



Original Article

Evaluation of Adjuvant Intratympanic Dexamethasone Administration in the Treatment of Sudden Sensorineural Hearing Loss

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OBJECTIVE: The treatment of idiopathic sudden sensorineural hearing loss (ISSHL) depends mainly on the steroids, and there is an increasing number of studies about not only systemic usage but also local administration of steroids to the target organ. The aim of this study is to determine the effects of intratympanic steroid (ITS) administration as adjuvant to systemic steroid (SS) treatment in the management of ISSHL.

MATERIALS and METHODS: Seventy-nine patients (41 F, 38 M) with a mean age of 48.2 years were included in the study. The data were collected by retrospective analysis of the patient records. The hearing levels of 36 patients treated with only SS (group I) and 43 patients treated with SS and ITS concomitantly (group II) were evaluated with pure tone audiometry tests at 500, 1000, 2000, 4000, and 8000 Hz frequencies in the pre-treatment period and 1 and 3 months after treatment.

RESULTS: The mean values of hearing thresholds in the audiometry performed in the pretreatment period and 1 and 3 months after treatment in the SS treatment group were 52.2 ± 20 , 39.5 ± 25.3 , and 35.3 ± 25.3 , respectively, while in the IT+SS treatment group, these values were determined as 60.7 ± 19.9 , 38.3 ± 23.8 , and 33.2 ± 22.7 , respectively. The improvements in mean hearing thresholds by time were statistically significantly different between the 2 groups ($p < 0.05$).

CONCLUSION: Among patients with ISSHL, it has been determined that initial SS treatment with concomitant ITS administration may improve the hearing gain. This improvement was more notable in patients with non-profound hearing loss.

KEY WORDS: Hearing loss, sudden, transtympanic treatment

INTRODUCTION

Sudden sensorineural hearing loss is defined as the development of sensorineural type hearing loss of 30 dB or more in 3 consecutive frequencies in 72 hours^[1]. Its annual incidence in the population is 5-20 cases in 100,000, and this condition is generally idiopathic and unilateral, with an equal distribution among genders. Although it may be determined in all age groups, it is most commonly reported in between the ages of 40-53 years^[2]. Its treatment is still controversial. Since spontaneous healing ratios are high among untreated patients (32% to 65%), the comparison and standardization of the efficacies of different treatment modalities are difficult^[3]. Even though there is no universally accepted standard protocol in the treatment of ISSHL currently, after the study of Wilson in 1980, the most commonly established treatment modality has been steroids^[3,4]. The success rates of SS treatment range from 49% to 79%. The exact mechanism of how steroids may improve hearing is still unknown. It has been thought that steroids act mainly by reversing the inflammation in the internal ear. Moreover, they may have the effects of stabilizing endolymph hemostasis by a mineralocorticoid effect, improving stria vascularis functions and potentially cochlear blood flow^[3,5]. Intratympanic usage of steroids is increasing in recent years. While this modality was established in patients who do not respond to SS or as salvage treatment in whom SS treatment has many risks, it was later reported that initial ITS treatment may also be successful alone^[6]. ITS administration was proven for 2 reasons: first, the drug may reach the perilymph with high concentrations through direct passage to the internal ear by way of the semipermeable round window, and second, by this way, the systemic side effects of SS administration, especially in risky patients, is avoided. In animal studies of Chandrasekhar and Parnes et al.^[7,8], steroids were determined to reach higher concentrations in the internal ear with local application compared with systemic use. Also, ITS treatment may have a longer therapeutic window (6 weeks for IT and 10-14 days for oral steroids). Since it may decrease the excretion of systemic inflammatory mediators, its effect is thought to be increased in combined treatment^[7-9]. The aim of this study is to report our experience on the effects of ITS administration, concurrent with SS treatment, in the management of ISSHL.

