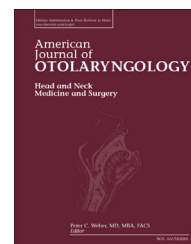


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Sudden Sensorineural Hearing Loss: Results of intratympanic steroids as salvage treatment^{☆,☆☆}

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ABSTRACT

Objective: The aim of the present study was to verify the efficacy and the safety of intratympanic dexamethasone to treat sudden sensorineural hearing loss as salvage therapy.

Materials and methods: A prospective study was conducted on patients affected by idiopathic sudden hearing loss who were treated before with some systemic therapy, but without recovery of the hearing. The patients able to undergo the study, but who refused salvage treatment were considered as control group. A solution of Dexamethasone 4 mg/ml was then injected through the posterior-inferior quadrant filling completely the middle ear. The follow-up in the following 6 months included an audiogram every month.

Results: The number of patients treated with salvage therapy was 36. The patients who refused treatment were further 10. The salvage treatment was done with a mean delay of 24.3 days from the onset of symptoms. Mean hearing threshold after the onset of sudden hearing loss at PTA was 66.5 dB. After the failed treatment the mean PTA was 59.6 dB. The mean PTA after the intratympanic steroid administration was 46.8 dB, with a mean improvement of 12.8 dB. No hearing change was noted in the 10 patients who refused salvage therapy. The patients that assumed systemic steroid as first therapy showed a better PTA threshold after the salvage intratympanic treatment ($p < 0.01$). A significant difference ($p < 0.05$) of hearing recovery was evidenced between non-smoker patients and those with smoking habit.

Conclusions: Our data showed that a salvage treatment with intratympanic dexamethasone should be suggested to all patients who failed the first systemic treatment. The systemic steroid therapy done before the salvage treatment seems to exert a protective role for the inner ear, as shown by our series. On the contrary the smoke habit is a negative prognostic factor in the hearing recovery.

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1. Introduction

The loss of hearing of at least 30 dB over at least 3 contiguous frequencies occurring within 3 days or less is known as Sudden Sensorineural Hearing Loss (SSHL). In more than 90% of patients, the true cause of the hearing loss is not discovered, constituting an idiopathic disease. The estimated incidence of such disease is 5 to 20 cases per 100,000 annually [1]. However the exact incidence is underestimated, because many patients who recover early (within first few days) are unlikely to seek medical care [2]. The rate of spontaneous recovery is approximately between 32% and 70% which encourage some otologists not to treat SSHL patients [3].

The lack of consensus in the management of SSHL is due to difficulty in finding the true etiology of the deafness. Numerous treatments have been described: steroids, antiviral drugs, osmotic diuretics, anticoagulants, vasodilators, hyperbaric oxygen, carbogen; most therapies showed some benefits in restoring hearing notwithstanding the lack of robustness of the data.

The most widely employed drugs in the management of SSHL are steroids that are administered as a single agent or associated with other drugs. Several placebo-controlled trials reported encouraging results in terms of recovering of hearing loss [4,5], although other authors discussed such efficacy in the treatment of SSHL [1,3,6,7].

Although the treatment is started within a reasonable time after onset of the hearing loss, the result is not always achieved and about 30%–40% of patients have no benefits after systemic treatment.

The aim of the present study was to verify the efficacy and the safety of intratympanic dexamethasone (ITD) to treat SSHL patients as salvage therapy after other treatments.

2. Materials and methods

A prospective study was conducted on patients affected by idiopathic SSHL who were treated before with some systemic therapy, but without recovery of the hearing (less than 10 dB of PTA threshold recovery). The patients included

were referred to our departments from January 2011 to December 2011. The inclusion criteria were: an SSHL of at least 30 dB across 3 contiguous frequencies over a period of 3 days and a previous systemic treatment that gave no recovery of hearing. The patients with the following characteristic were excluded: history of middle ear pathology, previous intratympanic treatments administered elsewhere for the same disease. The patient evaluation included: thorough history, otoscopy, bedside peripheral vestibular system examination, pure tone audiometry (repeated weekly) and MRI of internal auditory canal and cerebello-pontine angle. History detailed: onset of hearing loss, otological symptoms related with hearing loss, drugs consumed in the past days and presence of others systemic diseases. The bedside examination was done for spontaneous and positional nystagmus, Romberg test, Fukuda test, Halmagyi test and Head Shaking test.

