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Therapeutic Efficacy of the Combination of Intratympanic Methylprednisolone and Oral Steroid for Idiopathic Sudden Deafness

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Abstract

Objective. The purpose of this study was to compare the efficacy of systemic steroid alone and combined with intratympanic methylprednisolone in the treatment of patients with idiopathic sudden sensorineural hearing loss.

Study Design. Prospective, randomized controlled trial.

Settings. Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey.

Subject and Methods. Seventy-nine patients who met the inclusion criteria for idiopathic sudden sensorineural hearing loss were included in this study. Patients were randomly divided into 2 groups according to treatment: group A received combination therapy (intratympanic methylprednisolone + oral steroid) and group B received oral steroid alone. Of the 79 patients included, 6 patients missed the 1-month follow-up visit. Overall, 73 patients (37 combination group, 36 oral steroid group) who completed the 1-month follow-up and study intervention were included in the per-protocol analysis. Both the relationship between certain prognostic factors and the clinical outcome after treatment were analyzed.

Results. Combination therapy showed significant hearing improvement and speech discrimination scores compared with the use of systemic steroids alone ($P < .05$). In hearing outcomes in patients with severe hearing loss, combination therapy had statistically significant hearing improvement compared with oral steroid alone ($P < .05$).

Conclusion. We recommend that combination therapy can be considered as initial treatment especially for patients with severe hearing loss.

Keywords

idiopathic sensorineural hearing loss, intratympanic steroids, combination therapy

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as greater than 30 dB in at least 3 consecutive frequencies within 3 days or less.[1] The incidence varies between 5 and 20 in 100,000 cases. Although the exact cause of ISSNHL is still controversial, the main theories include viral infection of the labyrinth, vascular insult, perilymphatic fistula, and autoimmunity. Spontaneous recovery in untreated patients ranges from 32% to 65%.[2] Prognosis of the disease depends on various factors, such as severity of hearing loss at the time of diagnosis, treatment delay time, age, presence of vertigo, and type of hearing loss.[3]

The lack of consensus in the management of ISSNHL is due to difficulty in finding the real etiology of the hearing loss. Numerous treatment protocols have been reported for many years, including steroids, vasodilators, antiviral agents, anticoagulants, hyperbaric oxygen, and carbogen.[4-6] The most commonly used therapy is steroid therapy. Steroids can be administered either through an oral route or intratympanic injection. Intratympanic steroid (ITS) injection has the advantage of direct steroid uptake through the round window membrane and higher perilymph steroid levels. Previous studies showed that ITS resulted in significantly higher perilymph concentrations than intravenous or oral administration.[7,8]

The purpose of this study was to compare the therapeutic efficacy of systemic steroid alone and combination with intratympanic methyprednisolone (ITMP) in the treatment of patients with ISSNHL.

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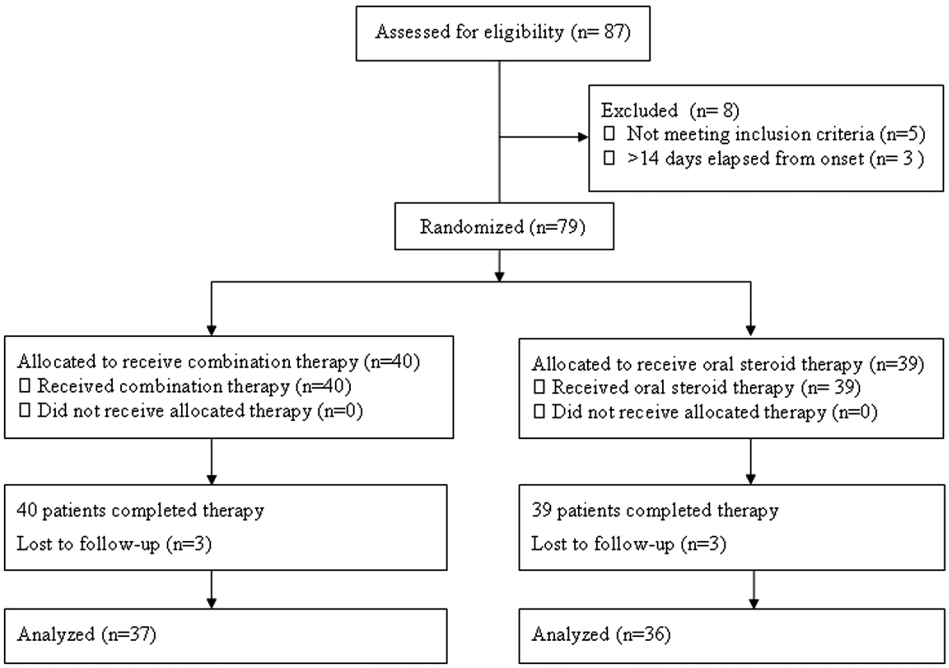

