Intratympanic Methyl Prednisolone Salvage Therapy for Sudden Hearing Loss

Ani İşitme Kaybında İntratimpanik Metil Prednizolon Kurtarma Tedavisi

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ABSTRACT Objective: The aim of the study was to determine effectiveness of intratympanic methyl prednisolone injection as a salvage therapy for sudden sensorineural hearing loss in patients who did not have complete recovery with systemic treatment. **Material and Methods**: Sixteen patients with sudden hearing loss who did not have complete recovery or had a partial recovery with systemic treatment enrolled in this prospective study. After the topical anesthesia, 0.4-0.5 mL of methyl prednisolone (40 mg/mL) was administered into the middle ear from the postero-inferior quadrant of the tympanic membrane. Pure tone audiometry test was performed before each injection and after the final injection. A change more than 10 dB in the pure tone average was considered as an alteration in hearing (improvement or worsening). Complete recovery was accepted when the pure tone average was 20 dB or lower. **Results:** The mean onset of intratympanic methyl prednisolone treatment after the hearing loss was 16±6.6 days (range: 7 -30 days). The average number of injections was 3.8±1.3 (range: 2-6). The improvement in pure tone average was statistically significant [initial median of pure tone average was 85 dB (minimum 28 dB, maximum 107 dB), final median of pure tone averages was 42.5 dB (minimum 12 dB, maximum 107dB), p=0.007]. Eleven (68.75%) patients improved, but no change was observed in 5 (31.25%) patients. Two (12.5%) patients attained complete recovery. Four (25%) patients improved to 30 dB or less in pure tone average. Statistically significant improvement was also obtained at 250, 500, 1,000, 2,000, 4,000 and 6,000 Hz frequencies. **Conclusion:** These results suggested that intratympanic methyl prednisolone treatment for sudden hearing loss in patients who did not respond to systemic therapy appears to be a good alternative for better hearing results.

Key Words: Hearing loss, sudden; methylprednisolone; salvage therapy; steroids

ÖZET Amaç: Bu çalışmanın amacı, sistemik tedaviye yeterli yanıt alınamayan ani işitme kayıplı hastalarda kurtarma tedavisi olarak uygulanan intratimpanik metil prednizolon tedavisinin etkinliğini araştırmaktır. **Gereç ve Yöntemler:** Bu prospektif çalışmaya, sistemik tedaviye yanıt alınamayan veya kısmi yanıt alınan 16 ani işitme kayıplı hasta alındı. Topikal anestezi sonrasında 0,4-0,5 mL metil prednizolon (40 mg/mL), timpanik membran posteroinferior kadranından orta kulağa enjekte edildi. Her enjeksiyon öncesinde ve tedavi sonunda saf ses odyometri testi yapıldı. Saf ses ortalamasında 10 desibelden daha fazla değişiklik, değişim olarak kabul edildi (iyileşme veya kötüleşme). Saf ses ortalamasının 20 dB ve daha aşağıdaki değerleri tam iyileşme olarak kabul edildi. **Bulgular:** İşitme kaybı başlangıcı ile intratimpanik metil prednizolon uygulaması arasındaki ortalama süre 16±6,6 gündü (7-30 gün arasında). Ortalama enjeksiyon sayısı 3,8±1,3 idi (2-6 arasında). Saf ses ortalamasındaki iyileşme istatistiksel olarak anlamlı bulundu [enjeksiyon öncesi saf ses ortalaması ortanca değeri 85 dB (en küçük 28 dB, en büyük 107 dB), enjeksiyon sonrası saf ses ortalaması ortanca değeri 42,5 dB (en küçük 12 dB, en büyük 107 dB), p=0.007]. On bir (%68,75) hastada iyileşme saptanırken 5'inde (%31,25) değişiklik olmadı. İki olguda tam iyileşme (%12,5) sağlandı. Dört olguda (%25) ise 30 dB ve altında saf ses ortalaması elde edildi. Ayrıca, 250, 500, 1000, 2000, 4000 ve 6000 Hz frekanslardaki ortalama iyileşme istatistiksel olarak anlamlı bulundu. **Sonuç** Sistemik tedaviye yeterli yanıt alınamayan ani işitme kayıplı hastalarda daha iyi işitme sonuçları elde etmek için uygulanacak intratimpanik metil prednizolon tedavisi iyi bir alternatif olarak görünmektedir.

