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EFFICACY AND SAFETY OF INTRATYMPANIC STEROID TREATMENT FOR IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS

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ABSTRACT

Objectives: This study was planned to evaluate the efficiency and safety of Intratympanic (IT) injection of methylprednisolone (IT-MP) on idiopathic sudden sensorineural hearing loss (ISSHL) patients as an initial therapy, by weighing against the outcome with intravenously administered dexamethasone (IV-DEX) treatment. **Materials and Methods:** A prospective, nonrandomized, comparative study was conducted for 50 patients presenting with ISSHL. Twenty-five patients were managed with intratympanic methylprednisolone as a single and initial treatment, and 25 with intravenous dexamethasone. The hearing level was described using the Pure Tone Average (PTA in dB) hearing level at four frequencies (0.5, 1, 2 and 4 kHz). Hearing gain was expressed as absolute hearing gain and relative hearing gain. Complete hearing recovery was defined as the final PTA within 10 dB of baseline. Partial recovery was defined as a final PTA with a ≥ 50% relative recovery. **Results:** Mean hearing improvement was significantly higher in IT MP group than in IV DEX group (50.7±22.11, versus 29.5±28.0, $p<0.01$). We found a high rate of relative recovery of hearing in IV DEX group, which was because of significant hearing level of the unaffected ear. Similar percent of patients in both groups had complete recovery, but in the IV DEX group 42% patients had no recovery (versus 10% in IT MP group).**Conclusion:** Intratympanic treatment of ISSHL may be a first choice , since it can be delivered in outpatient settings with no serious side effects and low complication rate.

Key words: Intratympanic (IT) injection, sensorineural hearing loss, dexamethasone.

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSHL) was defined as a 30 dB loss over three continuous frequencies occurring in less than 3 days, with no marked vestibular symptoms and no identifiable cause. The common causative etiologies are viral infection, intralabyrinthine

membrane breaks, vascular occlusion, identified for ISSHL **(1)**. Different etiologies and doubtful pathogenesis makes a ground for empirical treatment of ISSHL. Treatment of sudden sensorineural hearing loss (SSNHL) is very critical and challenging issues of the current otorhinolaryngology. The systemic steroids administration is conventional treatment strategy to care for ISSHL. Although proven effective in randomized, double blind, placebo- controlled trials, other studies have questioned the efficacy of systemic steroids in the treatment of ISSHL **(2-4)**. Today steroid therapy is considered to be the most effective and common method for SSNHL treatment. At the same time, a huge number of side effects appear to be associated with the long-term systemic use of steroids. A new approach, intratympanic (IT) administration of steroids gives the impression that it may be an expedient method of controlling of ISSHL. The use of IT steroids has developed into three protocols for cure of ISSHL: as initial or primary treatment, as additional treatment given concurrently with systemic steroids and when of systemic steroids are not effective for ISSHL. Most of the studies related to the use of IT steroids in the treatment of ISSHL has described the experience in treatment after failure of systemic therapy **(5-8)**. Two researchers showed in their studies that the Intra tympanic steroids therapy is more effective in the treatment of ISSHL when used with systemic steroids **(9, 10)**. Only two studies assessed the efficacy of IT steroidal therapy on ISSHL patients as a primary and single therapy **(11, 12)**. Neither the optimal dosage of systemic steroids nor the treatment duration has been precisely defined, so they are often picked up empirically and are far from being accurate. The purpose of this study has been to evaluate the efficacy and safety of IT administered methylprednisolone (IT-MP) on ISSHL patients as a primary therapy, by comparing the results with intravenously administered dexamethasone (IV-DEX) treatment.

MATERIALS & METHOD

From January 2013 to May 2014, a prospective, nonrandomized, comparative study was conducted for 50 patients presenting with ISSHL. All patients underwent a standard evaluation protocol (ENT examination, basic audiometry, laboratory investigations, including full blood count, biochemistry and serology for borreliosis in selected cases, thyroid function tests and antigen nonspecific serologic tests; auditory brain stem response and magnetic resonance imaging with contrast only in patients with no recovery of hearing). The hearing level was explained using the pure tone average (PTA in dB) hearing level at four frequencies (0.5, 1, 2 and 4 kHz). Pure tone audiometry was performed just before the treatment and each injection, three weeks and two months after the treatment.

Randomization was not possible as some of the patients denied any invasive procedure for the management of their hearing loss and they were coped with IV DEX. The patients were informed about the new treatment and the possible benefits and risks. Informed consent was obtained from all patients, who agreed with IT MP treatment. The institutional Ethical boards of the Mahatma Gandhi Medical College & Hospital, Jaipur, approved the present study.