The patients able to undergo the study, but who refused salvage treatment were considered as control group.

Intratympanic injection was done in supine position with the head rotated to 45° to the unaffected side. Under microscope a myringotomy was done in the anterior-inferior quadrant of the tympanic membrane in order to allow the exit of the air in the middle ear during drug injection. A solution of Dexamethasone 4 mg/ml was then injected through the posterior-inferior quadrant filling completely the middle ear. The patient maintained the position of the head for 20 min and was instructed to avoid swallowing, speaking and movements of the head. The intratympanic injection was repeated five times every two days.

An audiogram was done weekly during the treatment protocols in both the groups.

The follow-up in the following 6 months included an audiogram every month.

Patients lost during the follow-up and with evidence of retrocochlear disease at MRI (i.e.: vestibular schwannoma) were excluded from the analysis.

A response to the treatment was considered if a change was recorded in PTA by calculating Δ PTA as the difference between the PTA before salvage treatment and the last PTA recorded during follow-up (at least after two months).

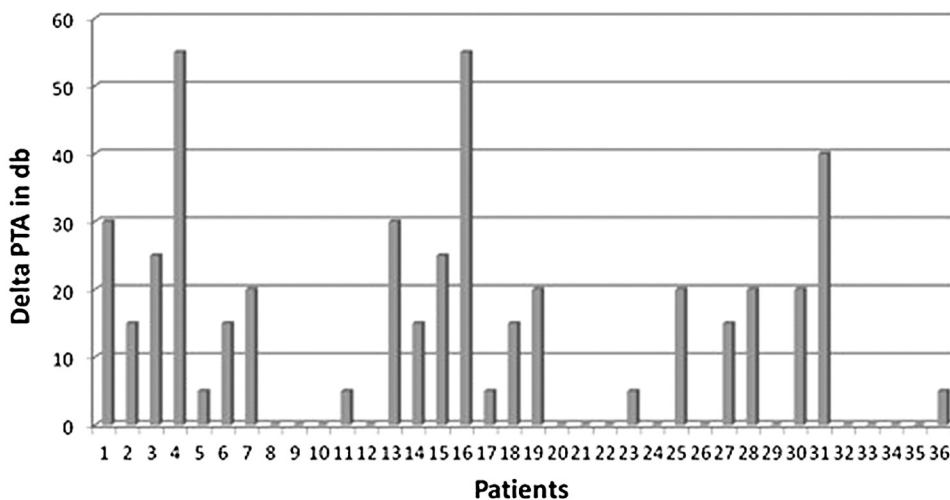


Fig. 1 – Delta PTA (First Therapy PTA – Post Salvage PTA) in decibel for every patients.