Anahtar Kelimeler: İşitme kaybı, ani; metilprednizolon; kurtarma tedavisi; steroidler

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Thirty decibel (dB) or more sensorineural hearing loss which develops in at least three consecutive audiometric frequencies within three days or less is defined as sudden hearing loss (SHL).[1] SHL is usually unilateral and accepted a medical emergency.[2] Although many factors have been blamed such as viral infections, immunologic disorders and vascular events, etiology is generally idiopathic.[1] To date, a number of treatment methods have been tried in the treatment of SHL. Among them, systemic steroids are drugs of proven therapeutic efficacy and widely used in the treatment of SHL.[3,4] There is no specific standard for effective steroid dose and the method of administration. However, the degree of improvement in hearing is closely related to a high concentration of steroids in the inner ear.[5] Compared to systemic steroid application, a higher concentration of steroid was found in the inner ears of the animals after intratympanic steroid injection.[6,7] Another important advantage of intratympanic steroid injection is absence of systemic side effects of steroids. Dexamethasone or methyl prednisolone is usually preferred for intratympanic steroid injection. Intratympanic steroid injection can be applied as the primary treatment or as a salvage therapy.[8] It especially appears as an effective method when applied as a salvage therapy in patients with SHL, when systemic therapy has failed.[7,9-16]

In this study, we aimed to determine the efficacy of intratympanic methyl prednisolone (IT-MP) therapy in SHL patients who failed after systemic treatment.

MATERIAL AND METHODS

This prospective study was approved by the local ethics committee of Gülhane Military Medical Academy. Sixteen patients with SHL in whom complete recovery could not be achieved (pure tone average ≤20dB) with systemic treatment given for 7 days (systemic steroids, hyperbaric oxygen or combined therapies) prospectively enrolled in the study between 2008 and September 2010. There were 9 males and 7 females. The mean age was 46.5±15.7 years (ranging between 19-68 years). Study protocol was explained to all of patients and they signed informed consent forms. Idiopathic SHL was diagnosed based on its classic definition, excluding inner ear trauma (barotrauma and temporal bone fracture), perilymphatic fistula, middle ear inflammatory diseases and retro-cochlear lesions. History, complete ear-nose-throat and neuro-otological examination, audio-vestibular testing and imaging studies were used to confirm the diagnosis. Patient with history of otologic surgery, acute or chronic otitis media, Meniere's disease or fluctuating hearing loss were excluded from the study. Before intratympanic injection, a cotton impregnated with a topical anesthetic cream (EMLA 5% cream; 25 mg/g lidocaine, 25 mg/g prilocaine hydrochloride, Astra Zeneca) was placed over the tympanic membrane for 15 minutes. Methyl prednisolone 40 mg/mL (Prednol-L 40 mg, 1 ampul, Mustafa Nevzat, Co.Turkey) was prepared for intratympanic injection. Following the topical anesthesia, the patient's head was rotated to opposite side for 45 degrees, and 0.4-0.5 mL of methyl prednisolone was administered into the middle ear through the postero-inferior quadrant of eardrum using a 27-gauge two-millimeter syringe, under microscopic view. The patient was asked to remain lying down at the same position for 30 minutes without coughing and swallowing, as much as possible. Intratympanic injections are planned to be 2 times per week. Pure tone audiometry test was performed before each injection and after the final injection. The mean air conduction thresholds at 500, 1,000 and 2,000 Hz frequencies was used in the calculation of pure tone average (PTA). Complete recovery was accepted when the PTA was 20 dB or lower. A change more than 10 dB in the PTA was considered as an alteration in hearing (either improvement or worsening). To decide for any change the PTA, two doses of intratympanic injections were performed. The injections were discontinued when there was no response, or PTA was 20 dB or lower.

The mean onset of the IT-MP injection after the beginning of the hearing loss was 16.1±6.5 days (range: 7-30 days). The average number of the injections was 3.8±1.3 (range: 2-6).

