ORIGINAL ARTICLE

Comparison of Treatment Results According to Mode of Steroid Administration in Idiopathic Sudden Sensorineural Hearing Loss

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Objective: To analyze the recovery rates of sudden sensorineural hearing loss (SSNHL) according to steroid treatment regimen and other factors such as severity of initial hearing loss and initial audiogram patterns.

Materials and Methods: A retrospective study from January 2005 to March 2010. A total of 854 patients diagnosed with SSNHL within 14 days of the onset of symptoms were included. The patients were divided by 3 treatment modalities (systemic steroid, sequential intratympanic steroid injection after systemic steroid, and intratympanic steroid injection). The threshold of pure tone audiometry and patient characteristics were analyzed. The level of final hearing recovery was evaluated more than 6 months after the completion of each treatment.

Results: Overall recovery rates in the systemic steroid group, sequential intratympanic steroid injection after systemic steroid group, and intratympanic injection group were 68.7%, 73.7%, and 59.0%, respectively. Sequential intratympanic steroid injection resulted in significantly higher recovery rate in patients with profound hearing loss when compared with systemic steroid therapy. Sequential intratympanic steroid injection and systemic steroid showed worse recovery rate according to initial severity of hearing loss. Intratympanic steroid injection did not affect recovery rate according to initial severity of hearing loss.

Conclusion: Among patients with profound hearing loss at initial exam, sequential intratympanic steroid injection after systemic steroid improved hearing recovery when compared with systemic steroid or with intratympanic steroid injection. Based on these results, we believe that a sequential intratympanic steroid injection after systemic steroid therapy may improve patients' prognoses in the setting of profound hearing loss.

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Introduction

Idiopathic sudden sensorineural hearing loss (SSNHL) is a rare emergency in otology. It involves hearing loss higher than 30 decibels (dB) in more than three consecutive frequencies for 12 hours to 3 days.[1] Approximately 5-20 persons in 100,000 are affected annually.[2]

Various treatments have been introduced in the management of idiopathic SSNHL. Based on the hypothesis that SSNHL is caused by a viral infection or is an autoimmune response, oral steroid is used to reduce the inflammation in the inner ear. However, systemic steroid treatment may induce severe complications, and the dose that passes through the blood-perilymph barrier and reaches the inner ear is insufficient compared with the systemic burden placed by the overall dose.[3] As a means to reduce the side effects of such systemic treatment, the intratympanic steroid injection method was introduced, with diverse treatment outcomes reported. Theoretically, in the intratympanic steroid injection method, steroid is absorbed directly through the round window and a relatively high concentration of steroid could reach the perilymph without a systemic

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distribution.[4] Intratympanic injection has been shown to act locally, and systemic toxicity of steroid is not reported.[3] However, the shortcomings of this treatment method are the risk of permanent perforation of ear drum and inconsistent absorption of steroid through the round window.

The intratympanic steroid injection is usually performed in the following methods: 1) initial intratympanic injection without systemic steroid, 2) adjunctive treatment given concomitantly with systemic steroid, and 3) salvage therapy after failure of systemic steroid. Among these methods, efficacy of intratympanic steroid injection as salvage therapy was reported in several studies especially for the recovery of hearing threshold in low frequencies. Little has been reported about the efficacy of routine use of sequential intratympanic steroid injection after systemic steroid treatment, and about its efficacy when compared to other steroid treatments.

The aim of this retrospective review study was to evaluate SSNHL patients who were treated with steroid were divided into three groups according to the mode of steroid administration: the group treated with systemic steroid alone, the group treated with sequential intratympanic steroid injection after systemic steroid, and the group treated with intratympanic steroid injection alone; the treatment outcomes of the three groups were compared. In addition, the overall general clinical characteristics of SSNHL patients were examined.