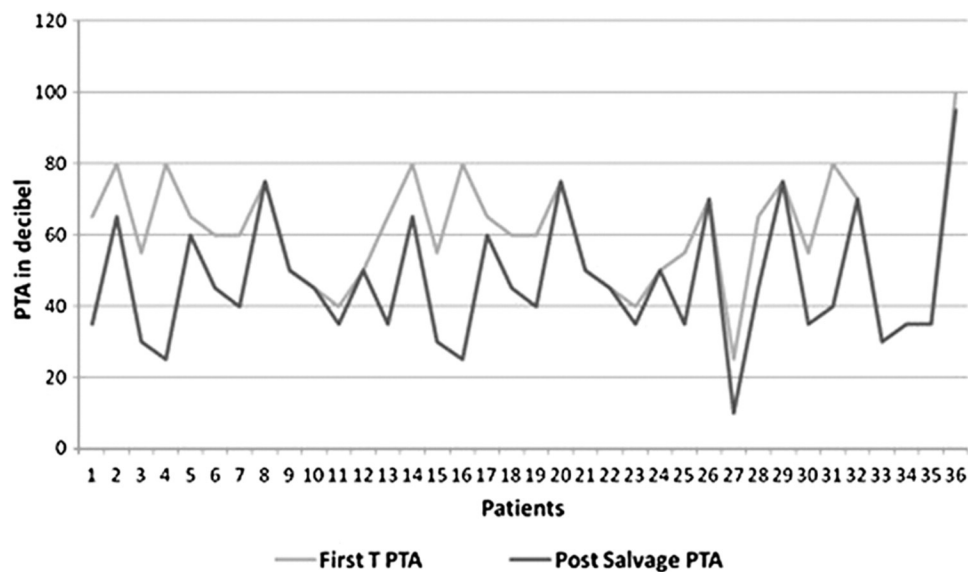


Fig. 2 – Comparison between First Therapy PTA and Post Salvage PTA for each patients.

Data were entered in a database created within EpiInfo 3.5.1 software. All the data were analyzed using the R statistical software package. Absolute and relative frequencies were calculated for qualitative variables, while quantitative variables were summarized as mean (\pm standard deviation and range). Categorical variables were analyzed using the chi-square test (Mantel-Haenszel). Odds ratio (OR) with 95% confidence intervals (95% CIs) were also calculated. Differences in means were compared with the Student t-test. All variables found to have a statistically significant association (two-tailed p -value < 0.05) with improved PTA in the univariate analysis were included in a multivariate regression model. The significance level chosen for all analysis was 0.05, two-tailed. All patients signed an informed consent before the treatment and our Review Boards approved the present study.

3. Results

The number of patients treated with salvage therapy was 36, of which 20 patients were female. The patients who refused treatment were further 10. The mean age of the whole series was 49.4 years. The salvage treatment was performed with a mean delay of 24.3 days from the onset of symptoms and about 2 days from the end of the first therapy done (Table 1).

Hearing threshold after the onset of sudden hearing loss at PTA was 66.5 dB (range 25–100 dB; SD \pm 17.1 dB). After the failed treatment administered the PTA was 59.6 dB (range 25–100 dB; SD \pm 16.7 dB). The PTA after the intratympanic steroid administration was 46.8 dB (range 10–95 dB; SD \pm 17.9 dB), with a mean improvement of 12.8 dB (SD \pm 15.2 dB) (Figs. 1–2). No hearing change was noted in the 10 patients who refused salvage therapy.

The otoneurologic symptoms presents in the patients were: true vertigo in 47.2% and tinnitus in 91.7%. In the group of salvage treatment 9 patients were smokers of more than 20 cigarettes per day, 5 patients were diabetics and 5 suffering untreated hypertension.

The first treatment administered was a systemic steroid therapy in 41 patients (89%), of which 22 received also intravenous osmotic diuretics (i.e. mannitol or glycerol). Osmotic diuretics alone were administered in 4 patients unable to take systemic steroids. Hyperbaric oxygen and

Table 1 – Sociodemographic characteristics, symptoms, comorbidities and audiometric outcomes of the patients with sudden hearing loss (n=46).

