



HOKKAIDO UNIVERSITY

Title	The Short- and Long-Term Outcome of Intratympanic Steroid Therapy as a Salvage Treatment for Acute Low-Tone Sensorineural Hearing Loss without Episodes of Vertigo
Author(s)	Morita, Shinya; Nakamaru, Yuji; Fujiwara, Keishi et al.
Citation	Audiology & neuro-otology, 21(3), 132-140 https://doi.org/10.1159/000444577
Issue Date	2016-07
Doc URL	https://hdl.handle.net/2115/66407
Rights	This is the peer-reviewed but unedited manuscript version of the following article: Audiol Neurotol 2016;21:132-140 (DOI: 10.1159/000444577). The final, published version is available at http://www.karger.com/?doi=10.1159/000444577
Type	journal article
File Information	AudiolNeuro0tol21_132.pdf



**The short- and long-term outcome of intratympanic steroid therapy as a
salvage treatment for acute low-tone sensorineural hearing loss without
episodes of vertigo**

¹Shinya Morita, M.D., ¹Yuji Nakamaru, M.D., Ph.D., ¹Keishi Fujiwara,
M.D., Ph.D., ²Keiji Iizuka, M.D., Ph.D., ¹Masayori Masuya, M.D., ¹Aki
hiro Homma, M.D., Ph.D., ¹Atsushi Fukuda, M.D., ¹Satoshi Fukuda, M.
D., Ph.D.

Affiliations: ¹Department of Otolaryngology - Head and Neck Surgery,
Hokkaido University Graduate School of Medicine, Sapporo, Japan

²Department of Otolaryngology, Kushiro City General Hospital, Kushiro,
Japan

Corresponding author:

Shinya Morita

Department of Otolaryngology - Head and Neck Surgery

Hokkaido University Graduate School of Medicine.

Kita 15, Nishi 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan

Tel: +81-(0)11-706-5958; Fax: +81-(0)11-717-7566

E-mail address: shinyamorita@huhp.hokudai.ac.jp

Running head: Intratympanic steroid therapy for ALHL

Financial Support: None

Conflict of Interest: No conflicts of interest exist for any author

Keywords: intratympanic steroid therapy; outcome; acute low-tone sensorineural hearing loss; recurrence; Ménière's disease.

Abstract

Objective: To evaluate the hearing outcomes of intratympanic steroid (ITS) treatment for patients with acute low-tone sensorineural hearing loss (ALHL) after the failure of initial therapy and to investigate the recurrence and progression to definite Ménière's disease (MD) during long-term follow-up.

Methods: We retrospectively reviewed the medical records of 90 patients with refractory ALHL who were followed-up for at least 1 year between January 2000 and April 2014. Patients who responded poorly to initial medical treatment received intratympanic dexamethasone injections (ITS group) or isosorbide administration for 4 weeks (Diuretic group) as salvage treatment options according to their choice of management. The control group did not receive ITS or the diuretic due to their refusal of both medical treatments. The hearing outcomes were evaluated at 1 month, 1 year and 5 years after the completion of second-line therapy, and the rates of recurrence and progression to MD were measured during a follow-up period of at least 1 year.

Results: Twenty-seven patients in the ITS group, 39 patients in the diuretic group and 24 patients in the control group were enrolled. Of these, 12 patients in the ITS group, 15 patients in the diuretic group and 12 patients in the control group were followed-up for over 5 years. We found that the recovery rates and the audiometric functional values after 1 month and 1 year in the ITS group were significantly higher than those in the diuretic and control groups. However, there were no significant differences in the

recovery rates or the audiometric functional values after 5 years, or in the rates of recurrence and progression to MD among the groups.

Conclusions: Salvage ITS therapy can provide a relatively good short-term hearing outcome for ALHL patients who have persistent hearing loss despite conventional treatment. However, both recurrence and progression to MD after treatment were observed in some patients during long-term follow-up.