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MATERIALS and METHODS

The data of this study were obtained through retrospective screening of the records of hospitalized patients with a diagnosis of ISSHL in Ege University Hospital between January 2008 and December 2013. It was approved by the ethical committee of Ege University Hospital (B.30.2.EGE.0.21.05.00/EY/86-64). Patients with tympanic membrane or middle ear pathologies in the micro-otoscopic examination, patients with a history of fluctuating hearing loss, patients who experienced middle-ear surgery, oncology patients, patients treated with chemotherapy, patients with a history of radiotherapy to the head and neck region or exposed to ototoxic agents, those with a history of acoustic trauma or barotrauma, pregnant patients, patients with a history of any treatments for SSHL, patients treated with a different modality other than the standard protocol of our clinic, and patients with incomplete records in the follow-up were excluded from the study. While involving patients for this study, exclusion due to the presence of hypertension, diabetes, vertigo, or tinnitus or according to the severity of hearing loss was not performed. The data of 79 cases with complete records and treated with standard protocols were analyzed. All patients were informed about the ISSHL treatment protocols applied in our clinic, the advantages or disadvantages of these modalities, and their complications. Concomitant ITS application with SS treatment was advised to all patients. The treatment of patients who accepted SS with or without ITS application was managed after obtaining their verbal and written consent.

A total of 36 patients treated with only SS were included in group I, and 43 patients treated with concomitant ITS application and SS were involved in group II, and the treatment outcomes of these 2 groups were compared. In the SS treatment protocol, methylprednisolone was applied in 500 cc 5% dextrose over 2 hours intravenously for 10 days. Its initial dose was 1 mg/kg (maximum 80 mg), and this treatment was disrupted on the 10th day by decreasing the dose once every other day.

In the standard ITS administration, 4 mg/mL dexamethasone was applied and started on the same day as SS treatment. Injection was performed with the patients in the supine position with the head turned to the healthy ear at an angle of 45° under oto-microscopic view without anesthesia from the posteroinferior quadrant with a 22-gauge needle and 1-mL syringe until the tympanic cavity was fully filled. After injection, patients were told not to move for 20 minutes in the same position and not to gulp as much as possible in order to avoid leakage from the Eustachian tube. Patients were recommended not to swallow their saliva and to pour out their saliva to an emesis basin, put just near their mouth. The same procedure was applied 3 times, once every other day. During ITS application, dry ear precautions were recommended to the patients. Bed rest and a salt-restricted diet were endorsed to all patients.

In the pure tone audiometry test applied 1 and 3 months after the end of the treatments, the hearing thresholds were measured at 500, 1000, 2000, 4000, and 8000 Hz frequencies. In the evaluation of the success of the ISSHL treatments, different criteria, which are not yet widely accepted, were used. Generally, a minimum 20-dB gain in pure-tone average (PTA) is regarded as significant success in studies^[3]. In this study, a minimum 20-dB gain in PTA, determined in different times, was regarded as a positive response to the treatment. PTA was

calculated as an average of the measured thresholds at 500, 1000, and 2000 Hz frequencies.

Treatment response may diminish with increased severity of hearing loss. In the literature, it has been reported that the prognosis may be worse though salvage treatment among ISSHL patients with initial profound hearing loss^[10]. According to the grades of hearing impairment of the World Health Organization, hearing threshold levels of more than 80 dB on average are regarded as profound hearing loss^[11]. In this study, the treatment response of patients with an initial PTA of greater than 80 dB was evaluated separately.

Statistical Analyses

The statistical analyses of data were performed with the Statistical Package for the Social Sciences (SPSS) for Windows, version 17.0 (SPSS Inc., Chicago, USA). In the analysis of variance of hearing thresholds in the audiometry in the pretreatment period and 1 and 3 months after the treatment in each group and among all patients, one-sample t-test was used, and in the analysis of the significance of these variations between groups, independent-samples t-test was used. The association of data with age, gender, and vertigo was analyzed with independent-samples t test. In the analysis of hearing threshold alterations with audiogram type, one-way ANOVA test was used. The evaluation of treatment response of patients with an initial hearing level of greater than 80 dB and the analysis of differences between groups were performed with chi-square and Mann-Whitney U-tests. The statistical significance level was regarded as $p < 0.05$.