Materials and Methods

A retrospective review was performed for patients' records at three tertiary hospitals from January 2005 to March 2011. The inclusion criteria were made for any patient who had been diagnosed with idiopathic SSNHL by pure tone audiometry (PTA) and history taking. This inclusion criterion identified 1,207 such patients, and the medical records of these patients were further reviewed for the following exclusion criteria: contraindication for systemic steroid administration (uncontrollable diabetes patients, kidney or liver dysfunction patients, or systemic disease patients), hearing loss because of central cause, and treatment initiation after 14 days from onset of symptom. The following numbers of patients were excluded from this study: 274 patients with systemic diseases (diabetes, hypertension, and other systemic diseases), 23 patients who were not treated sufficiently, 36 patients whose treatment was initiated more than 14 days from onset of symptoms, and 20 patients for whom medical records were inadequate. Ultimately, a total of 854 patients were included in the study analysis.

The hearing thresholds were averaged at 500 Hz, 1 kHz, 2 kHz, and 3 kHz. The level of initial hearing loss was classified according to the degree of hearing loss: mild (26-40 dB HL), moderate (41-55 dB HL), moderately severe (56-70 dB HL), severe (71-90 dB HL), and profound (higher than 91 dB HL) hearing loss. The pattern of audiogram was categorized into ascending, descending, or flat type hearing loss according to the formula:

α = (500 Hz + 1 kHz + 2 kHz) / 3 – (4 kHz + 6 kHz + 8 kHz) / 3

If α was greater than 15 dB, the hearing loss was considered as ascending type; if α was lesser than -15dB, as descending type; and α within +/- 15 dB was considered as flat type hearing loss.[5] A hearing loss was categorized as a concave type, when mid frequency was lowered primarily and as a convex type, when mid frequency was relatively preserved.[6]

The recovery of hearing loss was evaluated based on the result of PTA according to Siegel's classification method six months after treatment.[7] By this classification, the overall recovery rate was calculated for complete recovery group (CR), partial recovery group (PR), and slight recovery group (SR),[8] and the experimental variables were analyzed within each recovery group.

Systemic steroid group

The patient who received systemic steroid treatment was hospitalized for 6-8 days, placed on a low salt diet, and was given a medication (ginko biloba) to improve blood circulation. The oral steroid therapy consisted of a methylprednisolone regimen consisting of 80 mg on days 1 to 4, 60 mg on days 5 and 6, and 40 mg from day 7 until discharge. After discharge, the regimen was 40 mg on day 8, 20 mg on days 9 and 10, and 10 mg on days 11 to 14. Following this, the steroid dose was gradually tapered off over the course of 2 weeks. In addition,

almitrine bismesylate and buflomedil pyridoxalphosphate were used to improving blood circulation were prescribed for the duration of steroid therapy.[1,2] During the hospitalization period, PTA was performed daily.

Intratympanic steroid injection group

Similarly to the systemic steroid group, the group of patients who were treated with intratympanic steroid injection was prescribed rest, low salt diet, and blood circulation drug in addition to the local steroid injection. These patients were managed on an outpatient basis, and were seen in clinic at 3-4 day intervals for a total of four intratympanic injections. Prior to each injection, the pattern of hearing was assessed by performing PTA. Each injection was performed under a microscope, and 0.3-0.4 cc of dexamethasone (Dexamethasone®, 5 mg/mL) was injected to the anterior superior quadrant (ASQ) area of the drum in the involved ear using a 25-gauge spinal needle connected to a 1 cc syringe. After the injection, the laying on the opposite side was maintained for 20 minutes to allow the injected dexamethasone to come into and maintain contact with the round window, and the patients were instructed not to swallow saliva or talk during this period.

Sequential steroid injection after systemic steroid group

The patients in this group were treated with oral steroid first, followed by intratympanic steroid injection second. During the hospitalization period, the patients received the same treatment as that provided to the patients in the systemic steroid group. After completion of 14 days systemic steroid treatment, each patient was discharged and was given a total of four intratympanic steroid injections over a two week period (identical to intratympanic steroid injection group). Each patient had been given an explanation regarding the intratympanic steroid injection prior to treatment, and the injections were performed only if a patient had agreed to the intratympanic steroid injection in addition to systemic steroid therapy.

