%)	Present	3 (11)	4 (15)	0.6854
	Absent	24 (89)	23 (85)	
Diabetes, *n* (%)	Present	11 (41)	11 (41)	1
	Absent	16 (59)	16 (59)	

Abbreviations: ITS, intratympanic steroid; SS, systemic steroid.
Notes: The significant differences observed before the adjustment in patient background characteristics, including age, auditory acuity on the healthy side at the initial examination, the presence or absence of the history of steroid therapy administered by the previous physician, and the presence or absence of diabetes, disappeared after propensity score matching.

the cure rate in the SS group was significantly higher than that in the ITS group.

In contrast, compared with the SS group, in terms of patient background characteristics, the ITS group had more number of older patients and patients with poorer auditory acuity in the unaffected ear, which may have influenced the treatment. According to a Japanese nationwide epidemiological survey by the Research Group on Intractable Hearing Impairment,[12] advanced age (≥65 years) is an independent factor of treatment resistance.

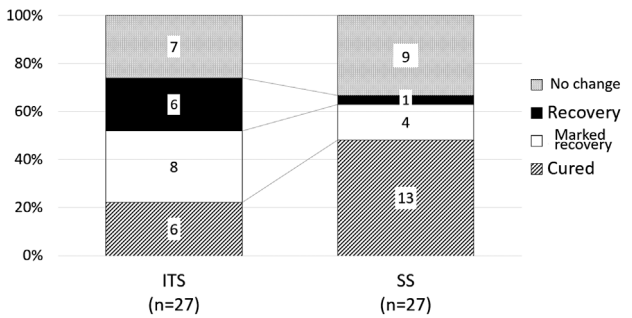

Fig. 2 A comparison of treatment outcomes after propensity score matching. The cure rate was significantly higher in the systemic steroid group than in the intratympanic steroid group.

In the ITS group, the rate of the presence of diabetes was high; the physician at the previous clinic may have been reluctant to administer SS therapy. Bae et al reported that the rate of diabetes was higher in the ITS monotherapy group than in the SS combination therapy group and that ITS was administered to only a subset of patients.[13] Therefore, a comparative study was performed after patient background characteristics were adjusted using PSM, and a significantly higher cure rate was found in the SS group than in the ITS group.

Based on our literature review, eight randomized controlled trials compared ITS monotherapy with SS therapy as primary treatments.[3–10] Of them, one study reported superiority of ITS therapy, whereas the other seven reported noninferiority of ITS therapy (see ►**Table 4**). At first glance, they seem to contradict the results of the present study. However, the criteria for auditory acuity recovery in those

Table 4 A randomized controlled trial comparing intratympanic steroid injection therapy and systemic steroid therapy as primary treatments

Reference	Number of patients (ITS/SS)	Steroid, dose	Administration method	Complications	Auditory acuity improvement index	Improvement rate	Statistically significant difference
Battaglia et al[4]	17/18	DEX (0.5–0.7 mL, 12 mg/mL)	Once/week for three doses	None	PTA > 15 dB	59%	Yes
Hong et al[5]	32/31	DEX (0.3–0.4 mL, 5 mg/mL)	Administered for 8 consecutive d	None	PTA > 15 dB	Not mentioned	No
Dispenza et al[6]	25/21	DEX (4 mg/mL)	Four doses over 4 wk	Not mentioned	PTA > 10 dB	80%	No
Rauch et al[3]	129/121	mPSL (40 mg/mL)	Four doses over 2 wk	Earache (54%) Tympanic perforation (3.9%)	PTA > 10 dB	77%	No
Lim et al[7]	20/20	DEX (0.3–0.4 mL, 5 mg/mL)	Four doses over 2 wk	Not mentioned	PTA > 10 dB	55%	No
Swachia et al[8]	20/22	mPSL (40 mg/mL)	Administered twice a week for four doses	Earache (35%)	PTA > 10 dB	80%	No
Tsounis et al[9]	34/35	mPSL (62.5 mg/mL)	Four doses over 10 d	None	PTA > 15 dB	71%	No
Ermutlu et al[10]	19/16	DEX (0.5–0.7 mL, 4 mg/mL)	Three doses over 5 d (following ear pressure-relieving perforation)	Dizziness (21%)	PTA > 10 dB	84%	No