RESULTS

The data of 79 patients (41 F, 38 M) were analyzed in the study. In group I, 21 (58%) of 36 cases were female, while 15 (42%) were male, and in group II, 20 (46.5%) of 43 cases were female, while 23 (53.5%) were male. There was no significant difference between groups in regards to gender ($p=0.49$). The mean ages were similar in both groups. The mean age of group I was 48.1 ± 14.4 (min 13, max 76 years) years and 48.4 ± 14.0 (min 21, max 78 years) years in group II. In this study, there were 16 patients present, 8 in each group, older than the age of 60 years. There was only one patient in this study younger than the age of 20 years, and he was included in group I.

Vertigo was present on admittance in 5 (13.8%) cases in group I and in 7 (16.2%) cases of group II. There was no significant difference in regards to the presence of vertigo on admittance between groups ($p=0.745$).

When the time that passed between the beginning of hearing loss and start of treatment was evaluated, this period was 3.9 ± 2.6 (min 1, max 13) days in group I and 3.6 ± 2.5 (min 1, max 11) days in group II, and there was no significant difference between groups in regards to this parameter ($p=0.724$).

The mean IT dexamethasone dose administered in each intervention was 0.44 ± 0.12 mL in group II.

The mean values of initial hearing threshold before the treatment were 52.2 ± 20.0 in group I and 60.7 ± 19.9 in group II, and there was no statistically significant difference between groups in this regard ($p=0.612$). The distribution of hearing threshold levels measured at

500, 1000, 2000, 4000, and 8000 Hz frequencies with audiometry between groups in the pretreatment period and 1 and 3 months after treatment is summarized in Table 1. The distribution of alterations in mean hearing threshold level according to the frequencies in groups I and II in time is shown in Figure 1.

When the hearing threshold values 1 and 3 months after treatment compared with the pretreatment values and the alterations (Δ Value) were investigated (Table 2), it was determined that in both groups and in all patients, there was a statistically significant decrease after treatment ($p=0.00$). When the 2 groups were compared in regards to these differences (Δ values), improvements in the concomitant ITS group (group II) were significantly better than those of group I (Table 2). However, a statistical significance between groups was not present in alterations in the 1-month results compared with pretreatment values at 4000 Hz frequency ($p=0.086$) or in alterations in 1-month

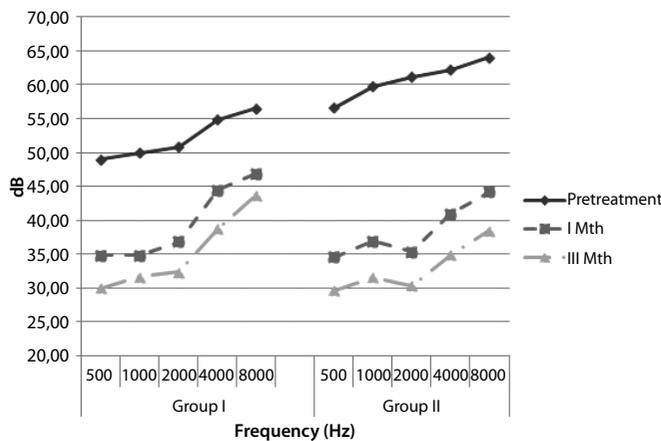


Figure 1. The alterations in mean hearing threshold levels in time according to frequency

Table 1. The distribution of hearing threshold levels according to time, frequency, and group

	F (Hz)	Group I	Group II	Overall
Pretreatment	500	49.03±22.80	56.63±23.55	53.16±23.37
	1000	50.00±22.42	59.77±21.96	55.32±22.57
	2000	50.83±21.46	61.16±20.87	56.46±21.63
	4000	54.86±22.34	62.21±22.34	58.86±22.50
	8000	56.53±23.57	64.07±22.92	60.63±23.37
Month 1	500	34.86±28.47	34.53±24.64	34.68±26.28
	1000	34.86±28.75	36.98±25.26	36.01±26.75
	2000	36.81±28.59	35.35±25.48	36.01±26.78
	4000	44.44±26.85	40.93±27.41	42.53±27.04
	8000	46.94±26.87	44.19±28.32	45.44±27.53
Month 3	500	30.00±27.15	29.65±24.33	29.81±25.49
	1000	31.67±28.66	31.63±24.07	31.65±26.09
	2000	32.36±27.71	30.35±24.36	31.27±25.79
	4000	38.75±27.32	34.88±24.43	36.65±25.69
	8000	43.75±27.11	38.49±26.96	40.89±26.98

F: frequency. Values are expressed as mean±SD in dB

results compared with pretreatment values at 8000 Hz frequency ($p=0.077$).