Figure 1. Patient flow diagram.

Patients and Methods

Patient Selection and Study Design

This nonblinded, randomized, controlled clinical study included 79 patients diagnosed with ISSNHL between December 2009 and January 2013. The Institutional Review Board of the Katip Celebi University approved this study, and written informed consent was obtained from each patient (2009/11-52). The inclusion criteria (eligibility criteria) of the patients were as follows: (1) unexplained sudden sensorineural hearing loss, which was defined as a sensorineural hearing loss of at least 30 dB at 3 contiguous frequencies over a period of $\leq$3 days; (2) time from the onset of hearing loss to the treatment of $\leq$14 days; (3) no initial treatment before; (4) no history of ear disease in the affected ear; (5) and unilateral sudden hearing loss. Patients with chronic otitis media, trauma, previous radiotherapy or chemotherapy, recent use of ototoxic drugs, liver or renal dysfunction, retrocochlear lesion, and interval to first treatment greater than 14 days from onset were excluded from the study. A total of 87 patients were assessed for eligibility. Eight patients were excluded for not meeting eligibility criteria. Seventy-nine patients were randomly assigned to 2 groups according to treatment: group A received ITMP + oral steroid (combination therapy), and group B received oral steroid alone. The blocked randomization was used in this study. Of the 79 patients included, 6 patients missed the 1-month follow-up visit (3 combination, 3 oral steroid group). Overall, 73 patients (37 combination group, 36 oral steroid group) who completed the 1-month follow-up visit and continued with the study intervention were included in the per-protocol analysis. A patient flow diagram is illustrated in **Figure 1**.

ITMP Therapy

ITMP was performed 4 times for 2 consecutive weeks (once every 3 days). After confirming an intact tympanic membrane, local anesthesia was administered with a cotton ball soaked with lidocaine 10% pump spray (Xylocaine, 10 mg/dose; AstraZeneca Korea, Seoul, Korea), which was applied to the tympanic membrane for approximately 10 minutes. While the patient lay in the supine position with his or her head tilted 45° to the healthy side, a perforation was made in the anterosuperior portion of the tympanic membrane with the tip of a dental syringe, and 0.4 mL of 62.5 mg/mL methylprednisolone was administered. During this procedure, patients were instructed to avoid swallowing or moving for 30 minutes.

Systemic Steroid Treatment

All patients were hospitalized for 1 week, and all were treated with a 14-day course of oral steroid (1 mg/kg of oral methylprednisolone and 10 mg taper every 3 days). Patients received proton pump inhibitors for gastrointestinal protection, and patients were instructed to avoid a diet with salt.

Audiologic Evaluation

Pure tone audiometry was performed just before every injection. Follow-up pure tone audiometry was obtained at the first, second, and fourth week. Pretreatment and posttreatment audiograms were examined, and hearing thresholds at 250, 500, 1000, 2000, 4000, and 8000 Hz were noted. Pure tone average (PTA) was calculated as an average of the threshold measured at 0.5, 1, 2, and 3 kHz. Also, speech discrimination scores (SDS) were noted. Audiograms were obtained before treatment and at the first, second, and fourth week after the initial steroid treatment.

Table 1. Demographic and clinical features of patients in combination therapy and oral steroid alone.

