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RESEARCH ARTICLE

Intratympanic steroids as a salvage therapy for severe to profound idiopathic sudden sensorineural hearing loss

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ABSTRACT

Background: Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as a decline in hearing affecting three or more frequencies by 30 dB

Objective: The aim of this study was to evaluate the results of intratympanic steroids as a salvage treatment for severe ISSNHL.

Materials and methods: A regimen of three IT steroid injections was offered to patients who failed a 7-days intravenous steroid treatment. Eighty-four patients underwent IT salvage treatment (IT group). Their outcomes were compared with those of 255 patients with severe ISSNHL who received the same intravenous steroid regimen without salvage IT steroid therapy (Control group).

Results: 56% of the patients in the IT group had a hearing improvement of >15 dB after one month. The average hearing improvements were 26.5 ± 28 dB and 27.9 ± 24 dB in the IT group and the Control group, respectively ($p = .67$). However, patients with a type E audiogram pattern (total deafness), displayed a substantial hearing gain.

Conclusion: Intratympanic steroids failed to show a global auditory benefit as a salvage treatment in patients with severe ISSNHL.

Significance: Our data suggest that a salvage treatment with intratympanic dexamethasone may be offered to patients with total deafness for whom the first systemic treatment has failed.

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Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as a decline in hearing affecting three or more frequencies by 30 dB or greater over 72 hours or less with no identifiable etiology.

During 2006 and 2007, the annual incidence of ISSNHL was 27 per 100,000 patients in the United States. The incidence increased with increasing age, ranging from 11 per 100,000 for patients younger than 18 years to 77 per 100,000 for 65 years and older patients. There was an overall slight male preponderance with a male-to-female ratio of 1.07:1. This was more pronounced in patients 65 years and older, with a ratio of 1.30:1 [1].

The etiology and natural history of ISSNHL are still obscure. Many studies have assessed the percentage of spontaneous recovery in different curves; in 2014 Filipo et al. published a spontaneous recovery in the flat curve of 25% of patients [2]. However, the real number of patients that recover spontaneously from ISSNHL is currently unknown, as the true incidence of this disease is probably underestimated because many who recover spontaneously within the first days never seek medical therapy.

Various therapies are proposed without a universally accepted standard protocol. Corticosteroids, antiviral agents, vasodilators, hyperbaric oxygen therapy (HBOT), anticoagulants, anti-inflammatory drugs, and other approaches have been suggested alone or combined, with variable percentages of efficacy reported in literature [3,4].

Currently, oral steroids are the most common choice of treatment and are considered as the best treatment option [5]. However, the use of intratympanic (IT) steroids has become an attractive alternative [6]. On the basis of the available literature, it seems that IT steroids can be a valuable solution for ISSNHL patients who cannot tolerate systemic steroid therapy or when systemic therapy fails as first line therapy [7].

The rationale for the efficacy of IT treatment entails a mechanism of diffusion through the round window into the cochlea, which has been described as following a tonotopy from the base of the cochlea to its apex. Therefore, the results of IT steroid therapy should be evaluated according to each frequency change and not only according to pure tone average. On the basis of this information, we designed a study to address the efficacy of IT steroids for patients

with severe ISSNHL after the failure of systemic treatment; we used a large control group of patients with the same features of severe-to-profound ISSNHL at one month.

Materials and methods

Study design

From September 1997 to September 2008, 550 patients, male and female with severe-to-profound ISSNHL were recruited by the ENT Emergency Room staff of the department of a Lariboisière hospital of Paris.

The diagnosis of severe-to-profound ISSNHL was based on the following criteria: ISSNHL of at least 30 dB at three or more consecutive frequencies in fewer than three days, unilateral hearing loss, no history of treatment at another center, no identified etiological factors to explain the hearing loss, no history of a previous otologic disease or operation on the affected ear, no history of previous chemotherapy or radiotherapy, and admission for first-line therapy within 30 days after the onset of hearing loss. All patients were treated with primary steroid therapy that consisted of 1 mg/kg/d dexamethasone (DXM) administration intravenously for seven days. Three hundred and thirty-nine (339) patients, 206 male and 133 female, with severe unilateral ISSNHL did not respond to primary therapy with systemic steroids. Failure to respond was defined as an improvement in the pure tone average (PTA at 500, 1000, 2000, and 4000 Hz) of less than 20 dB on day seven after the conclusion of primary therapy. These patients were divided

into two groups to evaluate the efficacy of IT salvage therapy: The first group consisted of 84 patients who received IT salvage therapy (IT group) and the second group consisted of 255 patients who did not receive IT therapy (control group). The initial evaluation patterns of ISSNHL were classified into five subgroups according to the following audiogram shapes: low tone (type A), flat (type B), high tone (type C), cup-shaped (type D), and total or subtotal (type E) (Figure. 1). The two groups were compared and analyzed.