There were no statistically significant associations between age ($p=0.368$), gender ($p=0.467$), or presence of vertigo in the pretreatment period ($p=0.546$) or alterations in hearing threshold level (in terms of PTA) in time.

The number of patients in whom a 20-dB hearing gain (in terms of PTA) was determined 1 month after treatment was 14 (38.8%) in group I and 24 (55.8%) in group II. On the other hand, in the 3-month evaluation, the number of those patients was 19 (52.7%) in group I and 30 (65.2%) in group II. When groups were compared in regards to the number of patients with a 20-dB hearing gain in PTA in the 1st and 3rd months, there were statistically significant differences in favor of group II ($p=0.039$ for the 1-month evaluation and $p=0.028$ for the 3-month evaluation).

There were 13 patients (16.6%) with an initial hearing level of greater than 80 dB. Among them, 5 (13.9%) were in group I while 8 (18.6%) were in group II. There was no statistically significant difference in regards to the distribution of these patients among groups. Initial 1- and 3-month mean hearing threshold levels of these patients were 89.6 ± 7.6 , 79.3 ± 25.4 , and 77 ± 27.3 in group I and 90.7 ± 8.8 , 81.2 ± 26.3 , and 79.8 ± 28.3 in group II, respectively. This decrease was not statistically significant for either group ($p=0.22$ for group I, $p=0.16$ for group II). Two patients in group I and 4 in group II among these patients had a hearing recovery (min 20-dB hearing gain) in the 3-month evaluation, and there was no significant difference between groups ($p=0.094$).

For both groups, hearing recovery among patients with an initial hearing level of lower than 80 dB was statistically significantly better than in patients with an initial hearing level of greater than 80 dB ($p=0.000$). There was no significant difference in this point between groups I and II ($p=0.98$).

Table 2. The distribution of alterations in hearing threshold levels in time according to frequency and group

	F (Hz)	Group I	Group II	p
A	Δ 500	14.17±16.71	22.09±18.17	0.010
	Δ 1000	15.14±16.88	22.79±18.59	0.013
	Δ 2000	14.03±15.94	25.81±19.24	0.002
	Δ 4000	10.42±14.56	21.28±20.85	0.086
	Δ 8000	9.58±13.22	19.88±21.17	0.077
B	Δ 500	19.03±17.68	26.98±20.00	0.006
	Δ 1000	18.33±18.97	28.14±19.61	0.018
	Δ 2000	18.47±18.74	30.81±18.83	0.002
	Δ 4000	16.11±18.48	27.33±22.13	0.001
	Δ 8000	12.78±16.54	25.58±23.20	0.004

A: difference between average of 1-month and pretreatment values; B: difference between average of 3-month and pretreatment values; F: frequency. When the p-value was <0.05, the difference was regarded as statistically significant between groups. Values are expressed as mean±SD in dB

When all patients (n: 79) were investigated according to the type of audiogram curve before the treatment, 42 (53.2%) of them had flat, 26 (32.9%) had down-sloping, and 11 (13.9%) had up-sloping curves. At the end of the 3rd month after treatment, mean hearing gain was 26.6±21.2 dB in patients with plain-type audiograms, while this level was 17.6±14.3 dB in patients with down-sloping-type audiograms and 18.8±15.4 dB in patients with up-sloping-type audiograms. In the investigation of patients according to the curve type, in the comparison of alterations between the pretreatment period and 3-month levels, there was a statistically significant difference at 500, 4000, and 8000 Hz frequencies (p=0.021, 0.018, and 0.032, respectively). The alterations determined by time according to the type of curve are shown in Figure 2.