Ethical approval and Statistical Methods

This study was designed to be retrospective and authors had received an approval from ethical standards committees of three hospitals (KHNMC IRB-2012-083, KMC IRB 2012-064, CSMC IRB 2012-058).

For data analysis, SPSS version 12.0 was used. As for statistical analysis methods, chi-square test, ANOVA, Fisher's exact test, logistic regression analyses were applied. A p-value of less than 0.05 was considered to be statistically significant.

Results

In the evaluation of final hearing threshold, the number of patients with CR, PR, SR, and no recovery (NR) of systemic steroid group were 168 (34.6%), 81 (16.7%), 85 (17.5%), and 152 (31.3%), respectively. In the sequential steroid injection after systemic steroid group, 97 patients (34.0%) had achieved CR, 59 (20.7%) had PR, 54 (18.9%) had SR, and 75 (26.3%) patients had NR. In the intratympanic steroid group, 11 patients (13.3%) had achieved CR, 15 (18.1%) achieved PR, 23 (27.7%) had SR, and 34 (41.0%) had NR. Thus, the final hearing differed significantly by the type of treatment (p=0.031) (Table 1.).

Overall recovery rates in the systemic steroid group, sequential intratympanic steroid injection after systemic steroid group, and intratympanic injection group were 68.7% (334/486), 73.7% (210/285), and 59.0% (49/83), respectively. In both the systemic steroid group and the sequential intratympanic steroid injection after systemic steroid group, recovery rate differed significantly according to the severity of initial hearing ($p<0.001$, $p=0.022$). Recovery rates in both groups were higher in patients with mild hearing loss (85.1% and 88.6%, respectively) than with profound hearing loss (52.8% and 69.0%, respectively; $p<0.05$). In contrast, recovery rate did not correlate with initial severity of disease in the intratympanic injection group (p=0.908). Recovery rates within each range of initial hearing loss were independent of treatment modality ($p>0.05$) (Table 2.).

The overall recovery rate was significantly higher in the sequential intratympanic steroid injection after systemic steroid group than in the intratympanic injection group (73.7% vs. 59.0%, p=0.014), and this difference was similarly observed in the systemic steroid group and intratympanic steroid injection group (68.7% vs. 59.0%, p=0.082). The overall recovery rates were similar in the

Table 1. Baseline demographic and clinical characteristics of patients according to steroid administration routes.

	Number of patients (%)			
	Systemic steroid group (n=486)	**Sequential intratympanic steroid injection after systemic steroid group (n=285)**	**Intratympanic steroid group (n=83)**	**p value**
Age (Mean ± SD)	49.2 ± 16.6	48.2 ± 16.1	52.2 ± 16.3	0.150
Sex (M / F)	196 / 290	127 / 158	41 / 42	0.082
Side (R / L)	228 / 258	137 / 148	44 / 39	0.790
Interval to initiation of treatment (days)	2.9 ± 1.6	2.9 ± 1.0	2.2 ± 1.8	0.684
Severity of initial hearing loss				
Mild	87 (17.9%)	44 (15.5%)	10 (12.0%)	0.104
Moderate	88 (18.1%)	54 (18.9%)	14 (16.9%)	
Moderately severe	97 (20.0%)	48 (16.8%)	18 (21.7%)	
Severe	106 (21.8%)	68 (23.9%)	18 (21.7%)	
Profound	108 (22.2%)	71 (24.9%)	23 (27.7%)	
Final hearing state				
Complete recovery	168 (34.6%)	97 (34.0%)	11 (13.3%)	0.031
Partial recovery	81 (16.6%)	59 (20.7%)	15 (18.1%)	
Slight recovery	85 (17.5%)	54 (18.9%)	23 (27.6%)	
No recovery	152 (31.3%)	75 (26.4%)	34 (41.0%)	

Table 2. Recovery rate according to administration modes of steroid and severity of initial hearing loss.

