Original Article

Methylprednisolone Intratympanic Injection in Idiopathic Sudden Sensorineural Hearing Loss: A Retrospective Review of 167 Cases

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Objective: To investigate if methylprednisolone intratympanic membrane injection (IT) as a salvage treatment gave an additional hearing improvement in patients with idiopathic sudden sensorineural hearing loss [ISSNHL].

Material and Methods: A retrospective medical chart review of 167 patients diagnosed as ISSNHL with onset of hearing loss prior to methylprednisolone IT 30 days or less. Patients, who did not response to 1-week course of high dose oral steroid, were given 4 times of methylprednisolone IT within 1 week. Data were analyzed to compare hearing improvement.

Results: There were 167 patients with ISSHNL included in the present study, 63 (37.7%) males and 104 (62.3%) females. Age range was 14 - 87 years old (median 52, mean±SD: 51.56±14.51). Median onset of ISSNHL before starting methylprednisolone IT was 8 days (mean±SD; 13.42±12.62 days) and mean of initial PTA of pathological ears were 70.96±26.54 dB. Methylprednisolone IT provided improvement in hearing 25.1% with statistical significance ($p<0.001$) after 30 days of treatment. The common side effects were pain and vertigo. Twelve patients (7.18%) had tympanic membrane perforation, but there was no serious adverse effect.

Conclusion: Methylprednisolone IT is an effective salvage treatment in ISSNHL and could be considered as a primary treatment for patients

Keywords: Sudden hearing loss, sudden sensorineural hearing loss, Intratympanic steroid, Intratympanic injection

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Incidence of idiopathic sudden sensorineural hearing loss [ISSNHL] has been reported in USA about 5 - 20 to 100,000 population[1]. During 2006 - 2008, there were 315 out of 4,129 patients diagnosed as ISSNHL at Neuro-Otology unit, Siriraj Hospital[2]. Standard criteria for diagnosis of ISSNHL were sudden onset of hearing loss within 24 - 72 hours and audiogram showed loss of hearing at least 30 decibels in three consecutive frequencies[3,4].

Many theories have been proposed for the causes of ISSNHL, which frequently mentioned were viral and autoimmune theory. From viral theory, presenting of viral prodromal symptom[5] and rising of viral titer[6] prior to onset of ISSNHL were usually found. Patients with underlying autoimmune diseases presented with ISSNHL responsed to corticosteroid and immune suppressive drugs[7,8] in the autoimmune theory.

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Standard treatment for ISSNHL is prednisolone 1 mg/kg/day for 7 - 14 days, started as soon as possible after the onset of ISSNHL. Wilson et al[9] reported improvement of hearing was about 61% with corticosteroid comparing to placebo if treatment was started in the golden period. Others treatments such as hyperbaric oxygen, volume expander and antiviral drugs had no statistically significant improvement of hearing[10,11].

Recent studies found glucocorticoids receptors in the inner ear[12]and high concentration in both cochlear and vestibular tissues in the animal studies[13]. Glucocorticoids have a protective mechanism of the acute hearing loss by increasing glutathione (GSH) synthesis, which is an antioxidant in the inner ear[13]. A corticosteroids intratympanic membrane injection (IT) is a new modality, which had postulated by Silverstein et al[14]. The animal experiment demonstrated the concentration of corticosteroids (hydrocortisone, dexamethasone and metyhlprednisolone) via IT application, had higher concentration than oral or intravenous application[15]. The objective of the present

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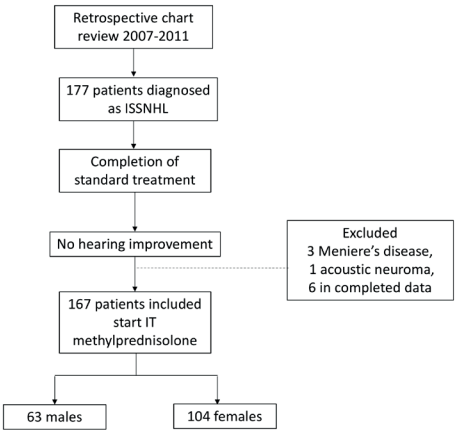

Figure 1. Diagram of the study.

study was to investigate if corticosteroid IT as a salvage treatment gave any additional hearing improvement in ISSNHL patients, and any adverse side effects in this procedure.

Materials and Methods

The present study was approved by the IRB of the Siriraj Hospital, Mahidol University. The authors *retrospectively medical chart reviews* of the patients diagnosed as ISSNHL from 2007 to 2011.