When patients were evaluated in regards to the complications that developed after ITS application, vertigo was reported in 5 cases lasting for 1-2 minutes during injection; however, more severe vertiginous symptoms, such as nausea and vomiting, were not reported. Patients expressed that they did not feel pain more severe than the administration of intramuscular injection. Otitis media, otorrhea, and sustained or transient tympanic membrane perforations were not recorded in any of the cases after ITS application.

DISCUSSION

The etiology, pathophysiology, and treatment of ISSHL still continue to be discussed currently, and ISSHL is one of the most challenging issues of otolaryngology. With many different treatment modalities studied at present, systemic steroid treatment has been the most commonly used modality. But, there have been few randomized studies on this topic. The treatment ratios of ITS in ISSHL changes range largely between 12% and 100%^[12]. Type of steroid, way, dose, time, and frequency of administration; the passage ratios of steroids to the inner ear; factors belonging to the patients; low number of patients involved in some studies; and subjectivity of criteria determining recovery may be responsible for this large range.

The 3 protocols of ITS administration are: as a first-line therapy without SS, as a concomitant treatment to SS, and as salvage treatment among cases with unsuccessful previous SS treatments. Many of the ITS studies in the literature are as salvage treatment among cases that are unresponsive to initial SS treatment. Haynes et al.^[3], Plaza et al.^[13] and Dispenza et al.^[14], reported that in cases that are unresponsive to SS-only treatment, ITS applied as salvage treatment is effective.

The data about ITS usage as a primary initial therapy are consid-

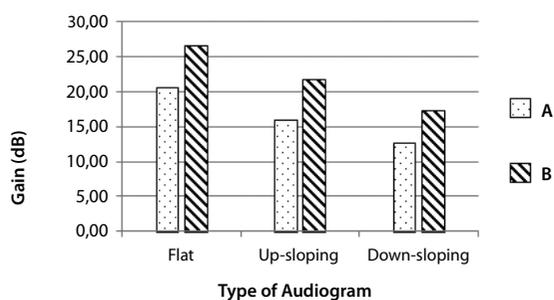


Figure 2. Mean gain of hearing threshold levels according to audiogram type A: difference between average of 1-month and pretreatment values; B: difference between average of 3-month and pretreatment values

erably unsatisfactory. In 2 studies comparing only SS and only ITS treatments, although Kara et al.^[15] determined ITS to be more effective, Hong et al.^[16] did not determine any differences. In a study in which ITS was given as a primary initial treatment (methylprednisolone, twice a week for 2 weeks), Labatut et al.^[17] reported this method as a safe, effective, and well-tolerated office-based procedure.

About the local administration of steroids, myriad different application protocols (timing, dosing, frequency, duration, and number of injections) have been offered. The mainly defined application methods include injection, ventilation tube, Microwick, microcatheter, endoscopic and laser-assisted myringotomy^[3, 12]. In this study, the injection method was applied, because it is less invasive than other methods, cost-effective, easily performable, well tolerated, and safe. However, there is no standard dose, frequency, or time of ITS application. In the literature on the injection method, dexamethasone has been used at 0.3 to 0.7 mL in amounts in each time, a dosage at once or multiple dosages, with different frequencies or times of reaching 4 weeks period^[3, 6, 12]. The mean dose of dexamethasone used in this study was 0.43 mL, and it was compatible with the literature. It is warranted to standardize the application way, frequency, time, and dosages of steroids applied in ISSHL treatment.

There are some doubts in the literature about the type of steroid used in IT treatment. The most commonly used agents are dexamethasone and methylprednisolone, and the superiority of one of them to the other has not been reported. In an animal study of Parnes et al.^[8], it was determined that MP passes to the perilymph in high concentrations and stays there for a long time. However, as shown in the study of Hargunani et al.^[18], dexamethasone may be measured in low amounts, since it binds to the receptors in the internal ear more commonly, and the ratios of its free form decrease, which in turn may cause dexamethasone to be more effective, theoretically. Moreover, in many patients, a burning sensation is reported in the ear and throat after MP injections. This condition may frustrate the patients' concordance and may be a reason of the disruption of treatment. In order to avoid this side effect, the addition of lidocaine to the injection has been experienced, but the effects of this combination on the internal ear are not known, and since annoying interactions may be seen, some authors do not recommend this application. Since dexamethasone is one of the steroids with very potent anti-inflammatory effects, it seems to be a suitable option. In this study, dexamethasone was used in the ITS application.