	Combination Therapy (n = 37)	Oral Steroid Alone (n = 36)	*P* Value
Age, y	52.32 ± 12.94	51.6 ± 16.77	.817[a]
Gender (female/male)	21/16	15/21	.197[b]
Initial PTA, dB	80.7 ± 22.81	76.3 ± 27.18	.405[a]
Initial SDS, %	29.7 ± 20.96	43.3 ± 30.71	.061[a]
Dizziness	28	27	.947[b]
Tinnitus	9	9	.251[b]
Duration time, d	4.7 ± 4.0	5.14 ± 3.52	.594[a]

[a]Mann-Whitney *U* test.
[b]χ^2 test.

Table 2. Hearing outcomes of combination therapy and oral steroid alone.

	Combination Therapy (n = 37)	Oral Steroid Alone (n = 36)	*P* Value
PTA improvement (dB) at 2 wk	41.20 ± 18.35	24.5 ± 16.27	.000
PTA improvement (dB) at 4 wk	44.05 ± 21.53	25.72 ± 19.77	.000
SDS improvement (%) at 2 wk	36.21 ± 20.06	19.85 ± 16.40	.001
SDS improvement (%) at 4 wk	41.08 ± 21.98	20.06 ± 22.69	.000

Abbreviations: PTA, pure tone average; SDS, speech discrimination score.

Evaluation Criteria

Treatment results were evaluated by pure tone audiometry, using the average hearing levels at 500-, 1000-, 2000-, and 3000-Hz frequencies. Posttreatment second- and fourth-week mean PTA was used for statistical analysis. Efficacy of treatment was also categorized according to Siegel's criteria[9] as follows:

1. Healing: final threshold more than 25 dB.
2. Partial improvement: gain of more than 15 dB, final hearing threshold 25 to 45 dB.
3. Slight improvement: gain of more than 15 dB, final hearing threshold more than 45 dB.
4. No response: gain of less than 15 dB and final hearing threshold more than 75 dB.

Statistical Analysis

All values are expressed as mean ± standard deviation. Statistical analysis was performed using SPSS 20.0 (SPSS Inc, Chicago, IL). The data normality test and homogeneity of variance test within 2 groups were done with the Shapiro-Wilk normality test. Both the relationship between certain prognostic factors (age, gender, initial PTA, initial SDS, time from onset to initial treatment, presence of vertigo, and tinnitus) and the clinical outcome after treatment were analyzed using χ^2, Mann-Whitney *U*, and Fisher exact tests. A *P* value of $<.05$ was considered significant.

Results

Seventy-three patients were included in this study. Thirty-seven patients were in group A (combination therapy), and 36 were in group B (oral steroid group). The 2 groups were well matched in terms of demographic and ISSNHL characteristics. There were no significant differences between the 2 groups in demographic, clinical, and audiologic features of the patients (**Table 1**).

Comparison of Hearing Improvement between Treatment Groups

The overall rate of hearing improvement was 89% (33/37 patients) in group A and 61.1% (22/36 patients) in group B. Group A had 4 patients (10.8%) with no recovery, 9 (24.3%) with slight recovery, 10 (27.0%) with partial hearing recovery, and 14 (37.8%) with complete hearing recovery. Group B had 14 patients (38.8%) with no hearing recovery, 5 (13.8%) with slight recovery, 7 (19.4%) with partial recovery, and 10 (27.7%) with complete hearing recovery. There was a statistically significant difference between group A and group B according to Siegel's criteria of hearing improvement (*P* = .049). The overall PTA improvements for group A and group B on the second week were 41.20 ± 18.35 dB and 24.5 ± 16.27 dB, respectively (*P* = .000). In the fourth week, PTA improvement rose to 44.05 ± 21.53 dB, whereas it was found to be 25.72 ± 19.77 dB for group B (*P* = .000). In addition, SDS improvement was significantly better in group A when compared with group B in the second and fourth week (*P* = .001 and *P* = .000; **Table 2**).

We analyzed hearing improvement in patients according to the level of initial PTA. Severe hearing loss was defined as a PTA of 70 dB or greater. Regarding the patients with severe hearing loss, group A showed a significant improvement in PTA compared with group B (*P* = .001). Furthermore, patients

Table 3. Hearing outcomes of patients with severe hearing loss.