	Number or recovered patients (%)			
Initial severity of hearing loss	**Systemic steroid group**	**Sequential intratympanic steroid after systemic steroid group**	**Intratympanic steroid group**	**Total**
Mild	74 (85.1%)	39 (88.6%)	5 (50.0%)	118 (83.7%)
Moderate	64 (72.7%)	42 (77.8%)	10 (71.4%)	116 (74.4%)
Moderately severe	62 (63.9%)	32 (66.7%)	10 (55.6%)	104 (63.9%)
Severe	77 (72.6%)	48 (70.6%)	11 (61.1%)	136 (70.8%)
Profound	57 (52.8%)	49 (69.0%)	13 (56.5%)	119 (58.9%)
Total	334 (68.7%)	210 (73.7%)	49 (59.0%)	593 (69.4%)

systemic steroid group and the sequential intratympanic steroid injection after systemic steroid group (68.7% vs. 73.7%, p=0.145). When these groups were subdivided by severity of hearing loss at initial presentation however, the likelihood for no recovery was significantly higher for the systemic steroid group than for the sequential intratympanic steroid injection after systemic steroid group in the subset of patients with profound hearing loss (odds ratio; OR 1.993, 95% confidence interval; CI 1.062–3.731, p=0.043). Likewise, the likelihood for no recovery was significantly higher in the intratympanic injection group than in the sequential intratympanic steroid injection after systemic steroid group in the subset of patients with mild hearing loss at initial presentation (OR 7.800, 95% CI 1.655–36.760, p=0.005) Additionally, the likelihood for no recovery was significantly higher in the intratympanic steroid injection group than in the systemic steroid group in the subset of patients with mild hearing loss at initial presentation (OR 5.692, 95% CI 1.443–22.459, p=0.007) (Figure 1.).

When we analyzed the relationship between audiogram patterns and recovery rates by treatment groups, we found that those with ascending audiograms had the highest recovery rate (86.1%), followed by patients with flat (69.1%), concave (65.8%), descending (59.5%), and convex (57.5%) audiograms (p=0.011) among the patients in the systemic steroid group. Overall recovery rate also was significantly different according to audiogram pattern (p=0.023) (Table 3.).

In patients with mild hearing loss, ascending type of audiogram pattern was the most common, and flat type of audiogram pattern was the most common in severe and profound hearing loss patients (Table 4.).

Discussion

SSNHL is an emergency disease by which hearing loss develops suddenly in a few hours to a few days. If it is not promptly treated, a patient with SSNHL may experience permanent hearing impairment. Nevertheless, its etiology has not been elucidated yet, and reliable treatment methods have not been established.

Since the etiology of SSNHL is unclear, steroid and other anti-inflammatory agents, blood circulation improvement agents, vasodilators, antiviral agents, and diuretics are used. Some studies have reported that the

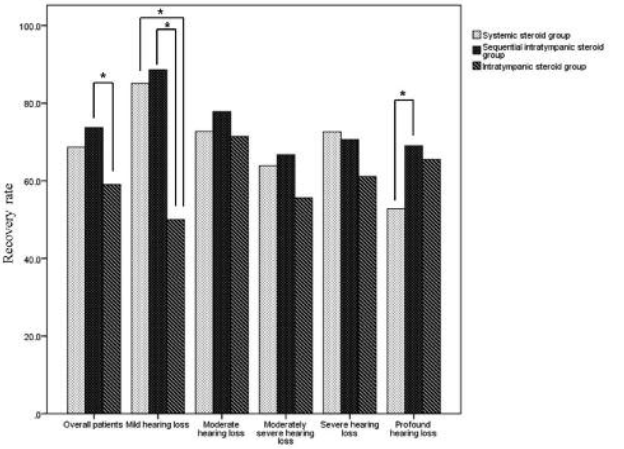

Figure 1. Recovery rate according to administration modes of steroid and severity of initial hearing loss.

Table 3. Recovery rate by administration modes of steroid and audiogram patterns.