There are few studies evaluating the efficacy of combined initial IT+SS therapy. In a multicenter, double-blinded, placebo-controlled study of Battaglia et al.^[19], with only high-dose prednisone, only IT dexamethasone (once a week for 3 weeks), and their combination, it was determined that the combination treatment resulted in more hearing gain than others. In a randomized, prospective study, Arslan et al.^[20] reported that SS+IT methylprednisolone (0.5 mL, every other day, 5 injections) may increase the healing ratios. On the other hand, in a study of Ahn et al.^[21] comparing 0.3 mL IT dexamethasone application on 1, 3, and 5 days concomitant with SS with only SS treatment, they reported that ITS treatment concomitant with SS does not cause significant improvement. In a prospective, randomized, controlled trial of Park et al.^[22], IT dexamethasone treatment concomitant with SS was compared with ITS administration after SS treatment and was

not different in regards to hearing recovery. The results of our study indicate that ITS administration concomitant with SS significantly improves hearing recovery.

There are many factors that may affect the prognosis in ISSHL. The main factors for worse prognosis include childhood or advanced age groups, a time period of longer than 2 weeks from the beginning of hearing loss until the treatment, profound hearing loss, presence of vertigo, and hearing loss in high frequencies [4, 6, 10, 12]. Although there were few patients, a significant association of advanced age with treatment success could not be determined in this study. Since there was only 1 patient younger than the age of 18 years, this evaluation could not be performed. In all evaluated patients, treatment was started in the first 2 weeks after the beginning of hearing loss (3.7±2.5 days), and because of this reason, the effects of a delay in treatment on hearing gain could not be evaluated.

Initial profound hearing loss is considered as a factor of worse prognosis [10]. Lautermann et al. [23] reported that in ISSHL patients with severe hearing loss, ITS treatment adjuvant to SS resulted in significant improvements in treatment success. Similarly, in our study, it was determined that in patients with an initial hearing level of greater than 80 dB, the prognosis was worse, and ITS application did not have significant benefits in this patient group.

The effects of the audiogram pattern in hearing recovery have been studied before. It has been suggested that patients with up-sloping-type audiogram curves (distinct hearing loss at low frequencies) respond better to treatment, while patients with down-sloping-type audiogram curves (major hearing loss at high frequencies) have a worse prognosis [4, 12]. The theoretical reason of this may be that the basal part of the cochlea may be more sensitive to ischemia and that locally administered steroid may affect the basal part of the cochlea to a lesser degree after passing the round window membrane. We also determined better hearing recovery among patients with up-sloping-type audiograms. When response to treatment was investigated, no association between ITS administration and audiogram type was determined.

Although there is no known major complication of ITS administration, the most commonly reported adverse effects include transient otalgia, vertigo, otorrhea, and small tympanic membrane perforations [3, 24]. In this study, no complications other than short-lasting vertigo and otalgia in a few patients were reported.

When the handicaps of studies about ISSHL treatment in the literature are evaluated, most of them are not randomized, double-blinded, or placebo-controlled. Since steroids have been used at different types, dosages, times, frequencies, and ways and since treatment responses were evaluated with different criteria, the results of these studies can never be compared.

The primary constraints of this study were the low number of patients and retrospective design. The statistical results might be a consequence of the limited number of patients recruited and retained in this study, and this factor might not allow us to show the beneficial effects of ITS in ISSHL sufficiently. Prospective, randomized, double-blind studies with more samples are suggested.

In the light of the data obtained in this study, in ISSHL patients admitted in the first 2 weeks, combined systemic and intratympanic steroid treatment may be suggested as an initial treatment, since it may improve hearing recovery, especially patients with non-profound hearing loss. There are many hanging questions about the role of ITS in ISSHL treatment waiting to be answered. Large-scale studies are warranted in order to standardize the way, dosages, frequencies, and time of steroid administration and recovery evaluation criteria in those patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University (B.30.2.EGE.0.21.05.00/EY/86-64).

Informed Consent: Written informed consent was not obtained due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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