Introduction

Acute low-tone sensorineural hearing loss (ALHL) is defined as hearing impairment confined to the low frequencies with preservation of high-frequency hearing acuity and no episodes of vertigo [Morita et al., 2010; Okada et al., 2012; Shimono et al., 2013]. ALHL appears to partially overlap with the low-tone type of idiopathic sudden sensorineural hearing loss (ISSNHL). However, it was revealed that ALHL has a relatively high incidence of spontaneous hearing recovery as well as recurrence and/or progression to definite Ménière's disease (MD) after long-term follow-up [Fushiki et al., 2009; Imamura et al., 1997; Junicho et al., 2008; Yamasoba et al., 1994]. These characteristic clinical courses, together with the results of electrocochleographic (ECoG) examination, glycerol tests, vestibular-evoked myogenic potential (VEMP) and 3 tesla magnetic resonance imaging (MRI) after intratympanic or intravenous gadolinium injection, suggest that the pathogenesis of ALHL may be attributable to cochlea-specific endolymphatic hydrops (EH) [Junicho et al., 2008; Noguchi et al., 2004; Nozawa et al., 2002; Shimono et al., 2013; Yamasoba et al., 1994; Yamasoba et al., 1993; Wang et al., 2010]. Thus, ALHL has been interpreted as a potential early stage of MD and an independent disease entity distinct from ISSNHL [Morita et al., 2010; Selivanova et al., 2005; Shimono et al., 2013; Yamasoba et al., 1993].

Although no consensus has been reached regarding the best therapeutic strategy for ALHL, treatments using steroids and/or mild diuretics have been recommended with relatively good hearing outcomes reported [Fuse et al., 2002; Morita et al., 2010; Okada et al., 2012]. Nevertheless, 20-33% of

patients respond poorly to conventional therapy, with occasional exacerbation of symptoms and progression to definite MD observed [Fuse et al., 2002; Morita et al., 2010; Okada et al., 2012]. Recently, there have been many reports indicating that intratympanic steroid (ITS) administration effectively improves hearing in patients with ISSNHL or MD [Barrs et al., 2001; Li et al., 2015; Martin-Sanz et al., 2015; Selivanova et al., 2005]. In particular, ITS salvage treatment has been recommended for ISSNHL patients with incomplete hearing recovery after initial management failure [Stachler et al., 2012]. However, few studies have documented the use of ITS administration as a salvage treatment for ALHL [Selivanova et al., 2005].

In this retrospective study, our purpose was to evaluate the hearing outcomes of ITS treatment for patients with ALHL after the failure of initial therapy and to investigate the recurrence and progression to definite MD during long-term follow-up.

Materials and Methods

Patients

We retrospectively reviewed the medical records of patients diagnosed with ALHL in the Department of Otolaryngology, Head and Neck Surgery, Hokkaido University Hospital and Affiliated Hospitals between January 2000 and April 2014. We used the diagnostic criteria for ALHL proposed by the Acute Severe Hearing Loss Study Group, the Ministry of Health, Labor and Welfare of Japan [Morita et al., 2010; Okada et al., 2012; Shimono et al., 2013], as follows: 1) sensorineural hearing loss of sudden onset without vertigo (but may be accompanied with a slight dizzy sensation); 2) no other known cause; 3) the sum of pure tone hearing thresholds at low frequencies of 125, 250 and 500 hertz (Hz) is 70 decibel (dB) or more; 4) “definite” ALHL is defined when the sum of pure tone hearing thresholds at high frequencies of 2000, 4000 and 8000 Hz is 60 dB or less; and 5) “probable” ALHL is defined when the sum of pure tone hearing thresholds at high frequencies of 2000, 4000 and 8000 Hz is more than 60 dB but the difference between the affected and contralateral sides is 10 dB or less.

The inclusion criteria of the subjects were as follows: 1) “definite” ALHL; 2) duration from the onset of symptoms to the beginning of initial therapy was 30 days or less; 3) no change or progression according the hearing outcome criteria of ALHL (as mentioned below) after 14-16 days of initial medical treatment; 4) follow-up for at least 1 year; and 5) purely sensorineural hearing loss for which possible causes were ruled out after adequate examination such as history-taking, physical examination, otoscopic

examination, pure tone audiometry, speech audiometry, impedance audiometry, distortion product otoacoustic emissions, equilibrium function test, blood test including full blood count, blood biochemistry, serological and immunological tests and computed tomography and/or MRI.