FAILED TREATMENTS BEFORE SALVAGE IT-MP AND ACCOMPANIED DISORDERS

Before salvage IT-MP therapy, 12 patients had undergone intravenous systemic therapy twice a day for 7 days (dexamethasone 4 mg, piracetam 2 gr, vitamin-B complex, vitamin-C 250 mg, clorpheniramine maleate 8 mg, in 250 mL isotonic solution). Six of them had taken oral methyl prednisolone (1 mg/kg) before the salvage therapy. Moreover, 9 of them had undergone hyperbaric oxygen (HBO) therapy in addition to systemic treatment. For HBO therapy, 100% oxygen in 2.5 ATA pressure was inhaled by patients for 90 minutes twice a day for 3 days, followed by 75-minute institution once a day which was continued based on the response. Two patients had partial benefits from systemic therapies partially (gain=20 dB in two cases, post-systemic treatment PTA=73 dB and 77 dB). The history revealed that one patient had diabetes mellitus, another had diabetes mellitus and hypertension and the other one had paroxysmal atrial tachycardia. The patient with paroxysmal atrial tachycardia could not tolerate HBO therapy after two sessions. Hemotympanum developed after one session of HBO therapy in another patient who failed after oral steroids and parenteral therapy.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences software (SPSS 11.5 for Windows, SPSS Inc., Chicago, ILS, USA) was used in the statistical analysis. Wilcoxon Signed Ranks test was used to compare pre- and post-treatment hearing thresholds. Median, minimum and maximum values were used to compare pre-and post-treatment hearing thresholds. Mean and±standard deviation were used in calculation of means of ages, number of injection and the admission day. Values $p<0.05$ were accepted as statistically significant.

RESULTS

Statistically significant improvement was obtained in PTA after IT-MP [initial median PTA was 85 dB (minimum 28 dB, maximum107 dB), final median PTA was 42.5dB (minimum 12 dB, maximum 107dB), p=0.007] (Table 1). Eleven (68.75%) patients improved more than 10 dB, but no change was observed in 5 (31.25%) patients. None of the patients had worsening of PTA. Two (12.5%) patients attained complete recovery (20 dB or less). Four (25%) patients improved to 30 dB or less in PTA. The mean gain in 16 patients was 24.5 dB (range between -9 and 68 dB). Distributions of pre- and post-treatment PTA are shown in Table 2. Comparison between pre- and post-IT-MP thresholds at 250, 500, 1,000, 2,000, 4,000 and 6,000 Hz also yielded significant differences (Table 1). Improvement was obtained at all six frequencies.

There were no serious unexpected complications. All patients experienced dizziness lasting 5-10 minutes after the injections. Six patients felt ear pain and 10 patients felt nasopharyngeal pyrosis due to escape of the steroid along the Eustachian tube.

TABLE 1: Comparison of pure tone averages and air conduction thresholds.

Means	Before intratympanic methyl prednisolone therapy: median (minimum-maximum) dB	After intratympanic methyl prednisolone therapy: median (minimum-maximum) dB	p
PTA	85 (28-107)	42.5 (12-107)	0.007*
250 Hz	77.5 (15-100)	27.5 (5-110)	0.011*
5,00 Hz	80 (15-100)	35 (10-110)	0.007*
1,000 Hz	82.5 (35-110)	50 (15-100)	0.002*
2,000 Hz	82.5 (20-115)	60 (10-110)	0.002*
4,000 Hz	80 (25-120)	67.5 (10-115)	0.013*
6,000 Hz	85 (25-120)	65 (10-115)	0.003*

PTA: Air pure tone average; Hz: Hertz; dB: Decibel. *Statistically significant.

TABLE 2: Distribution of hearing levels before and after intratympanic methyl prednisolone injection.

	Before-treatment	After-treatment
dB interval	The number of ears %	The number of ears %
0-20	-	2 (12.5%)
21-30	1 (6.25%)	2 (12.5%)
31-40	-	3 (18.75%)
41-50	2 (12.5%)	2 (12.5%)
51-60	1 (6.25%)	2 (12.5%)
61-70	1 (6.25%)	1 (6.25%)
71-90	8 (50%)	2 (12.5%)
>90	3 (18.75%)	2 (12.5%)

DISCUSSION

Up to date, a number of different treatment methods have been tried in the management of SHL. Among these, high-dose systemic steroid therapy is the most widely accepted one by many physicians, and many studies have demonstrated the efficacy of this treatment. Despite the mechanism of action of steroids have not been fully understood, the degree of hearing improvement is closely related to high concentration of steroids in the inner ear.[5] In spite of systemic treatments given for two weeks, there is no response in 30-50% of the patients.[1,6] An additional treatment must be searched for these patients. In addition, high-dose systemic steroid therapy may cause unfavorable effects on accompanying diseases such as diabetes mellitus, hypertension, gastric ulcer, glaucoma, osteoporosis and tuberculosis, and may lead to avascular necrosis of femoral head, myopathies, psychological disorders, susceptibility to infection by suppressing the immune system, and the use of steroids is limited in pregnant women.[5,10,17] In patients with no response to the systemic therapy, readministration of systemic steroids not be possible because of these side effects.