The IT MP group consisted of 25 patients. The IT MP treatment consisted of 0.3-0.8 mL sterile aqueous suspension of methylprednisolone

(Lemod Solu, Hemo-farm, Vrsac, Serbia) warmed to body temperature, in a concentration of 80 mg/mL instilled slowly with a fine needle (21 gauge) and 1 mL-syringe through the posterior-inferior quadrant of the tympanic membrane of the affected ear. Local anaesthesia was achieved with topical lignocaine chloride 2% (Lidokainhlorid, Galenika, Belgrade, Serbia). MP was allowed to perfuse the middle ear for 30 minutes with the patient`s head tilted at 45 degree . Patients were instructed to swallow as little as possible and stay still. The procedure was performed four times within a 13- day period. The IV DEX group consisted of 25 patients. They were treated intravenously with 40 mg of dexamethasone for three consecutive days followed by 3 days of 10 mg. Furthermore, they received protection against peptic ulcer disease with oral ranitidine during steroid treatment.

The Pure Tone Average in unaffected ear was considered as the baseline hearing or presumed premorbid hearing in the affected ear. Hearing gain was stated either as absolute hearing gain which is defined as dB values from initial PTA minus dB values from final PTA or as relative hearing gain which is defined as (absolute hearing gain divided by initial PTA minus baseline PTA). A threshold value of 100 dB HL was assumed if the average hearing loss exceeded the limits of the audiometric equipment. Complete hearing recovery was defined as the final PTA within 10 dB of baseline. Partial recovery was defined as a final PTA with a $\geq$ 50% relative recovery.

Quantitative variables have been described by mean ± standard error of mean (SEM), whereas frequency distribution tables have been used for categorical variables. Data analysis was performed using independent sample Student t-test. All tests have been 2-sided and level of statistical significance was set at 5%.

RESULTS

Fifty patients were enrolled in the study. Twenty-five patients were treated with intratympanic methylprednisolone as a primary therapy, and 25 with intravenous dexamethasone.

Table 1 summarizes the profiles of the patients in IT MP and IV DEX groups. There were no significant differences in age, duration between onset and treatment and initial hearing loss between the two groups, but there was a difference in hearing threshold in unaffected ears (Student's t test).

In the IT MP group, 12 (48%) of the 25 patients showed complete recovery, six had partial, whereas two patients showed no hearing recovery. Both of them had more than 30 days between onset and treatment. Four patients had initial hearing loss more than 100 dB, and all of them had relative recovery about 80%.

In the IV DEX group, 12 (48%) of the 25 patients showed complete recovery, whereas ten patients had no hearing recovery. Table 2 summarizes the clinical outcomes in the IT MP and IV DEX groups.

In IT MP group, the average amount of medication injected ranged between 0.3-0.8 ml (mean 0.5 ml) for each injection. Most of patients received four injections (four had three, and one had two injections). The reason for discontinuation of treatment was complete recovery of hearing. The average amount of time elapsed between injections was 4 days and

average total time from the first injection to the last injection was 13 days, ranging from 8 days to 15 days.

No unexpected adverse events occurred during the injections or follow-up period. Five patients had a mild ear pain occurring during the first post- injection hour. No perforation or infection was noticed in any of the patients at their last follow -up visit.

Table 1: General data regarding groups IT-MP & IV-DEX:

	IT-MP	IV-DEX	p (Student's t-test)
Number of Patients	25	25	
Age (yr) **Mean ± SEM** **Range**	 45.3±13.7 25 - 67	 53.5± 15.1 17 – 74	t = 0.407, p= 0.686; NS
Duration before Treatment (d) **Mean ± SEM** **Range**	 11.2± 9.9 2 - 47	 11.9±9.6 2 – 36	t = 0.051, p= 0.960; NS
Initial Hearing Level (dB) **Mean ± SEM** **Range**	 71.3±12.4 40 - 100	 72.9±19.6 45 - 100	t = 0.069, p= 0.945; NS
Hearing Level of unaffected ear (dB) Mean ± SEM	14.7±11.9	25.8±11.7	t = 0.665, p= 0.509; NS

IT-MP: Intratympanically administered MethylPrednisolone treatment, IV-DEX: Intravenously administered Dexamethasone, SEM: Standard Error of Mean, NS: Not Significant, SIG: Significant.

Table 2: Recovery after IT-MP & IV-DEX Treatment:

	IT-MP	IV-DEX	p (Student's t-test)
Number of Patients (n)	25	25	
Absolute Recovery (dB) **Mean ± SEM** **Range**	 66.3±12.4 0 - 80	 19.9±19.1 0 - 80	t = 2.038, p= 0.047; SIG
Relative Recovery (%) **Mean ±SEM**	 83.1±11.4	 39.9±17.9	t = 2.036, p= 0.047; SIG

IT-MP: Intratympanically administered MethylPrednisolone treatment, IV-DEX: Intravenously administered Dexamethasone, SEM: Standard Error of Mean, NS: Not Significant, SIG: Significant.

DISCUSSION

To evaluate the influence of IT steroids on hearing levels in patients with ISSHL we included patients with no previous treatment and compared them with patients who received systemic steroids.