	Number of recovered patients (%)			
	Systemic steroid group	Sequential intratympanic steroid injection after systemic steroid group	Intratympanic steroid group	Total
Flat	103 (69.1%)	54 (67.5%)	16 (57.1%)	173 (67.1%)
Ascending	87 (86.1%)	42 (85.7%)	9 (75.0%)	138 (85.2%)
Descending	50 (59.5%)	44 (81.5%)	8 (53.3%)	102 (66.7%)
Concave	52 (65.8%)	46 (76.7%)	12 (66.7%)	110 (70.1%)
Convex	42 (57.5%)	24 (57.1%)	4 (44.4%)	70 (56.5%)
Total	334 (68.7%)	210 (73.7%)	49 (59.0%)	593 (69.4%)

Table 4. Distribution of audiogram pattern according to severity of initial hearing loss.

	Number of patients (%)					
	Mild hearing loss	Moderate hearing loss	Moderately severe hearing loss	Severe hearing loss	Profound hearing loss	Total
Flat	26 (18.4%)	26 (16.7%)	29 (17.8%)	50 (26.0%)	127 (62.9%)	258
Ascending	43 (30.5%)	36 (23.1%)	26 (15.9%)	37 (19.3%)	20 (9.9%)	162
Descending	37 (26.2%)	32 (20.5%)	43 (26.4%)	24 (12.5%)	17 (8.4%)	153
Concave	22 (15.6%)	37 (23.7%)	48 (29.4%)	35 (18.3%)	15 (7.4%)	157
Convex	13 (9.3%)	25 (16.0%)	17 (10.5%)	46 (23.9%)	23 (11.4%)	124
Total	141	156	163	192	202	854

only treatment which is effective for idiopathic SSNHL is steroids, though the action mechanism of steroid has not been elucidated yet.[1,2,7] However, it is generally believed that steroid treatment prevents edema in the nerve and/or adjacent tissues, reduces collagen formation, and wounding by the anti-inflammatory action.[9] Thus, steroids appears to exert these changes on the auditory nerve and the cochlear area, where injury occurs by viral infection.[10] In regard to the recovery rate after steroid administration, several investigators have already reported recovery rates higher than those of untreated cases.[11]

The steroid delivery method to the cochlear area can be broadly characterized as either systemic or local. Systemic administration can be administered oral or intravenous routes, and the treatment regimens are diverse. Prednisolone is administered with an initial dose of 60-80 mg per day (1mg/kg/day), and typically, this dose is decreased gradually over the course of 1-2 weeks. For patients demonstrating partial recovery, prednisolone administration may be extended for approximately 10 days.[12] The efficacy of systemic administration has been demonstrated in several studies previously, and depending on the study, recovery rates of 41-61% have been reported.[8] Nevertheless, systemic steroid administration has shortcomings in that it may exacerbate diabetes, hypertension, and other underlying diseases of patients, and it does not act effectively locally target the cochlear area. Side effects of the systemic administration of steroid are diverse, including but not limited to avascular necrosis, epistaxis, drug-induced liver dysfunction, acne, and gastroenteritis.

Intratympanic steroid injection to SSNHL patients was reported for the first time in 1996 by Silverstein,[13] and additional studies had been conducted by various investigators.[14,15] The recovery rate for intratympanic steroid injection has been reported to be approximately 61.5-77.3%.[16,17] Intratympanic steroid injection has advantages in that the concentration within the perilymph is higher than that from the systemic steroid administration, and side effects and complications of systemic administration such as adrenal suppression or liver dysfunction rarely develop with the injection therapy.[14] In addition, the steroid could be administered safely to patients with diabetes, hypertension, or other underlying diseases that restrict the administration of high dose systemic steroid. Nevertheless, the possibilities of permanent ear drum perforation, temporary dizziness caused by physical and temperature stimulation to the lateral semicircular canal during the injection, and development of otitis media due to the stimulation of the tympanic cavity should be kept in mind.[14,15,18] In this study, we excluded the patients with systemic diseases who cannot endure the systemic steroid treatment and there was no complication with systemic use of steroid. Also intratympanic steroid injection was performed without reported complications, such as permanent perforation of tympanic membrane and otitis media. There was no complications about any kind of steroid treatment.

