

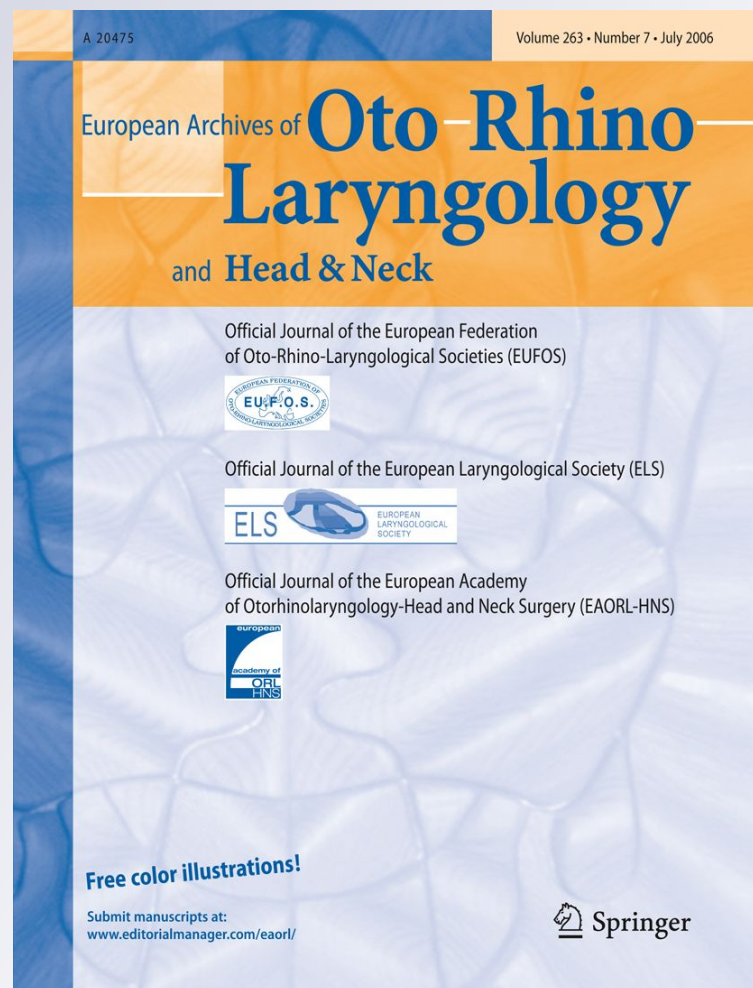
*Treatment of sudden sensorineural hearing loss with transtympanic injection of steroids as single therapy: a randomized clinical study*

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**European Archives of Oto-Rhino-Laryngology and Head & Neck**

ISSN 0937-4477  
Volume 268  
Number 9

Eur Arch Otorhinolaryngol  
(2011) 268:1273-1278  
DOI 10.1007/  
s00405-011-1523-0



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## Treatment of sudden sensorineural hearing loss with transtympanic injection of steroids as single therapy: a randomized clinical study

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Received: 27 October 2010 / Accepted: 1 February 2011 / Published online: 16 February 2011  
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**Abstract** The aim of this study was to verify the efficacy and the safety of transtympanic dexamethasone to treat sudden sensorineural hearing loss as first and single drug method. Considering ethical implication of performing a minimally invasive procedure on middle ear, we matched such proposed treatment with systemic prednisone administration that represents the widest adopted protocol. Randomized prospective study was conducted. The inclusion criterion was a sudden sensorineural hearing loss of at least 30 dB across three contiguous frequencies over a period of 24 h. Group A received transtympanic steroid injections; Group B received oral administration of steroids. 25 patients were treated with transtympanic therapy whereas 21 underwent systemic treatment. The mean of initial PTA was 59 dB for the whole series: 65 dB for group A and

51 dB for group B. The recovery better than 10 dB was obtained in 80% of patients of group A and in 78.1% of patients of group B, with a total of 80.5%. The mean relative gain in PTA was 41.16% in the group A and 44.7% in the group B. In the frequencies tested (0.5, 1, 2, and 4 kHz) PTA improvements after transtympanic treatment were higher than after systemic treatment, but these differences were not statistically significant ( $P = 0.61$ ). Both transtympanic and systemic treatment had similar clinical recovery times. This prospective randomized clinical study showed good result in terms of hearing recovery, better than the expected results of the simple observation without treatment. We can consider transtympanic administration as a first line treatment, because of the statistical analysis confirmed similar results with systemic therapy, reducing possible side effects of systemic drug administration. The delay of treatment does not influence the outcome, allowing treating patients within 10 days of onset.