Inclusion criteria:

- Patients with a history of sudden onset of hearing loss at least 30 dB in 3 consecutive frequencies within 24 - 72 hours.
- Time between onset of hearing loss to IT treatment was 30 days or less.
- Patients were treated with oral predinisolone 1 mg/kg/day for 7 days as a standard treatment at the first visit. Failed to response to oral prednisolone, which was defined as pure tone average (PTA: 0.5, 1, 2 KHz) improvement less than 15 dB at the end of first week of oral steroid or did not improved from their hearing base line
- Patients agreed to be treated with IT methylprednisolone with their signed consents.

Exclusion criteria:

- Patients who did not agree to treat with IT methylprednisolone or with intravenous steroids.
- Patients with infection of external or middle ears, fluctuating hearing loss, sensorineural hearing loss from surgery, and central nervous system diseases and psychological problems.

Procedures

All patients underwent ENT examination, auditory brainstem response for exclusion of retro-cochlear lesions and blood chemistries testing.

The procedure was performed after 10% lidocaine spraying into ear canals 30 minutes. Methylprednisolone (125mg/2ml) loaded in a 1-cc tuberculin syringe with needle no 25, 1.5-inch in length, was injected through myringotomy until it was fully filled the middle ear 4 times within 1 week. The patient had to lie with the affected ear on top for 30 minutes.

Audiological testing was performed at the initial of IT, prior to 3rd IT and monthly after completion of IT. Change in PTA ≥15 dB was considered as an improvement. Change less than this was considered as no improvement. All patients were followed up at least 1 year after completion of the IT course of IT.

Statistical Analysis

The authors used IBMâ SPSS Version 20 for analyze the data. Comparison between improved and no-improved group using paired sample t-test and Mann-Whitney for parametric and nonparametric data. A Chi square test were used to analyze categorical data and odds ratio. $P<0.05$ is considered as a statistical significance.

Results

One hundred and seventy-seven patients were recruited. Four patients with fluctuating hearing loss was finally diagnosed as three Meniere's disease and one acoustic neuroma. There were six incompleted data. All of them were excluded. There were 167 patients recruited (Figure1). There were 63 (37.7%) males and 104 (62.3%) females. Age range was 14 - 87 years old (median 52, mean±SD: 51.56±14.51). Pathological ears were 78 (46.7%) on the right and 89 (53.3%) on the left ears. Median duration of hearing loss before starting IT was 8 days (mean±SD; 13.42±12.62 days). Mean of initial PTA of pathological ears were 70.96±26.54 dB. Median of initial WRS of pathological ears and at 30 days after treatment was 28% and 48 %, consecutively (mean±SD; 38.72±30.05% and 48.09±36.83%), Table 1. Sixty-three patients had underlying diseases: were diabetes, hypertension, dyslipidemia and combined diseases, Table 2. Both PTA and WRS improvement were statistically significant at prior to 3rd IT injection and 30 days after IT ($p<0.001$), Table 3.

Comparison of the characteristics of the patients between hearing improvement (IM) and no improvement (no-IM) groups showed in Table 4 and 5. There were

42 (25.1%) IM patients (changes of PTA ≥15 dB from baseline) and 125 (74.9%) no-IM patients. There were no statistical significant in age, sex, duration of hearing loss, initial WRS, final PTA and final WRS zof patients except initial PTA (p<0.001). Furthermore, there were statistical significance between initial PTA ≤60 and >60 dB as well as underlying diseases (p<0.01, crude OR- 0.262, 95%CI (0.139,0.713) and p-0.042, crude OR-2.36, 95%CI (1.065,5.21)).

The common immediate side effects were pain and burning sensation due to drug passing through the eustachian tube, though patients had painkiller drugs before starting of IT treatment. Vertigo could be found because of thermal stimulation as caloric testing. There were tympanic membrane perforation in 12 out of 167 patients (7.18%). There was no serious adverse effect during the time of IT and the follow-up.