Battaglia et al.[19] reported the additional gain of recovery with concomitant intratympanic steroid injection with systemic steroid; however, Ahn et al.[20] reported that there was no additional therapeutic effect in the combined therapy. As such, the concomitant use of intratympanic steroid injection with systemic steroid still remains controversial. Initial intratympanic injection without systemic steroid has been used as an alternative to systemic steroid if a patient has a systemic disease which precludes systemic steroid treatment. Recent comparative studies have reported that the efficacy of intratympanic steroid injection was similar to or better than systemic steroid treatment.[21-23] Rauch et al. performed a randomized, prospective, multicenter study with intratympanic steroid injection and reported the efficacy of intratympanic steroid injection to be indifferent from that of systemic steroid treatment.[24] Various prospective controlled studies reported the efficacy of salvage intratympanic steroid injection after systemic steroid, and it was considered be a good choice for patients who demonstrated poor recovery with systemic steroid.[14,15,25,26] Theoretically, intratympanic injection would affect to the area of high frequency considering the location of round window, but there are diverse reports which showed recovery in high frequency and low frequency hearing losses.[14]

Regarding the timing of salvage intratympanic injection, a study reported that immediate salvage treatment resulted in higher rates of hearing recovery than salvage

treatment two weeks after the end of initial systemic steroid.[27]

Studies on additional intratympanic steroid injection were dominantly about salvage treatment. Because initial severity of hearing loss is considered as a major prognostic factor for SSNHL, the subject of salvage intratympanic steroid injection would be usually patients with profound hearing loss. In this study, sequential intratympanic steroid injection was performed regardless of initial severity of hearing loss and of hearing recovery after systemic steroid treatment. The result of sequential intratympanic steroid injection was compared to that of the systemic steroid treatment with intratympanic steroid injection.

Sequential intratympanic steroid injection showed similar overall recovery rate to systemic steroid injection, and this is a finding that corresponds to previous studies. When patients were subdivided by initial severity of hearing loss, sequential intratympanic steroid injection showed significantly higher recovery rate in profound hearing loss patients (Fig. 1.) This may be due to the effect of salvage treatment in sequential intratympanic steroid injection. In addition, flat and ascending type of audiogram pattern was the most common in profound hearing loss, and effect of sequential intratympanic steroid injection to the area of lower frequency may be cause of higher recovery rate in profound hearing loss patients. All of these findings were similar to previous studies. There was no difference between sequential intratympanic steroid injection and systemic steroid in mild, moderate, moderately severe, and severe hearing loss group.

Although mild hearing loss group was expected to have a good prognosis, intratympanic injection showed significantly lower recovery rate in patients with mild hearing loss. Intratympanic steroid injection showed no tendency of recovery according to initial severity of hearing loss. With intratympanic injection, direct transfer of drug to the inner ear through the round window membrane and maintenance of higher concentration in the inner ear fluid could be responsible for the constant recovery rate regardless of initial hearing loss. However, variables such as middle ear condition, anatomical variation, position of patient, speed of injection, and site of injection may affect the transfer of drug, which could be the cause of low recovery rate in patients with mild hearing loss. If a universal protocol to correct such variables were to be developed, efficacy of intratympanic injection might result in improved hearing recovery.

Conclusion

Of the treatment methods for SSNHL, the effectiveness of steroid treatment has already been demonstrated by several studies. Several methods of steroid administration, such as systemic administration, intratympanic injection, or sequential intratympanic injection after systemic steroid, have been reported. Nevertheless, the precise guideline to select patients for each method has not been established yet, and it is somewhat difficult to select treatment methods. In our study, the sequential intratympanic steroid injection had efficacy, especially in patients with profound hearing loss. Considering that intratympanic injection has minimal rates of complication, we suggest that a routine use of sequential intratympanic injection after systemic steroid to improve the prognosis of patients with profound hearing loss.

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