Age, mean in years \pm SD (range)	49.4 \pm 14.7 (17–74)
Gender, n (%)	
Male	21 (45)
Female	25 (55)
Side, n (%)	
Left	23 (50.0)
Right	23 (50.0)
Salvage treatment delay, mean in days \pm SD (range)	24.3 \pm 23.9 (7–153)
Initial PTA, mean in dB \pm SD (range)	66.5 \pm 17.1 (25–100)
First Therapy PTA, mean in dB \pm SD (range)	59.6 \pm 16.7 (25–100)
Post Salvage PTA, mean in dB \pm SD (range)	46.8 \pm 17.9 (10–95)
Delta PTA, mean in dB \pm SD (range)	12.8 \pm 15.2 (49–55)
Vertigo, n (%)	
Yes	22 (48)
No	24 (52)
Tinnitus, n (%)	
Yes	38 (83)
No	8 (17)
Smokes, n (%)	
Yes	14 (30)
No	32 (70)
Diabetes, n (%)	
Yes	10 (21)
No	36 (79)
Hypertension, n (%)	
Yes	10 (21)
No	36 (79)

Table 2 – First Approach treatment of the hearing loss of the patients treated with salvage intratympanic therapy (n=36).

	N=36
Steroids therapy, n (%)	
Yes	32 (88.9)
No	4 (11.1)
Hyperbaric oxygen, n (%)	
Yes	8 (22.2)
No	28 (77.8)
Osmotic diuretics, n (%)	
Yes	26 (72.2)
No	10 (28.8)
Antiviral drugs, n (%)	
Yes	3 (8.3)
No	33 (91.7)

antiviral drugs, associated to steroids, were done respectively to 8 and 3 patients (Table 2).

A salvage treatment delay categorization was made in accordance with median value (20 days). According to salvage treatment delay categorization there were no statistically significant differences between a delay less than or equal to 20 days and more than 21 days (Table 3).

The patients that assumed systemic steroid as first therapy showed a better PTA threshold after the salvage intratympanic treatment ($p < 0.01$) as displayed in Table 4.

A statistically significant difference ($p < 0.05$) of hearing recovery was evidenced between non-smoker patients and those with smoking habit, which recovered respectively (mean) 15.9 dB versus 3.3 dB (Table 5).

4. Discussion

The use of intratympanic steroid is a known procedure. Itoh and Sakata first reported its use in 1991 in treatment of patients with Meniere’s disease [8]. The first use of intratympanic therapy in SSHL was described by Silverstein in 1996 [9].

The rationale supporting the ITD administration is the round window membrane permeability to the drugs. Elevated perilymphatic concentration of steroids can be achieved after transtympanic administration, higher than after systemic administration [10,11]. The distribution of drugs shows a decreasing concentra-

Table 3 – Average PTA at different stages according to categorization of salvage treatment delay (n=36).

	Salvage treatment delay		p-value
	≤ 20 days (n=19)	> 21 days (n=17)	
Initial PTA, mean in dB±SD	62.6±20.8	70.9±10.8	0.33
First time PTA, mean in dB±SD	56.3±19.5	63.2±12.4	0.18
Post Salvage PTA, mean in dB±SD	46.8±20.0	46.8±15.9	0.95
Delta PTA, mean in dB±SD	9.5±11.2	16.5±18.3	0.28

Table 4 – Average PTA at different stages according to previous steroids therapy (n=36).

	Steroids Therapy		p-value
	Yes (n=32)	No (n=4)	
Initial PTA, mean in dB±SD	64.5±16.7	82.5±13.2	< 0.05
First time PTA, mean in dB±SD	57.6±15.6	75.0±18.7	< 0.05
Post Salvage PTA, mean in dB±SD	44.1±15.3	68.7±24.9	< 0.01
Delta PTA, mean in dB±SD	13.6±15.6	6.3±9.4	0.36

tion from basal turn of the cochlea to the apical portion, with maximum level near the inner aspect of the round window membrane [12]. The diffusion of molecules into inner ear fluids and compartments follows different pathways: with perilymphatic flow through the helicotrema (longitudinal) and across the spiral ligament (interscalar communication). Salt et al. found that whatever protocol adopted, did not influence the relative distribution of drugs into inner ear fluids, believing that this fact is secondary to the drug clearance from the perilymph [13]. However the cochlear pharmacokinetics are not clearly understood and the distribution of drugs along the human cochlea is different than that of rodents used for the study, and in the opinion of Mikulec et al. it is not a good model [14].