Discussion

Spontaneous recovery of ISSNHL had been reported ranges from 30 - 60% without any treatment[16]. Nevertheless, hearing improvement has been increased by steroids, which is the proved and commonly used as treatment for ISSNHL[3,17]. Long-term systemic steroid in patients who did not response to treatment can cause side effect such as edema, salt retention, gastrointestinal irritation and glucose intolerance[18]. In present study, diabetic patients were admitted to control blood glucose so they lost time and more expenses. Steroid IT is a promising route of treatment in patients with ISSNHL because the evidences of diffusion of drug directly through round windows in the animal studies. Silverstein[14] (1996) had first preliminary report of intraympanic steroid injection. Steroid IT had been report as a primary salvage and combined[3,18-20] therapy in patients with ISSNHL. Methyprednisolone showed the highest concentration and longest duration in perilymph and endolymph[15,21]. From this reason, we chose methylprednisolone as the drug of choice. This modality was considered in this hospital since 2007.

Table 1. Demographic data of patients

Characteristics		
Sex		
No. of patients -167	Male 63 (37.7%)	Female 104 (62.3%)
Side		
Total No. of ears -167	Right-78 (46.7%)	Left-89 (53.3%)
Age (years)		
- Mean	56±14.51	
- Median (min - max)	52 (14 to 87)	
Duration of hearing loss (days)		
Mean	13.42±12.62	
Median (min - max)	8 (0 to 30)	
Initial PTA of pathological ears (dB)		
Mean±SD	70.96±26.54	
PTA at 30 days after methylprednisolone IT		
Mean±SD	65.24±25.68	
Initial WRS of pathological ears (%)		
- Mean±SD	38.72±38.05	
- Median (min - max)	28 (0 to 100)	
WRS at 30 days after methylprednisolone IT		
- Mean±SD	48.09±36.83	
- Median (min - max)	48 (0 to 100)	

PTA- pure tone average, WRS- word recognition score

Table 2. Underlying diseases of patients

Underlying diseases	No (n-167)	Percentage
No underlying diseases	104	62.3
Underlying diseases	63	37.7
- DM	19	11.4
- HT	13	7.8
- DLP	5	3.0
- DM, HT	15	9.0
- DM, DLP	8	4.8
- HT, DLP	7	4.2
- DM, HT, DLP	1	0.6

DM- Diabetes Mellitus, HT-Hypertension, DLP- Dyslipidemia

Table 3. Comparison of PTA and WRS improvement between at first visits and follow-up of pathological ears

	PTA improvement (mean±SD) (dB)	PTA p-value	WRS improvement (%) Median (min - max)	WRS p-value
Prior 3rd IT	2.32 ± 9.92	p<0.001*	0 (0 to 100)	0.064
At about 30 days after IT	5.843 ± 14.478	p<0.001*	0 (20 to 100)	< 0.001*

* Statistical significant (PTA - Paired sample t-test, WRS - Wilcoxon signed rank test), IT = intratympanic membrane injection

Table 4. Characteristic of patients comparing between hearing improvement and no improvement group at about 30 days after IT injection

Characteristics of pathological ears	Improvement (IM)	No improvement (no-IM)	p-value
No of pathological ears (167)	42 (25.1%)	125 (74.9%)	
Age (years)			
- Mean±SD	50.97±15.35	51.11±15.05	
- Median (min - max)	52.5 (14 to 82)	52 (15 to 86)	0.391
Onset of hearing loss prior treatment (days)			
– Mean±SD	11.02±8.2	14.12±13.62	
- Median (min - max)	10 (1 to 30)	8 (1 to 30)	0.397
Initial PTA (dB)			
- Mean±SD	82.85±22.38	68.55±27.27	
- Median (min - max)	85 (33 to 120)	69 (12 to 120)	<0.001*
PTA at 30 days after treatment			
- Mean±SD	49.26±35.67	47.65±37.42	
- Median (min - max)	46 (10 to 98)	48 (13 to 120)	0.287
Initial WRS (%)			
- Mean±SD	30.1±36.8	41.56±38.18	
- Median (min - max)	8 (0 to 100)	32 (0 to 100)	0.113
WRS at 30 days after treatment			
- Mean±SD	61.26±21.01	66.11±26.84	
- Median (min - max)	67 (0 to 100)	63 (0 to 100)	0.836

Improved = change in PTA ≥15 dB from baseline, Same = no changes of PTA or changes in PTA <15 dB, * Statistical significance (Mann -Whitney U test and Chi-square test)

Table 5. Onset of hearing loss and PTA prior staring methylprednisolone IT and hearing improvement at about 30 days after completion of IT methylprednisolone