Some studies reported that hyperbaric oxygen therapy might be effective in patients with SHL when conventional therapy fails.[18,19] Muzzi et al. reported that salvage HBO therapy was effective especially at low frequencies and in older patients.[20] On the other hand, every patient may not tolerate HBO treatment. In addition, HBO therapy must be discontinued if side effects occur.[21] In these situations, intratympanic steroid injection may become the only alternative as the salvage therapy. In the study, two patients had to stop HBO therapy because one developed hemotympanum and the other could not tolerate it due to paroxysmal atrial tachycardia. Both improved with IT-MP (final PTAs: 30 dB and 15 dB, respectively).

Intratympanic steroid therapy has some advantages. When compared to systemic steroids, it results in a higher steroid concentration in the inner ear and has no systemic side-effects.[1,6,7] In the review of Plaza and Herraiz, it was reported that intratympanic steroid therapy was successful in 12 -75% of patients who failed with systemic steroids.[15] Slattery et al. could obtain 55% success by applying IT-MP as the salvage treatment.[16] Raymundo et al. observed 70% success (hearing recovery >20 dB) after applying IT-MP in patients who did not benefit from oral steroids.[22] Fitzgerald and McGuire performed intratympanic steroid as a primary treatment in patients with SHL.[23] They obtained 90% success when they performed it in the early period (in 14 days) of hearing loss, while they obtained 40% success in the late phase (after 14 days).[23] In the study of Ahn et al., intratympanic dexamethasone was given as the salvage treatment.[11] The patients were divided into four groups as follows: Those receiving no further treatment (control group), those receiving intratympanic dexamethasone within 2 weeks (early), between 2 weeks and 1 month (mid), and between 1 and 2 months (late) after initial treatment failure. In 16% of the control group hearing improvement was obtained. This rate was 43.8% in the early group, 30% in the mid group and 15.4% in the late group, respectively.[11] The authors also found that hearing improvement at 500 and 2,000 Hz frequencies was higher in early group compared to the control group.[11] Choung et al. observed that hearing gain at low frequencies (250, 500 and 1,000 Hz) was better with intratympanic dexamethasone who were refractory to oral steroids.[13] Differences of the success rates among the studies may be associated with the degree of the hearing loss, the dose of the

steroid given, frequency of injection, time interval between beginning of the therapy and the onset of the hearing loss, etiology and comorbid diseases. In our study, PTA improved in 68.75% of the patients, and 25% of the patients attained 30 dB or less PTA. In addition, significant improvement was achieved in 250, 500, 1,000, 2,000, 4,000 and 6,000 Hz frequencies. We did not divide patients according to time interval between beginning of the therapy and the onset of the hearing loss due to limited number of our patients. Results of the study are satisfactory although the study included a small group of patients. Aydın et al. reported that IT-MP had better hearing results compared to combined therapy (intravenous dextran and oral pentoxyfilline).[24] They administered 5 intratympanic injections regardless of the hearing results. We took PTA into consideration for deciding to continue the injections. When there was no improvement after 2 injections, we stopped the therapy. However, there is no standard protocol for intratympanic steroid therapy. Different injection numbers and steroid types have been tried in the studies to date. In our opinion, intratympanic steroid injection should be continued as long as there is improvement in hearing.

Parnes et al. reported that methyl prednisolone was absorbed better than dexamethasone through the round window membrane.[6] Cvorovic et al. reported that the mean hearing improvement was significantly higher in IT-MP group compared to intratympanic dexamethasone group when applied as the primary therapy.[25] We also preferred methyl-prednisolone in our study. However, new studies are needed to compare the therapeutic efficacies of methyl-prednisolone and dexamethasone.

Complications of treatment with intratympanic steroid injection are pain, short-term dizziness, otitis media and tympanic membrane perforation.[14] In our study, main complications were dizziness lasting 5-10 minutes, ear pain and nasopharyngeal pyrosis. All of them are minor and transient. There were no serious complications. In our experience, intratympanic dexametazon caused less pain, dizziness and nasopharyngeal pyrosis.

CONCLUSION

As a result, IT-MP treatment in patients who did not respond to systemic therapy appears to be a good alternative to obtain better hearing results in SHL. Side effects of the therapy are usually temporary and negligible. IT-MP treatment is a promising option for both physicians and patients seeking treatment.

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