Systemic steroid treatment is widely accepted and recommended as first line therapy in most countries [15] and in our region correspond to the most adopted protocol of treatment even when the patients refer to private ENT practitioners or public ENT ambulatory.

The definition of the true therapeutic intervention on hearing improvement is difficult to determine because of the natural history of SSHL includes a high rate of spontaneous recovery ranging from 31% to 89% [4]. However, the results presented in the present study confirm the efficacy of ITS as salvage therapy, although the number of patients was relatively low, but in line with similar report published.

A hearing improvement in patients with SSHL who failed to recover with primary systemic therapy was reported by several authors [16–20]. Also in our study the rate of recovery after salvage therapy was good and similar to already mentioned reports. The unchanged hearing recorded in those patients who refused the salvage treatment was indicative of the role of the intratympanic treatment in restoring some hearing function, even if minimal.

Table 5 – Average PTA at different stages according to smoking habit (n=36).

	Smoking habit		p-value
	Yes (n=9)	No (n=27)	
Initial PTA, mean in dB±SD	62.2±15.1	67.9±17.8	0.39
First time PTA, mean in dB±SD	54.4±15.5	61.3±16.9	0.29
Post Salvage PTA, mean in dB±SD	51.1±17.8	45.4±18.1	0.41
Delta PTA, mean in dB±SD	3.3±6.6	15.9±16.0	< 0.05

An interesting finding emerging from this prospective study was the relationship between smoking habit and refractoriness to treatment. Several studies have shown primary tobacco smoke to be associated with a significant hearing loss risk [21,22]. Smoke consumption has been reported to be a direct ototoxic agent (nicotine effect) and an indirect cause of ischemia in the cochlea through production of carboxyhemoglobin, vasospasm, increased blood viscosity, and its action in relation to blood vessel atherosclerosis [23]. This study linked the failure of intratympanic salvage therapy to tobacco smoking, and these data should be kept in mind when planning some salvage therapy in patients who smoke cigarettes during treatment.

Furthermore, the data analysis showed that the patients treated before with systemic steroids had some benefit in the inner ear homeostasis, although the hearing threshold was unmodified. All patients treated with steroids as first therapy had a better response to salvage therapy with some recovery of the hearing, respect those that had only diuretics or antiviral drugs.

The steroid action and the sensitivity of the inner ear to smoke could indicate that the effect of intratympanic steroid is linked to vascular supply, and to the oxygenation of the inner ear as consequence.

As shown in our previous report [2], the outcome is not strictly related to the time of treatment start after the hearing loss. This was also noted by Parnes et al. who treated 37 patients affected by several inner ear disorders [10] and by Ho et al. in 39 cases [24]. The absence of relationship between start of treatment and outcome is very important allowing to perform an ITS as salvage therapy also after several days of delay and further diagnostic exams as imaging.

5. Conclusions

Our data showed that a salvage treatment with intratympanic dexamethasone should be suggested to all patients who failed the first systemic treatment. The unchanged hearing of the group of patients who refused salvage therapy is indicative of some important action of the steroids into the cochlear recovery process. The systemic steroid therapy done before the salvage treatment seems to exert a protective role for the inner ear, as shown by our series. On the contrary the smoking habit is a negative prognostic factor in the hearing recovery. We agree with the last recommendation of the American Academy in the field of SSHL [25] that considers the salvage intratympanic steroids as a recommended therapy.