Indicators	Number of ears Hearing improvement		Crude OR 95% CI	*p*-value
	IM (n- 42)	No-IM (n- 125)		
Onset of hearing loss				
≤14 days	32 (76.2%)	89 (71.2%)		
>14 days	10 (23.8%)	36 (28.8%)	1.294 (0.577,2.906)	0.69
IInitial PTA (dB)				
≤60 dB	9 (21.4%)	58 (46.4%)		
>60 dB	33 (78.6%)	67 (53.6%)	0.315 (0.139,0.713)	0.006*
Age				
≤55	27 (64.3%)	73 (58.4%)		
>55	15 (39.7%)	52 (41.6%)	1.282 (0.621,2.646)	0.586
Underlying diseases				
No	32 (76.2%)	72 (57.6%)		
Yes	10 (23.8%)	53 (42.4%)	2.356 (1.065,5.210)	0.042*
Sex				
Male	14 (38.09%	51 (40.8%)		
Female	26 (61.9%)	83 (66.4%)	0.994 (0.468,2.111)	1.00

Improved (IM) = changes in PTA ≥15 dB from baseline, no improved (no-IM) = no changes of PTA or changes in PTA <15 dB (Odd ratio and Chi-square test)

Methylprednisolone IT was conducted in the patients as a salvage treatment after failed standard treatment of ISSNHL. Hearing improvement was 25.1% at 30 days after IT treatment with statistically significance (p<0.001), Table 4. Comparing to other studies, success rates after steroid IT for hearing improvement, which ranged between 20% - 100% in the literatures[17, 22], which was the same as the present study. Haynes, D. et al[23] reported recovery related to time of onset, which median number of days from onset of symptom in patients responding to IT was 14 days. The group did not response to IT was 31 days. From the present study, there were no statistical significant in duration of starting treatment which were ≤14 days and > 14 days (p = 0.69, crude OR = 1.294, 95%CI (0.57, 2.9), Table 5. However, the authors did not extend the period of IT treatment in patient with onset of hearing loss more than 30 days, so further study could be done to see possible changes of improvement in the delayed group. There was a statistical significance in the initial PTA between IM and no-IM group (p<0.001, Table 4). The IM group had worse initial PTA comparing to no-IM group. In addition, it also showed the initial PTA > 60 dB in IM group responded to IT treatment than those with initial PTA ≤60 dB This may because patient with initial PTA ≤60 dB had some hearing improvement from the systemic steroid prior to the start of the IT treatment, so the final PTA did not meet the criteria of hearing improvement. However, over all patients with hearing loss over 60 dB had less improvement with statistical significance (p = 0.006, crude OR 0.315, 95%CI 0.139, 0.713).

Patients diagnosed as ISSNHL had underlying diseases 65 out of 167 (37.7%), which were: DM, HT and DLP. There was a statistical difference in hearing improvement between patients with and without underlying diseases. However, patients with underlying diseases were likely to have less chance to improve hearing than those without underlying disease (p-0.041, crude OR-2.356, 95%CI (1.065,5.21), Table 5. Berjis et al. reported that diabetes was more frequent to develop sudden hearing loss than other cardiovascular diseases which was independent from blood sugar level[24]. These findings were also found in other studies[25,26]. Endothelial dysfunction[24], neuropathy, microangiopathic changes[26] and arterial stiffness[27] are probably the pathophysiology of hearing loss. Common underlying diseases in the present study were: DM (11.4%), DM plus HT (9%) and HT (7.8%). Nevertheless, IT should be considered as a first choice of treatment in patients with underlying diseases due to less disturbance to their diseases. One of DM patient recovered her hearing from profound hearing to her baseline after IT. This may be a result of partial improvement of hearing in DM patients before starting methylprednisolone IT and good control of blood sugar after completion of oral steroid.

Although there is no statistical significant in hearing improvement among patients age ≤55 and >55 years old. However, it seems likely that aged patients >55 years old had less response to methylprednisolone IT similar to the prior reports[1, 28].

Conclusion

Main treatment of ISSNHL is systemic corticosteroids, which can cause systematic disturbances especially in patients with diabetes. Methylprednisolone IT is an effective salvage treatment in ISSNHL and should be considered as a primary treatment to decrease systemic side effect. The common side effects are pain and vertigo. Twelve patients (7.18%) had tympanic membrane perforation, but there was no serious adverse effect.

What is already known on this topic?

Treatment of sudden sensorineural hearing loss.

What is this study added?

Success rate of intratympanic methylprednisolone injection as a salvage treatment of sudden sensorineural hearing loss and adverse side effects.

Potential conflicts of interest:

The authors declare no conflict of interest.

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