Patients (n = 73)	Combination Therapy (n = 37)	Oral Steroid Alone (n = 36)	*P* Value
Initial PTA <70 dB (n = 29)			
PTA improvement, dB	33.08 ± 9.65	28.19 ± 17.49	.377
SDS improvement, %	32.67 ± 17.29	15.88 ± 12.82	0.08
Initial PTA ≥70 dB (n = 44)			
PTA improvement, dB	49.32 ± 23.75	24.50 ± 21.66	.001
SDS improvement, %	45.12 ± 23.13	23.40 ± 28.14	.008

Abbreviations: PTA, pure tone average; SDS, speech discrimination score.

Table 4. Hearing improvement according to the frequency between the 2 groups.

	Combination Therapy (n = 37)	Oral Steroid Alone (n = 36)	*P* Value
0-0.5 kHz			
PTA improvement, dB	38.97 ± 21.06	22.94 ± 19.80	.001
1-2-3 kHz			
PTA improvement, dB	38.49 ± 21.10	26.39 ± 19.39	.014
4-6-8 kHz			
PTA improvement, dB	39.00 ± 19.16	27.50 ± 20.06	.009

Abbreviation: PTA, pure tone average.

in group A had statistically significant improvement in SDS compared with group B patients (P = .008). Regarding the patients with initial PTA <70 dB, no significant difference was observed between the groups in terms of PTA and SDS improvement (P = .377, P = .08; **Table 3**).

When hearing improvement was analyzed according to low (0-0.5 kHz), mid (1, 2, 3 kHz), and high (4-6-8 kHz) frequencies, group A showed significant gain when compared with group B at low (P = .001), mid (P = .014), and high (P = .009) frequencies (**Table 4**).

General data regarding the prognostic factors of the treatment failure are shown in **Table 5**. Eighteen of 73 patients failed to move into the successful treatment category and were therefore defined as the nonresponsive group. Between the 2 groups, there were no significant differences in age, gender, initial PTA, SDS, time from onset to initial treatment, or presence of vertigo and tinnitus.

Complications

Three patients complained of vertigo immediately after injection, and all of these patients recovered after 2 hours of rest. Otalgia occurred in 5 patients after injection, which was relieved after 1 hour. No case of residual tympanic membrane perforation and otitis media was noted. No long-term complications resulted from either oral steroid or intratympanic steroid in any of the patients.

Discussion

Idiopathic sensorineural hearing loss remains a challenging clinical problem. Although several etiologies have been reported, most of the treated cases are considered to be idiopathic. Systemic steroid therapy is a common treatment modality, with a reported success rate between 5% and 89%.[4,8,10] Steroids have many effects in the inner ear. Supression of immune response, improvement of decreased microvascular circulation, mineralocorticoid effects, or decrease in endolymphatic pressure are the effects of the steroids.

Silverstein et al[11] first applied the intratympanic steroid injection as treatment of ISSNHL, followed by other authors. Most of the studies showed the efficacy of intratympanic steroids as an initial treatment for ISSNHL or as a salvage therapy for the refractory ISSNHL patients.[12-14] Local administration of steroids offers the potential for direct delivery of high concentrations of steroid to the inner ear. Intratympanic steroid can be used alone or as a combination with systemic steroids in the treatment of ISSNHL. Rauch et al[15] performed a multicenter, prospective, and randomized study comparing the effectiveness of oral versus intratympanic steroid in patients with ISSNHL. The authors showed that intratympanic treatment was not inferior to oral steroid in hearing recovery, and therefore they concluded that it is a suitable alternative to oral prednisone.[15] In the current study, we compared the effectiveness of the combination therapy and systemic steroid alone in the treatment of ISSNHL. The combination therapy showed significant hearing improvement and SDS compared with the systemic steroids alone at all frequencies in our study. Similar to our findings, Battaglia et al[16] and Koltsidopoulos et al[17] demonstrated that combination therapy had a higher likelihood of hearing recovery than those treated with oral steroid alone. However, combined

Table 5. Analysis of prognostic factors affecting the responsiveness between 2 groups.