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**Keywords** Cochlea · Deafness · Round window · Sudden sensorineural hearing loss · Steroid · Transtympanic

### Introduction

The sudden onset of deafness characterizes several diseases. In more than 90% of patients, the true cause of the hearing loss is not discovered, constituting an idiopathic syndrome known as Sudden Sensorineural Hearing Loss (SSHL). The estimated incidence of such disease is 5–20 cases per 100,000 annually [1]. However, the exact incidence is not known mainly due to the lack of a widely accepted definition of the disease. The US National Institute for Deafness and Communication Disorders defines

SSHL as the idiopathic loss of hearing of at least 30 dB over at least three contiguous frequencies occurring within 3 days. The underestimation of the incidence is probably because many patients who recover early (within first few days) are unlikely to seek medical care.

The spontaneous recovery rate is approximately between 32 and 65% which encourage some otologists not to treat SSHL patients [2].

The high rate of spontaneous recovery is, furthermore, a confounding element in the evaluation of the treatment protocols. Every protocol applied should improve the recovery rate up to 65% that could be obtained theoretically in case of simple observation.

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, and carbogen; most of therapies showed some benefits in restore hearing notwithstanding the lack of robustness of the data.

The most widely employed drugs in management of SSHL were steroids. Steroid were either administered as a single agent or associated with other drugs. Several placebo-controlled trials reported encouraging results in terms of recovering of hearing loss [3, 4], although other authors discussed such efficacy in the treatment of SSHL [1, 2, 5, 6].

The disadvantages of systemic treatment with steroids are well-known long-term complications.

The knowledge of cochlear pharmacokinetic allowed otologists to adopt ways to administer drugs into inner ear spaces, bypassing the systemic circulation. The round window is the main access to inner ear for the drugs injected into middle ear cleft. This method was first used in the management of Meniere's disease with either Gentamicin or steroids. The transtympanic steroid (TTS) injection is an intriguing therapeutic option in management of SSHL. Several report in the recent years have showed some benefits after use of TTS: Haynes et al. [7] and Ahn et al. [8] reported improvement after use of TTS as salvage therapy after systemic steroid treatment failure; Battista [9] used TTS in profound SSHL without improvement of threshold; Kakehata et al. [10] founded the same efficacy between TTS and intravenous steroid administration. Based on mentioned reports, although with contrasting results, we think that TTS have promising potentiality, but requires some further verification, taking in account that the majority of the data are favorable with the use of TTS.

The aim of this study was to verify the efficacy and the safety of transtympanic dexamethasone to treat SSHL patients as first and single drug method. Considering ethical implication of performing a miniminvasive procedure on middle ear, we matched such proposed treatment with systemic prednisone administration that represents the widest adopted protocol.

## Materials and methods

A randomized prospective study was conducted on patients affected by idiopathic SSHL who referred to the department from January 2008 to December 2009. The inclusion criterion was a SSHL of at least 30 dB across three contiguous frequencies over a period of 24 h. Patients with the following characteristic were excluded: previous episode of hearing loss, history of ear pathology, previous treatments administered elsewhere, and contraindication to systemic steroid administration. 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 few days, and presence of others systemic diseases. The bedside examination was done by spontaneous and positional nystagmus, Romberg test, Unterberger test, Halmagyi test, and Head shaking test.

The patients were randomly divided in two groups according to treatment: Group A received transtympanic steroid injections; Group B received oral administration of steroids.

Transtympanic 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 completely filling 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 transtympanic injection was repeated weekly for a total of four injections.

The patients of Group B received an oral steroid treatment with 60 mg of Prednisone tapered over 14 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.

The criterion adopted in this study to assess a therapeutic effect was an improvement of 10 dB on PTA. This criterion was the widest adopted in the recent analysis on argument published in English literature [11–17].