The exclusion criteria of the subjects were as follows: 1) “probable” ALHL; 2) lost during follow-up period; 3) history of definitive ear disease, such as chronic otitis media, familial hearing loss, chronic noise exposure, ototoxic drug intake, head trauma, radiation therapy, acoustic neuroma and inner ear malformation; 4) history of metabolic, psychiatric, neurological, vascular, systemic and autoimmune disease, such as diabetes mellitus, hypercholesterolaemia, cerebral infarction, encephalorrhagia, hypertension, ischemic heart disease, hypothyroidism, sarcoidosis and connective tissue disease; and 5) pregnancy.

All patients had to be cleared for treatment, and informed consent was obtained from all patients after a full explanation of the potential risks and benefits. This research adhered to the tenets of the Declaration of Helsinki and was approved by our Institutional Review Board.

Experimental procedure

Patients with ALHL were initially treated with oral prednisolone (Shionogi & Co., Ltd., Osaka, Japan) tapered from 40-60 mg/day (0.8-1.2 mg/kg/day) for 14-16 days. They were also prescribed isosorbide (70%, 90ml; Kowa Company Ltd., Nagoya, Japan), vitamin B₁₂ and adenosine triphosphate disodium. After 14-16 days of initial medical treatment,

patients who showed no change or progression according to the hearing outcome criteria of ALHL (as mentioned below) were counseled about the risks and benefits associated with ITS injections and sequential isosorbide administration for 4 weeks as salvage treatment, the potential for spontaneous recovery and the potential for permanent hearing impairment despite second-line therapy. They were administered with ITS injections (ITS group) or isosorbide (Diuretic group), or underwent a wait-and-see approach (Control group) according to their choice of treatment.

Intratympanic injection technique

Tympanic membrane anesthesia using iontophoresis was applied into the external auditory canal with 4% lidocaine (AstraZeneca Co., Ltd., London, U.K.). Patients were placed in the supine position with their head turned to the unaffected side. The patient's head was tilted at an angle of 45 degrees toward the unaffected side with the chin upward so that the round window membrane was bathed. Dexamethasone disodium phosphate 0.5 ml (8 mg/2 ml; MSD, a subsidiary of Merck & Co., Inc., Kenilworth, N.J., U.S.A.) was injected into the middle ear through the anterior-superior portion of the tympanic membrane using a 1-ml tuberculin syringe with a 26-gauge needle under a microscope. Each patient was instructed to avoid swallowing and speaking, refrain from head motion during the procedure, and keep their unaffected ear pointed down for 30 minutes to prevent the product from clearing through the Eustachian tube. The procedure was done once weekly for 4 consecutive weeks. Patients were given fewer than 4 injections if their

hearing recovered before the fourth injection.

Follow-up

After the completion of therapy, subsequent clinical visits were scheduled every 1 to 3 months for the first year and every 3 to 6 months thereafter. The risks of fluctuation, exacerbation, recurrence of symptoms and progression to MD were carefully explained to the patients, and they were counselled to visit our department at once when they experienced an episode of hearing impairment or vertigo.

Audiometric and vestibular testing

Audiometry was performed by experienced audiologists using a pure-tone audiometer (AA-76 or AA-78; RION Co., Ltd., Tokyo, Japan) in a sound-proof room. The pure-tone thresholds for each ear were determined at frequencies of 125, 250, 500, 1000, 2000, 4000 and 8000 Hz for air conduction, and at 250, 500, 1000, 2000 and 4000 Hz for bone conduction with masking as appropriate.

We observed spontaneous nystagmus in patients when gazing forward, and gaze-evoked nystagmus when gazing approximately 30 degree to the left, to the right, upward, or downward. We then observed positional nystagmus using a charge-coupled device camera or a video-oculography system (Meditester VOG; Panasonic Healthcare Co., Ltd., Tokyo, Japan) in the forward, left, right, upward-and-forward, upward-and-left, and upward-and-right positions. Audiometric and vestibular tests were

performed multiple times at clinical examinations during the follow-up period.