Standard assessment

The standard assessment included tonal combined with stapedial reflex recording and vestibular caloric testing. Laboratory tests included a complete blood cell count, a coagulation profile, and blood glucose and lipid level tests. Auto-immune testing and virus serological evaluation were performed only in cases where herpes virus infection was suspected. Magnetic Resonance Imagery (MRI), including diffusion-weighted and FLAIR T2 sequences on the cerebral parenchyma as well as slice thickness T2-weighted MRI sequences on the internal auditory canals, was performed between days two and 30 after the onset of ISSNHL.

Inclusion criteria were (1) sensorineural hearing loss developed within 24 hours with a mean pure-tone audiogram with a minimum 60 dB loss on three subsequent frequencies; no improvement after conventional therapy (2) no marked vestibular symptoms (i.e. without nystagmus or vertigo), and (3) no clinically identifiable causes.

Figure 1. The five types of SNHL according to their audiogram shape. Type A: low tone; Type B: flat; Type C: high tone; Type D: cup-shaped; Type E: total or subtotal.

Procedures

Intravenous treatment

All patients included in this study received an initial intravenous steroid regimen during hospitalization. The protocol included a 7-day course of intravenous steroids (dexamethasone 1 mg/kg/d) that was administered to every patient.

Intratympanic steroid treatment

The patient was offered IT steroid therapy in case of additional hearing deterioration or in the absence of recovery, which were defined as the absence of improvement of at least 20 dB in PTA at the last day of i.v. steroid treatment. Eighty-four patients agreed to receive this treatment, which was delivered as an outpatient procedure. The therapeutic protocol for IT administration consisted in three sessions of IT injection of dexamethasone (DXM), carried out within a 10-day period. The IT steroid treatment consisted of 2 mL of a sterile aqueous suspension of dexamethasone at a concentration of 4 mg/mL. The patients lay in the supine position with their heads tilted 45° towards the opposite ear. The procedure was performed under a microscope. After confirmation of an intact tympanic membrane, local anesthesia was achieved via topical application of lidocaine and prilocaine in the external auditory canal for 20 minutes. Once the lidocaine and prilocaine were removed, a 25-gauge spinal needle and 2 mL syringe were used to puncture the postero-inferior quadrant of the tympanic membrane. Through the myringotomy, 1 mL of DXM (4 mg/mL) was slowly injected to perfuse the middle ear. The patient was asked to remain still in the supine position with their head tilted 45° towards the opposite ear for at least 20 minutes and to refrain from swallowing to maintain perfusion of the middle ear by the DXM.

Main outcome measurements

The final assessment of the patients was performed by evaluating the PTA one month after the treatment, i.e. between 30 and 45 days after SNHL onset. In the IT Group, PTA assessment was also performed before each transtympanic injection. The audiometric parameters used to assess the outcome were: (1) hearing recovery, defined as (initial PTA) – (PTA at day 30); (2) hearing recovery percentage calculated with the following formula: ((initial PTA) – (PTA at day 30))/(initial PTA) × 100%. “Complete hearing improvement” was defined as an improvement of more than 10 dB in PTA. Recovery was considered complete when the final PTA was above 25 dB. If final recovery was under the 25 dB threshold, then PTA improvement of 50% was considered “partial hearing improvement”. “No recovery” was defined as an improvement in PTA of equal or less than 10 dB regardless of PTA improvement percentage being better than 50%. Each frequency was also tested independently before and after treatment. The following variables considered to influence recovery were analyzed: age, sex, association with vertigo or vestibular deficit on caloric testing, and audiometric pattern

of SNHL. Time between onset of SNHL and onset of treatment, side effects, and subjective symptoms were also recorded.