All data were entered in a database created within EpiInfo 3.5.1 software. Absolute and relative frequencies were calculated for qualitative variables, while quantitative variables were summarized as mean  $\pm$  standard deviation.

Continuous data were compared with the Student's *t* test and one-way ANOVA. The two-tailed significance level chosen for all analysis was 0.05. The data were analyzed using *R* statistical software package [R Development Core Team. *R* statistical software package, version 2.2.0, 2005. Available at: [www.r-project.org](http://www.r-project.org)].

All patients signed an informed consent before the treatment and the Institutional Review Board approved this study.

## Results

Among 51 patients affected by idiopathic SSHL, we evaluated 46 patients that completed the protocol. Three patients were lost during the treatment and two patients had evidence of vestibular schwannoma at MRI.

25 patients (54.3%) were treated with transtympanic therapy whereas 21 (45.7%) underwent systemic treatment. The mean age of the whole series was 50 years (47 for group A and 54 for group B). The mean time of presentation after onset of symptoms was 6.8 days; the group A had a mean delay of starting treatment of 9.4 days and it was 3.8 days for group B. Tinnitus was present in 36 (78.2%) patients: 19 (76%) in group A and 17 (81%) in group B. Dizziness was always associated with tinnitus and was present in 13 (28.2%) of cases, equally distributed in two groups. The mean of initial PTA was 59 dB for the whole series: 65 dB for group A and 51 dB for group B. An improvement better than 10 dB was obtained in 20 (80%) patients of group A and in 17 (81%) patients of group B, with a total of 37 patients (80.5%). The mean relative gain in PTA was 41.16% in the group A and 44.7% in the group B. Worsening of hearing was recorded in one patient of group B during treatment who did not show any recovery. No complications related to the treatment were noted in both the groups.

Table 1 summarizes the baseline characteristics of the 46 patients studied.

The anagraphic and clinical baseline factors involved in PTA improvements in groups with transtympanic steroid and systemic treatments are summarized in Table 2. In both groups, mean improvements were higher but not statistically significant in patients aged 39–59 years, in males, in subjects without vertigo and tinnitus and in patients treated after 3–10 days of onset. Although not statistically significant, subjects with left ear hearing loss had a higher improvement in the group treated with transtympanic therapy and had a lower improvement in the group treated with systemic therapy.

A comparison between transtympanic and systemic treatments is shown in Fig. 1. In the frequencies tested (0.5, 1, 2, and 4 kHz), PTA improvements after

**Table 1** Baseline characteristics of patients with sudden loss hearing ( $N = 46$ )

	<i>N</i>	%
Age		
<39 years	12	26.1
39–59 years	19	41.3
>59 years	15	32.6
Sex		
Male	28	60.9
Female	18	39.1
Ear		
Left	26	56.5
Right	20	43.5
Vertigo		
Yes	13	28.3
No	33	71.7
Tinnitus		
Yes	36	78.3
No	10	21.7
Days before beginning treatment		
<3	15	32.6
3–10	23	50
>10	8	17.4

transtympanic treatment were higher than after systemic treatment, but these differences were not statistically significant ( $P = 0.61$ ).

Finally, the Fig. 2 shows that both transtympanic and systemic treatment had similar clinical recovery times (15.9 and 21.1 days, respectively;  $P = 0.63$ ).

## Discussion

The use of transtympanic steroid is a known procedure. Itoh and Sakata [18] first reported its use in 1991 in treatment of patients with Meniere's disease. The first use of transtympanic therapy in SSHL was described by Silverstein et al. [12].

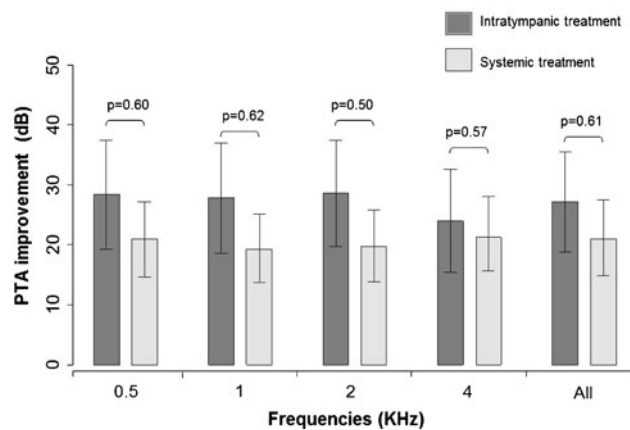
The value of systemic therapy with steroids was proved in several reports [3, 4, 15, 19–21], even if other authors did not find any improvement in patients after its use [1, 2, 6]. The TTS therapy emerged in the recent years as a promising treatment as salvage therapy after systemic treatment failure [7, 8, 22–24]. If systemic steroid is the most accepted treatment and the TTS was used as salvage treatment, why not use it as the first line therapy?