REFERENCES

- [1] Byl FJ. Sudden hearing loss: eight years' experience and suggested prognostic table. *Laryngoscope* 1984;647.
- [2] Dispenza F, Amodio E, De Stefano A, et al. Treatment of sudden sensorineural hearing loss with transtympanic injection of steroids as single therapy: a randomized clinical study. *Eur Arch Otorhinolaryngol* 2011;268:1273-8.
- [3] Mattox DE, Simmons FB. Natural history of sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 1977;463.
- [4] Wilson WR, Byl FM, Laird N. The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study. *Arch Otolaryngol* 1980;106:772.
- [5] Moskowitz D, Lee KJ, Smith HW. Steroid use in idiopathic sudden sensorineural hearing loss. *Laryngoscope* 1984;664.
- [6] Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss: II. A meta-analysis. *Arch Otolaryngol Head Neck Surg* 2007;133:582-6.
- [7] Cinamon U, Bendet E, Kronenberg J. Steroids, carbogen or placebo for sudden hearing loss: a prospective double-blind study. *Eur Arch Otorhinolaryngol* 2001;258:477-80.
- [8] Itoh A, Sakata E. Treatment of vestibular disorders. *Acta Otolaryngol Suppl* 1991;481:617-23.
- [9] Silverstein H, Choo D, Rosemberg SI, et al. Intratympanic steroid treatment of inner ear disease and tinnitus (preliminary report). *Ear Nose Throat J* 1996;75:468-71.
- [10] Parnes LS, Sun AH, Freeman DJ. Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. *Laryngoscope* 1999;109:1-17.
- [11] Chandrasekhar SS, Rubinstein RY, Kwartler JA, et al. Dexamethasone pharmacokinetics in the inner ear: comparison of route of administration and use of facilitating agents. *Otolaryngol Head Neck Surg* 2000;122:521-8.
- [12] Dispenza F, Kulamarva G, De Stefano A. Pharmacokinetics of drugs in transtympanic administration. *Otorinolaringol* 2010;60:141-4.
- [13] Salt AN, Ma Y. Quantification of solute entry into cochlear perilymph through the round window membrane. *Hear Res* 2001;154:88-97.
- [14] Mikulec AA, Plontke SK, Hartsock JJ, et al. Entry of substances into perilymph through the bone of the otic capsule after intratympanic applications in guinea pigs: implications for local drug delivery in humans. *Otol Neurotol* 2009;30:131-8.
- [15] Leong AC, Fairley JW, Padgham ND. Sudden hearing loss. *Clin Otolaryngol* 2007;32:391-4.
- [16] Herr BD, Marzo SJ. Intratympanic steroid perfusion for refractory sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg* 2005;132:527-31.
- [17] Banerjee A, Parnes LS. Intratympanic corticosteroids for sudden idiopathic sensorineural hearing loss. *Otol Neurotol* 2005;26:878-81.
- [18] Choung YH, Park K, Shin YR, et al. Intratympanic dexamethasone injection for refractory sudden sensorineural hearing loss. *Laryngoscope* 2006;116:747-52.
- [19] Haynes DS, O'Malley M, Cohen S, et al. Intratympanic dexamethasone for sudden sensorineural hearing loss after failure of systemic therapy. *Laryngoscope* 2007;117:3-15.
- [20] Roebuck J, Chang CY. Efficacy of steroid injection on idiopathic sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg* 2006;135:276-9.
- [21] Cruickshanks KJ, Klein R, Klein BE, et al. Cigarette smoking and hearing loss: the epidemiology of hearing loss study. *JAMA* 1998;279:1715-9.
- [22] Gopinath B, Flood VM, McMahon CM, et al. The effects of smoking and alcohol consumption on age-related hearing loss: the Blue Mountains hearing study. *Ear Hear* 2010;277-82.
- [23] Barone JA, Peters JM, Garabrant DH, et al. Smoking as a risk factor in noise induced hearing loss. *J Occup Med* 1987;29:741-5.
- [24] Ho GM, Lin HG, Shu MT. Effectiveness of intratympanic dexamethasone injection in sudden deafness patients as salvage treatment. *Laryngoscope* 2004;114:1184-9.
- [25] Stachler RJ, Chandrasekhar SS, Archer SM, et al. Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg* 2012;146:S1-35.