Statistical analysis

Quantitative variables were described as the mean ± Standard Deviation (SD), and frequency distribution tables were used for all categorical variables. A *t*-test was performed to compare the improvement percentages between IT and CONTROL groups for each SNHL pattern. A χ^2 test was used to compare the percentages of hearing recovery in each group. The Mann–Whitney *U*-test and Fisher *t*-test were performed to evaluate the auditory gain before and after treatment for each frequency and SNHL type. All tests were carried out based on two-tailed analysis, *p* < .05 was considered to indicate a statistically significant difference.

Results

Population

Patients’ baseline characteristics according to sex, affected ear, and pattern of initial audiogram are presented in Table 1. The mean ages of the patients were 50.9 and 50.3 years for the IT and control groups, respectively. The mean intervals from hearing loss onset to i.v. treatment administration were 11.8 and 8.1 days for the IT and control groups, respectively. There were no statistically significant differences between the two groups with regard to age, time to admission, mean PTA before and after first-line intravenous treatment, and audiometric patterns of ISSNHL (Table 2). Audiogram type E was less frequent in the control group when compared with the IT group but this difference was not statistically significant. For all patients, tinnitus was present in 77% of the patients, vertigo in 22% of the patients, hypertension in 17% of the patients, and diabetes mellitus in 6% of the patients, with no significant differences between the groups.

Table 1. Patients’ baseline characteristics according to sex, site of affected ear, and shape of initial audiogram.

	Control group (n = 255)	IT group (n = 84)	<i>p</i> value
Sex: Male/Female	62% (158)/38% (97)	57% (48)/43% (36)	.52
Affected ear: Right/Left	58% (147)/42% (108)	62% (52)/38% (32)	.58
Shape A	15% (38)	11% (9)	.49
Shape B	25% (65)	26% (22)	.96
Shape C	20% (52)	14% (12)	.35
Shape D	11% (29)	5% (4)	.14
Shape E	27% (71)	44% (37)	.07

Table 2. Mean PTA according to each type of ISSNHL after 7 days of IV steroid treatment.

PTA (dB)	IT group	Control group	<i>p</i> value
Type A	42.4 ± 17 (9/84)	45.3 ± 20 (38/255)	.79
Type B	59.4 ± 21 (22/84)	58.3 ± 25 (65/255)	.96
Type C	57.6 ± 21 (12/84)	53.7 ± 23 (52/255)	.99
Type D	68.4 ± 26 (4/84)	63.3 ± 31 (29/255)	.99
Type E	101.3 ± 21 (37/84)	98.3 ± 25 (71/255)	.83

Table 3. Main outcome measurements of hearing in Control group and IT group.

	Control group	IT group	<i>p</i> value
Complete hearing recovery (dB). final PTA <25 dB at day 30	29.0% (74/255)	22.6% (19/84)	.32
Partial hearing recovery (dB) PTA improvement of 50% at day 30	42% (106/255)	36% (30/84)	.41
Average hearing improvement (dB) after 30 days	27.9	26.5	.67
Hearing improvement >15 dB after 30 days	63% (160/255)	56% (47/84)	.32
No recovery = hearing improvement <10dB	30% (77/255)	32% (27/84)	.84

Table 4. Percentage of complete recovery for each audiogram pattern of both groups..

	Type A	Type B	Type C	Type D	Type E
IT group (19 pts)	21% (4pts)	15.8% (3pts)	15.8% (3pts)	15.8% (3pts)	31.5% (6pts)
Control group (74 pts)	24.3% (18pts)	17.5% (13pts)	18.9% (14pts)	16.2% (12pts)	22.9% (17pts)

Type A: low tone; Type B: flat; Type C: high tone; Type D: cup-shaped; Type E: total or subtotal

Table 5. Hearing improvement for each audiogram type (A, B, C D and E) at 500, 1000, 2000 and 4000 hz at one month for the IT group and Control group.