The rationale supporting the TTS administration is the round window membrane permeability to the drugs. Elevated perilymphatic concentration of steroids can be achieved after transtympanic administration, higher than

**Table 2** Factors involved in PTA improvement (difference between baseline PTA and recovered PTA) in patients after transtympanic and systemic treatment

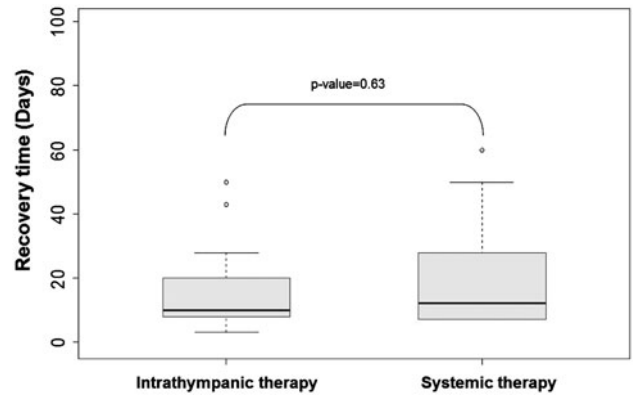
	Mean PTA improvement dB ± SD			
	Transtympanic treatment	P value	Systemic treatment	P value
<b>Age</b>				
<39 years	26.1 ± 22.5		8.3 ± 20.2	
39–59 years	29.4 ± 20.6	0.88	28.1 ± 9.6	0.08
>59 years	24.2 ± 18.8		19 ± 12.6	
<b>Sex</b>				
Male	25.7 ± 14.7	0.61	22.2 ± 16.3	0.66
Female	30.3 ± 22.6		19.5 ± 11.1	
<b>Ear</b>				
Left	28.2 ± 18.7	0.76	19.5 ± 16.3	0.63
Right	25.6 ± 23.3		22.5 ± 11.1	
<b>Vertigo</b>				
Yes	17.1 ± 16.4	0.12	19.2 ± 9.7	0.72
No	31.1 ± 20.6		21.7 ± 15.4	
<b>Tinnitus</b>				
Yes	24.6 ± 22.4	0.27	20.6 ± 14.9	0.81
No	35.2 ± 6.5		22.5 ± 9.6	
<b>Days before treatment</b>				
<3	10 ± 14.1		18.5 ± 15.5	
3–10	32.6 ± 22.2	0.17	25.7 ± 11	0.55
>10	19.8 ± 11.1		20 ± 0	

PTA pure tone average



**Fig. 1** PTA improvement (difference between baseline PTA and recovered PTA) at different frequencies (0.5, 1, 2, and 4 kHz) and at all four frequencies in patients treated with transtympanic and systemic therapy

after systemic administration [25, 26]. The distribution of drugs shows a decreasing concentration from basal turn of the cochlea to the apical portion, with maximum level near the inner aspect of the round window membrane. The diffusion of molecules into inner ear fluids and



**Fig. 2** Recovery time of patients after transtympanic and systemic treatment

compartments follows different pathways: with perilymphatic flow through the helicotrema (longitudinal) and across the spiral ligament (interscalar communication). Salt et al. [27] 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. However, the cochlear pharmacokinetics is 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. [28], it is not a good model.

The more diffuse transtympanic steroids administration protocols are three as: primary and exclusively treatment, adjunctive therapy to the standard procedure adopted (i.e., systemic steroids), and salvage therapy after failure of systemic one. In this study, we report only the results of the first line TTS therapy against the old protocol with systemic steroid therapy, but we adopted the TTS also as salvage therapy after systemic treatment failure.