Abbreviations: DEX, dexamethasone; ITS, intratympanic steroid; mPSL, methylprednisolone; PTA, pure-tone average; SS, systemic steroid.

studies were defined as ≥10 to 15 dB on pure tone audiometry, which correspond to recovery or higher when assessing the treatment outcome of ISSHL in Japan. That is, if we consider the findings of the present study using the aforementioned conditions, we can assume that the rates of auditory acuity recovery in the ITS and SS groups (64 and 71%, respectively) were not bad at all. In Japan, some studies reported high rates of improvement of 84.0%[14] and 60.0%[15] when using ITS monotherapy as a primary treatment, with a marked recovery or greater defined as improved auditory acuity. However, in routine clinical practice, even among patients with a marked recovery, some patients, such as those with profound hearing loss, may report insufficient subjective improvement in hearing loss.

Based on these results, we hypothesize that SS therapy is preferable as the primary treatment for young patients and those who are not at risk for complications from SS therapy. Conversely, we believe that ITS monotherapy is a viable treatment option for older patients, patients with psychiatric disorders, and patients at high risk for complications from SS therapy, such as pregnant women.

Intratympanic Steroid Treatment Protocol

Globally, DEX is generally administered at a dose of 4 to 5 mg/mL, and although the number of doses and interval between doses of DEX vary, it is administered for a total of three to eight doses on consecutive days or at intervals of a few days.[3–10,16–18] In Japan, DEX is administered at a dose of 3.3 mg/mL for 8 consecutive days[14] or as 3 to 16 doses every 2 days (a mean of 8 doses).[15] Although the dose concentration in our study was slightly lower than that used worldwide, there was not much difference in dosing intervals or number of doses. In the present study, the number of doses ranged from 2 to 4, and 91% of patients received 2 doses with a dosing interval of 3 to 12 (median, 7) days. Treatment was given at approximately 2-day intervals owing to the concerns of ongoing tympanic membrane perforation. However, the actual residual perforation rate was comparable to that in the existing reports (details are provided in the "Residual Tympanic Perforation" section). Therefore, if the improvement in auditory acuity is small, it is possible to consider increasing the number of doses.

Residual Tympanic Perforation

ITS therapy is generally provided using devices, for example, via tube placement[19] and lasers.[14] However, tympanocentesis is performed commonly, and the incidence of residual perforations ranges from 3.9 to 5.6%,[3,15,20,21] which is comparable to that reported in the present study. Regarding the use of tube and tympanocentesis, the tube method readily causes perforation, with a significant difference.[22] Therefore, tympanocentesis should be considered in cases where avoiding the risk of persistent perforation (e.g., to avoid puncture pain) is a priority.

At our institution, in cases where a thin crust is attached to the tympanic membrane, the timing of the subsequent dose administration is slightly postponed, and if possible, a puncture at the same site is avoided. According to some

studies, a delayed perforation occurs between 1 and 4 months after puncture.[21,23] Therefore, even if an improvement in auditory acuity is noted, a follow-up for a few months is recommended. However, in Japan, complications other than tympanic perforation, such as temporary dizziness and self-manageable earache, are not considered serious and are rarely reported.[17]

The present study has some limitations. First, this was a retrospective study with a small sample size. Second, four patients in the ITS group received secondary treatment following steroid therapy by their previous physician.

Conclusion

This study compared the effectiveness of ITS and SS therapy as primary treatments for ISSHL. The cure rate was significantly higher in the SS group than in the ITS group.

Conflicts of Interest
None declared.

Acknowledgments
None.

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