Hz	Type A	Type B	Type C	Type D	Type E
500 IT group	31.0 ± 29	27.3 ± 33	41.5 ± 35	61.3 ± 17	50.4 ± 33
500 Control group	33.1 ± 22	20.6 ± 27	19.3 ± 17	24.8 ± 32	41.6 ± 29
<i>p</i> value 500 Hz	.79	.35	.005	.04	.17
1000 IT group	19.5 ± 25	26.5 ± 32	32.5 ± 40	56.3 ± 17	49.1 ± 34
1000 Control group	28.7 ± 22	23.4 ± 29	25.9 ± 22	30.2 ± 35	35.3 ± 26
<i>p</i> value 1000 Hz	.24	.68	.47	.17	.02
2000 IT group	17.5 ± 19	20.6 ± 28	30 ± 37	42.5 ± 13	45.1 ± 36
2000 Control group	22.6 ± 22	23.1 ± 28	28 ± 23	26.4 ± 32	31.4 ± 25
<i>p</i> value 2000 Hz	.49	.73	.82	.34	.03
4000 IT group	10.5 ± 18	16.5 ± 27	22.0 ± 39	23.8 ± 5	37.1 ± 32
4000 Control group	13.1 ± 16	14.2 ± 25	17.4 ± 21	19.5 ± 27	25.1 ± 27
<i>p</i> value 4000 Hz	.65	.73	.59	.76	.05
All frequencies IT group	19.6 ± 21	22.7 ± 28	31.5 ± 36	45.9 ± 11	45.5 ± 31
All frequencies Control group	24.4 ± 19	41.3 ± 25	22.6 ± 17	25.2 ± 29	33.4 ± 24
<i>p</i> value	.47	.72	.25	.18	.03

Hearing improvement in dB according to each audiogram type.

For audiogram type A IT group *n* = 9/84 versus Control group *n* = 38/255.

For audiogram type B IT group *n* = 22/84 versus Control group *n* = 65/255.

For audiogram type C IT group *n* = 12/84 versus Control group *n* = 52/255.

For audiogram type D IT group *n* = 4/84 versus Control group *n* = 29/255.

For audiogram type E IT group *n* = 37/84 versus Control group *n* = 71/255.

Audiometric assessment after 7-day intravenous steroid treatment

After the initial i.v. steroid treatment, there was no significant difference between the IT group and the Control group in terms of mean PTA, which made the groups comparable. All patients had severe hearing loss, with a mean PTA of 78 dB in both groups (77 ± 29 dB and 78 ± 35 dB in the Control group and the IT group, respectively). Statistical analysis did not indicate any significant difference between the two groups for each audiogram pattern (Table 2).

Hearing outcome after treatment completion (Intratympanic group vs Control group)

Table 3 summarizes the audiometric results after treatment completion for the IT group and the Control group at one month. As for the main outcome measure, there was no significant difference in terms of hearing recovery between the groups; the average hearing improvement was 26.5 dB for the IT group and 27.9 dB for the Control group (*p* = .67). There were no significant differences between the groups for the other variables. In the Control group, 29.0% (74/255) of the patients had complete hearing recovery, and in

the IT group, 22.6% (19/84) of the patients had complete hearing recovery (*p* = .32). At day 30, 42% of the Control group (106/255) and 36% of the IT group (30/84) showed a partial hearing recovery (dB) PTA improvement of 50% (*p* = .41). With regard to the patients who did not recover their hearing (improvement <10 dB), there was no difference between the IT group and the Control group (*p* = .84). Similar non-significant results were observed when evaluating hearing recovery >15 dB after one month for the IT group and the Control group (*p* = .32). Table 4 shows the percentage of complete recovery for each audiogram pattern of both groups. Table 5 shows a comparison of the two groups according to each frequency tested and each audiogram pattern; this table indicates that patients who had a type E audiogram (total deafness) and received IT steroid treatment showed a statistically significant improvement in hearing recovery at 1000, 2000, and 4000 Hz when compared with control patients. Hearing recovery was 50.4 dB vs 41.6 dB at 500 Hz (*p* = .17), 49.1 dB and 35.3 dB at 1000 Hz (*p* = .02), 45.1 dB vs 31.4 at 2000 Hz (*p* = .03), and 37.1 dB vs 25.1 dB at 4000 Hz (*p* = .05) in the IT group versus the Control group, respectively (Table 4). When all hearing loss types were combined, the mean PTA recovery between IT

and Control groups was found to be significantly different (34.1 dB vs 25.8 dB respectively with $p = .01$).

Side effects

Two patients had a persistent pinpoint perforation three months after the treatment. One patient recovered spontaneously, and the second patient's condition was resolved in six months post-treatment after placement of a tympanic paper patch. Eight patients in the IT group experienced vertigo while being injected, but their symptoms resolved themselves within 1 min. One subject experienced a worsening of hearing of approximately 10 dB. This patient had an initial PTA of 103 dB. After treatment, the patient recovered hearing to 72 dB.

Discussion

The most frequently suggested theories as to the cause of ISSNHL include viral infection, inflammatory or immune-mediated reactions, and vascular insufficiency.