There are many advantages of TTS use. The primary, in the authors' opinion, is the possibility to treat all patients presenting with SSHL avoiding systemic effects of steroids and thus treating those patients in which systemic steroids are contraindicated (i.e., immunocompromised patients, diabetics, tuberculosis, HIV). High dose regimen of steroids may expose patients (elder ones in particular) to various adverse effects: glucose intolerance, avascular necrosis of the hip, insomnia, irritability, gastritis, and osteoporosis. Other advantages are: it is an office-based procedure, reduction in delay of start of treatment after diagnosis and to treat only the affected side and the possibility to combine TTS with other systemic drugs without dangerous pharmacological interactions.

However, there are some drawbacks of TTS: residual tympanic perforation, pain during and after treatment, infection, vertigo (usually temporary), and dysgeusia. Hearing loss has been reported following an injection of steroid.

To deliver dexamethasone into middle ear cleft many techniques are proposed: direct injection, delivery through a myringotomy with a tube, delivery with a wick placed on the round window through a myringotomy, and drug infusion by an implantable pump device. We preferred the direct transtympanic needle injection after an anterior-inferior needle myringotomy, but if patient requires a short treatment protocol, a 1-day protocol may be done placing a tube to permit several injections in a short period of time (24 h) [29]. The implantation of device into middle ear is not comfortable for the patients and did not show any additional benefits. Furthermore the concept of air evacuation is useful to permit a complete filling of the middle ear and thus maximum drug loading is possible. The amount of solution injected into middle ear varies between 0.3 and 0.6 ml. We tried to uniformly inject 0.4–0.5 ml of solution to avoid drug exposure discrepancies between the patients.

We adopted a weekly dose for a total of four injections in all the patients. Notwithstanding that the greater part of hearing recovery occurred after the first two injections, the treatment was not suspended, for the reason that we believe that restoring the ionic equilibrium inside cochlear fluids leads to stabilization of the hearing recovery.

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 65% [2, 3, 6]. However, the results presented in this study confirm the efficacy of TTS as first line treatment of patients with SSHL. The recovery rate was analogous between systemic steroids and TTS with a response in about 80% of patients; the obtained improvement rate was better than that expected with simple observation, which can reach 65% [2, 3, 6]. The high recovery rate obtained and the similar results between TTS and systemic therapy justify the adoption of such treatment modality as first choice in the department.

The difference between onset of hearing loss and start of the treatment that is present between the two groups was casually determined by randomization. It may be apparently a limitation of the study, but, on the contrary, could be a supporting point in favor of TTS use.

As showed in the series, the outcome was not related to the time of treatment after the hearing loss. This was also noted by Parnes et al. [25] treating 37 patients affected by several inner ear disorders and by Ho et al. [22] in 39 cases. The absence of relationship between start of treatment and outcome is very important to modify the prevalent notion to consider SSHL as an emergency, allowing the option to perform thorough examination including MRI, consequently avoiding wrong diagnoses. In the study, the two groups had a casual difference of start of treatment time (about 9 days in transtympanic treatment and about 4 days in systemic treatment). This could be apparently a

limitation for the analysis, but observing the outcome obtained, the TTS has a possible role as programmable treatment, maintaining the same efficacy of promptly administered steroids. However, reading the results, the delay of treatment have to be intended as a window of 10 days in which the treatment may start after a proper diagnostic itinerary.

## Conclusions

The treatment of SSHL remains a challenge for the otologists. This prospective randomized clinical study showed good result in terms of hearing recovery similar to the outcome of the systemic therapy and better than the expected results of the simple observation without treatment. The statistical analysis confirmed the equal results between systemic therapy with steroid and TTS; consequently we can consider TTS as a first line treatment, reducing possible side effects of systemic drug administration. Interesting information emerged about the treatment timing, as supported by results; the delay of treatment does not influence the outcome, allowing treating patients even after 10 days of onset. The TTS requires further verification and prospective study to improve the outcome: determination of the better interval between dosages and determination of the most useful dosage.

**Conflicts of interest** The Authors have not conflict of interest with organization cited in the study and declare that any financial support was obtained by private organization.

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