Here, we used methylprednisolone (80 mg/mL) injected through the tympanic membrane toward the round window, in the dose of 0.3-0.8 mL four times within 13-day period. Described techniques for steroid perfusion of the middle ear for ISSHL differ in many aspects, including the type of steroid used. Dexamethasone is the most common steroid used for intratympanic use **(6, 8, 10, 12)** followed by methyl-prednisolone. **(5, 9, 13)** Reports in literature also differ in the strength of the solution i.e. 2-4 mg/ml **(6)** to 25 mg/ml dexamethasone; **(7)** 32 mg/ml **(9)** to 62.5 mg/ ml Methylprednisolone. **(5)** The amount injected into the middle ear in most studies is between 0.3 and 0.5 mL, the approximate volume of the middle ear space. There are many techniques, that differ in method of delivery: transtympanic needle injection **(6, 8, 9, and 12),** delivery through a myringotomy **(7)**, delivery through a myringotomy with a tube. **(9)** Different researcher differ in the frequency of injections and duration of time to manage patients with intratympanic steroids i.e. from a single day to weekly transtympanic injections **(5,6,9)** to trans-tympanic injections given several times per week. **(7,9,14)** Further randomized, prospective, clinical studies are needed to elucidate the optimal dosages, technique and frequency of administration of steroids.

Animal experiments show that local application of corticosteroids into the middle ear results in higher inner ear concentration as compared to systemic application. **(13)** Parnes compared pharmacokinetic of methyl-prednisolone, dexamethasone and hydrocortisone in inner ear, and concluded that methylprednisolone had the highest concentration and longest half-life in perilymph. **(13)**

In the current study, there were no significant differences in age, duration between onset and treatment and initial hearing loss between the two groups.

There was a significant improvement in Mean hearing in IT MP group than in IV DEX group .The mean hearing was higher in IT MP group than in IV DEX group (50.7±22.11, versus 29.5±28.0, $p<0.01$). There was significant difference between hearing level of the unaffected ear (hearing threshold was worse in the IV DEX group) and it had influence on high rate of relative recovery of hearing in IV DEX group. There was no difference in mean relative recovery between the two groups. Similar percent of patients in both group had complete recovery, but in the IV DEX group 42%, patients had no recovery (versus 10% in IT MP group).

Only two papers have studied the effects on intratympanic corticosteroids as a primary therapy. **(11, 12)**Banarjee and Parnes reported successful hearing improvement in 50% (mean PTA improvement was 27 dB) when intratympanic methylprednisolone was used as a primary treatment.**(11)** Kakehata et al presented a case-control study, revealing that intratympanic method was also effective as initial therapy in

ISSHL, with less hazards than systemic steroids. They compared a group of 10 diabetic patients who were treated with intratympanic dexamethasone and showed successful hearing improvement in 70% (mean PTA improvement was 41 dB), and historical group of 21 patients who were treated with intravenous dexamethasone and had successful hearing improvement in 62% (mean PTA improvement was 25 dB). **(12)**

However, our results were based on small sample sizes like in the other studies, and variance in intratympanic treatment response is wide, between 27 dB **(11)** (trial with 26 patients) and 41 dB **(12)** (trial with 10 patients). We need larger sample sizes to establish valid conclusion of intratympanic steroid treatment as primary therapy of ISSHL. In addition, reporting the hearing improvement should be a more objective and standardized.

Furthermore, it is not very clear whether this effect was actually from intratympanic steroid or the natural course of disease. A main limitation of the study was no control group with any treatment. Weinaug **(15)** reported a spontaneous hearing recovery rate without treatment for sudden hearing loss of 25.6 dB and a relative hearing gain of 47%. The spontaneous recovery rate, defined as a hearing gain of at least 30 dB, was 73% as reported by Mattox and Simmons. **(3)** Wilson et al.**(1)** reported that 29 of 52 non-treated patients regained normal hearing ability (i.e., 56%).The average absolute hearing gain between the initial audiogram and the final audiogram in IT MP group was 50.7 dB; the mean relative recovery was 78%. The recovery rate of our IT MP group seems high compared to other reports of spontaneous recovery rates.

In our study, we did not find unexpected adverse events during the injections or follow-up period. Five patients had a mild ear pain treated with analgesics. Reported complications were rare and included pain, vertigo, otitis media, tympanic membrane perforation, dysgeusia, and chronic otitis media and further hearing loss. **(5, 6, 10, 12, 13)**

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Ethical approval: The study was approved by the institutional ethics committee

CONCLUSION

Following these encouraging results, it seems that intratympanic treatment of ISSHL may be a preferable choice as primary therapy, since it can be delivered in outpatient settings, with no serious side effects and low complication rate. Furthermore, future controlled studies with larger sample sizes should contribute even more to confirm these findings.

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