Owing to the differences in etiopathogenesis of ISSNHL, different therapeutic agents have been proposed including carbogen therapy, anticoagulants, antiviral agents, and hyperbaric therapy alone or in association with drugs [2]. One of the most accepted treatment choices is systemic steroid therapy but it is not always feasible due to the pre-existing conditions of patients (hypertension, diabetes, glaucoma, severe heart conditions, severe ulcers, hemorrhagic disorders, and renal failure). The IT route has two advantages: it allows a higher concentration of the drugs in the perilymph, and it minimizes the risk of systemic side effects. Nevertheless the pharmacokinetics of the drugs and their effects on the inner ear are still unclear [9]. Most studies have shown the benefits of IT steroids in the treatment of ISSNHL in patients in whom previous systemic therapy had failed [10]. The time between the onset of symptoms and the beginning of therapy (delay) is between 0 and 15 days; this is a common inclusion criterion in the literature because after 15 days the efficacy of the therapy is significantly reduced. Considering this early beginning of the therapy it is possible that the evaluation of the short-term efficacy could be influenced by spontaneous recovery. In a recent randomized, triple-blind, placebo-controlled trial, spontaneous recovery was shown to occur in 25% of patients with flat curve [2].

This study aimed to compare auditory outcomes at one month in a control group type study for patients with severe to profound ISSNHL. To our knowledge, this is the largest retrospective control group study reported for IT steroids administered as a salvage treatment to patients with severe to profound ISSNHL. The main results of this study showed no significant benefits from IT steroid treatment although patients with total deafness did experienced a 45.5 ± 31 dB gain depending upon frequency.

The present study suggests that IT steroid administration is not effective as salvage treatment for patients with severe ISSNHL; however, for a subgroup of patients with total

deafness, IT steroid treatment may improve hearing. Better outcomes for patients with total deafness may be related to the sample sizes within the IT group, when divided by type of hearing loss. Patient groups with total deafness were relatively small and may not be representative. In our study, few side effects were reported, and tolerance of the treatment was very good in the vast majority of patients. Therefore, the benefit/risk ratio for patients with total deafness seems favorable, and IT steroid treatment could be considered as a salvage treatment for patients experiencing total deafness. Because steroids should diffuse through the round window at the base of the cochlea that codes for high frequencies, one might have thought that IT steroid treatment would produce a beneficial effect for higher frequencies. In our study, we did not find any favorable effects on these frequencies to support this hypothesis.

Intracochlear drug concentrations depend on the time the drug is in contact with the round window membrane (RWM). In addition, significant basal to apical concentration gradients in the cochlea have been measured after local drug application to the RWM, and there is increasing evidence that the time of exposure of drugs to the RWM influences the basal-apical drug distribution [11]. Better outcomes might have been expected for high frequencies due to this basal-apical drug gradient and the frequency tonotopy of the cochlea; however, this was not the case in our study. Some researchers have advocated the need for standardized techniques for the application of medications through the RWM [11]. Kakehata et al. investigated daily short-term IT dexamethasone administration using laser-assisted myringotomy (LAM) for ISSNHL patients without concurrent therapy; they reported a high response rate and high cure rate, and this treatment proved to be an alternative therapeutic option to high-dose systemic steroids as a first- and/or second-line treatment [12]. In addition, Park et al. have shown that RWM vibration can enhance the effect of intratympanic corticosteroid injection [13]. On the basis of the available literature, it seems that topical steroids can be a valuable solution for ISSNHL patients who either cannot tolerate systemic steroid therapy or are refractory to it [14,15], and some authors suggest a combination of intratympanic and oral steroids [10–16]. The issue remains whether IT steroid treatment may be a more beneficial option as a primary treatment [17]. Some works suggest a direct comparison of oral vs. IT corticosteroid showed no difference in efficacy [18,19]. The possible pharmacokinetic advantages of the continuous delivery of drugs to the RWM must be weighed against the invasiveness of the therapy, the time required, and the cost considerations associated with this application strategy. Plontke et al. used an implanted microcatheter to continuously deliver drugs to the RWM, which demonstrated efficacy in restoring severe ISSNHL. This application strategy appears feasible, but the limited placebo-controlled observation period and the absence of serious adverse events warrants further investigation for local inner ear drug delivery as a first- or second-line treatment option for ISSNHL [20].