Nonresponsive Patients (n = 18)	Combination Therapy (n = 4)	Oral Steroid Alone (n = 14)	*P* Value
Age, y	53.10 ± 12.24	52.45 ± 11.46	.642
Gender, female/male	2/2	6/8	.822
Initial PTA, dB	104.50 ± 6.40	85.36 ± 8.20	.221
Initial SDS, %	14.00 ± 8.00	24.29 ± 18.05	.092
Duration time, d	7.00 ± 5.03	6.00 ± 3.78	.748
Tinnitus	3	11	.880
Vertigo	1	3	.820
PTA improvement, dB	12.75 ± 5.25	7.07 ± 4.00	.070
SDS improvement, %	25.00 ± 44.82	8.00 ± 7.01	.785

Abbreviations: PTA, pure tone average; SDS, speech discrimination score.

treatment did not result in significant improvements in the studies by Ahn et al[18] and Lim et al.[19]

The results of this study indicate that the combination of ITMP and systemic steroids led to statistically significant hearing and SDS improvements in patients with severe ISSNHL. Steroids have both local effects (by directly influencing the inner ear) and systemic effects (by indirectly influencing the inner ear by systemic immunosuppression). The actions attributed to local steroids in the inner ear include ion homeostasis, antioxidant action, and downregulation of local proinflammatory cytokines. Among the systemic effects of steroids not achievable with intratympanic steroids are a decrease in the number of circulating blood leukocytes and inhibition of the formation of inflammatory mediators. Intratympanic steroids may not prevent systemwide immune responses from affecting the inner ear. These observations suggested that combination therapy would produce greater improvements in hearing than systemic steroids alone. In this study, combination therapy provided better hearing outcomes in patients with severe to profound hearing loss. In examining our data, we can speculate that combination therapy can be considered as the initial treatment in patients with severe to profound hearing loss. This subgroup analysis has not been shown throughout the literature. This is the main finding of this study.

The frequency-related hearing improvement has been studied in some previous studies. Lee et al[20] observed a significant hearing improvement only at a low frequency (0.5 kHz) with intratympanic steroid. Similarly, Ahn et al[18] showed greater hearing improvement only at 250 Hz with combination therapy. This phenomenon may be explained by the concentration of the steroids passing through the round window possibly being decreased from the base to the apex of the cochlea. In addition, apical hair cells are more resistant to toxic stimuli, including ototoxic drugs and noise, than basal hair cells. Hair cells in the apical turn may have a greater recovery ability.[21] However, combination therapy showed greater hearing and SDS improvement at all frequencies in our study.

We analyzed and compared the demographic and clinical characteristics of the nonresponsive patients between 2 treatment groups. Eighteen of 73 patients failed to move into the successful treatment category and were defined as the nonresponsive group. We were unable to demonstrate any statistically significant differences in demographic and clinical characteristics of the patients between the 2 treatment groups. These findings are in agreement with the results by Lee et al.[20]

Per-protocol analysis is performed in randomized studies. We also conducted a per-protocol analysis in our study. One of the alternatives of the per-protocol analysis is the intention to treat (ITT) analysis. ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. Per-protocol analysis excludes all protocol violators, including anyone who did not adhere to treatment, switched groups, or missed measurements. In the current study, 6 patients missed the 1-month follow-up visit. So, we used per-protocol analysis in this randomized study.

Conclusion

This prospective, randomized controlled trial showed that combination therapy had significantly better results than systemic steroids alone in ISSNHL. According to our data, combination therapy was also associated with significant hearing improvement in patients with severe hearing loss. Based on the results of this study, we recommend that combination therapy can be considered as initial treatment especially for patients with severe hearing loss.

Author Contributions

Onur Gundogan, drafting the article, acquisition of data, analysis and interpretation of data; **Ercan Pinar**, conception and design, acquisition of data, revising the article; **Abdulkadir Imre**, conception and design, drafting the article, analysis and interpretation of data; **Sedat Ozturkcan**, conception and design, revising the article, final approval; **Ozge Cokmez**, analysis and interpretation of data, drafting the article; **Ali Cihan Yigiter**, acquisition of data, analysis and interpretation of data, drafting the article.

Disclosures

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