In conclusion, the results of the present study suggest that IT steroid salvage treatment was not effective for patients with severe ISSNHL, although patients with total deafness seem to benefit from IT steroid treatment. Further studies are required to address several issues with IT steroid administration; namely, whether it can be used as a first-line treatment instead of the intravenous treatment for patients with ISSNHL.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

- [1] Alexander TH, Harris JP. Incidence of sudden sensorineural hearing loss. *Otol Neurotol*. 2013;34:1586–1589.
- [2] Filipo R, Attanasio G, Russo FY, et al. Intratympanic steroid therapy in moderate sudden hearing loss: a randomized, triple-blind, placebo-controlled trial. *Laryngoscope*. 2013;123:774–778.
- [3] Filipo R, Attanasio G, Viccaro M, et al. Hyperbaric oxygen therapy with short duration intratympanic steroid therapy for sudden hearing loss. *Acta Otolaryngol*. 2012;132:475–481.
- [4] Attanasio G, Covelli E, Cagnoni L, et al. Does the addition of a second daily session of hyperbaric oxygen therapy to intratympanic steroid influence the outcomes of sudden hearing loss? *Acta Otorhinolaryngol Ital*. 2015;35:272–276.
- [5] 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;106:772–776.
- [6] Seggas I, Koltsidopoulos P, Bibas A, et al. Intratympanic steroid therapy for sudden hearing loss: a review of the literature. *Otol Neurotol*. 2011;32:29–35.
- [7] Rohrmeier C, Koemm N, Babilas P, et al. Sudden sensorineural hearing loss: systemic steroid therapy and the risk of glucocorticoid-induced hyperglycemia. *Eur Arch Otorhinolaryngol*. 2013;270:1255–1261.
- [8] Salt AN, Plontke SK. Local inner-ear drug delivery and pharmacokinetics. *Drug Discov Today*. 2005;10:1299–1306.
- [9] Battaglia A, Burchette R, Cueva R. Combination therapy (intratympanic dexamethasone + high-dose prednisone taper) for the treatment of idiopathic sudden sensorineural hearing loss. *Otol Neurotol*. 2008;29:453–460.
- [10] Swan EE, Mescher MJ, Sewell WF, et al. Inner ear drug delivery for auditory applications. *Adv Drug Deliv Rev*. 2008;60:1583–1599.
- [11] Van Wijck F, Staecker H, Lefebvre PP. Topical steroid therapy using the Silverstein MicroWick in sudden sensorineural hearing loss after failure of conventional treatment. *Acta Otolaryngol*. 2007;127:1012–1017.
- [12] Kakehata S, Sasaki A, Futai K, et al. Daily short-term intratympanic dexamethasone treatment alone as an initial or salvage treatment for idiopathic sudden sensorineural hearing loss. *Audiol Neurotol*. 2011;16:191–197.
- [13] Park SH, Moon IS. Round window membrane vibration may increase the effect of intratympanic dexamethasone injection. *Laryngoscope*. 2014;124:1444–1451.
- [14] Lefebvre PP, Staecker H. Steroid perfusion of the inner ear for sudden sensorineural hearing loss after failure of conventional therapy: a pilot study. *Acta Otolaryngol*. 2002;122:698–702.
- [15] 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.
- [16] Gundogan O, Pinar E, Imre A, et al. Therapeutic efficacy of the combination of intratympanic methylprednisolone and oral steroid for idiopathic sudden deafness. *Otolaryngol Head Neck Surg*. 2013;149:753–758.
- [17] Filipo R, Covelli E, Balsamo G, et al. Intratympanic prednisolone therapy for sudden sensorineural hearing loss: a new protocol. *Acta Otolaryngol*. 2010;130:1209–1213.
- [18] Rauch SD, Halpin CF, Antonelli PJ, et al. Oral vs intratympanic corticosteroid therapy for idiopathic sudden sensorineural hearing loss: a randomized trial. *Jama*. 2011;305:2071–2079.
- [19] Filipo R, Attanasio G, Russo FY, et al. Oral versus short-term intratympanic prednisolone therapy for idiopathic sudden hearing loss. *Audiol Neurotol*. 2014;19:225–233.
- [20] Plontke SK, Löwenheim H, Mertens J, et al. Randomized, double blind, placebo controlled trial on the safety and efficacy of continuous intratympanic dexamethasone delivered via a round window catheter for severe to profound sudden idiopathic sensorineural hearing loss after failure of systemic therapy. *Laryngoscope*. 2009;119:359–369.