Outcome criteria

We used the hearing outcome criteria of ALHL proposed by the Acute Severe Hearing Loss Study Group, the Ministry of Health, Labor and Welfare of Japan [Morita et al., 2010; Okada et al., 2012; Shimono et al., 2013], as follows: 1) complete recovery, in which hearing levels at three low frequencies (125, 250 and 500 Hz) returned to within 20 dB of normal; 2) partial recovery, in which average hearing levels at three low frequencies (125, 250 and 500 Hz) improved by 10 dB or more compared to the initial audiogram, but were not recovered to within 20 dB of normal; 3) unchanged, in which the average hearing level at three low frequencies (125, 250 and 500 Hz) was within 10 dB of that at the initial audiogram; 4) progression, in which the average hearing level at three low frequencies (125, 250 and 500 Hz) exceeded that at the initial audiogram by 10 dB or more. In this study, complete or partial recovery was defined as hearing loss recovery. The functional values for the sum of hearing levels at three low frequencies (125, 250 and 500 Hz) were calculated by subtracting those at 1 month, 1 year and 5 years after the completion of second-line therapy from those after the initial therapy. Recurrence was defined as a second attack of hearing loss with or without vertiginous symptoms. Definite MD was diagnosed according to the criteria proposed by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology Head and Neck Surgery [Monsell et al.,

1995], as follows: 1) 2 or more definitive spontaneous episodes of vertigo of 20 minutes or longer; 2) audiometrically documented hearing loss on at least 1 occasion; 3) tinnitus or aural fullness in the treated ear; and 4) other causes excluded. The rates of recurrence and progression to MD were measured during a follow-up period of at least 1 year.

Statistical analysis

Statistical analyses were performed using GraphPad Prism software (version 6.0; GraphPad Software Inc.; La Jolla, CA, U.S.A.). Statistical differences were analyzed using the Mann-Whitney U-test for two independent groups and Kruskal-Wallis test for three independent groups, with a p value of less than 0.05 considered statistically significant. Audiological functional values were presented using box-and-whisker plots [Govaerts et al., 1998]. The horizontal line inside each box indicates the median, the top and bottom borders of the box mark the 75th and 25th percentiles, respectively, and the whiskers above and below the box mark the 90th and 10th percentiles, respectively. The circles beyond the whiskers indicate outliers beyond the 90th or 10th percentiles. A Kaplan-Meier time-to-event method was used to calculate the percentage of subjects who experienced recurrence or progression to definite MD. This method is suited to longitudinal and quantitative analysis, in which subjects undergo varying periods of follow-up. Rather than only looking at subjects who have had relatively short periods of follow-up, the Kaplan-Meier approach allows more efficient use of all available data to model the percentage of patients with

recurrence or progression to definite MD over time. The log rank test was applied to compare these outcomes.

Results

Subject profiles

A total of 392 patients were diagnosed with ALHL and performed initial medical treatment. Of these, 265 patients were excluded because of hearing improvement after initial treatment (n=241) or through missing follow-up (n=24). A total of 127 patients were refractory to initial treatment, 37 of whom were diagnosed with “probable” ALHL. Finally, a total of 90 patients with “definite” ALHL were enrolled in this study. The ITS group comprised 27 patients, the diuretic group 39 patients and the control group 24 patients.

Patient and control profiles are summarized in Table 1. The study population consisted of 24 males and 66 females, ranging in age from 13 to 61, with a median age of 49.5 years. Seven patients experienced dizziness (not vertigo), and nystagmus was observed in 19 patients at the initial examination. The duration from the onset of cochlear symptoms to the beginning of initial therapy ranged from 1 to 28 days, with a median of 8.5 days. The duration from the onset of symptoms to the beginning of second-line therapy ranged from 15 to 42 days, with a median of 22 days. The follow-up period ranged from 18 to 108 months, with a median of 36 months. Thirty-nine of 90 patients were followed-up for over 5 year; 12 patients in the ITS group, 15 patients in the diuretic group and 12 patients in the control group. The sum of hearing levels at three low frequencies (125, 250 and 500 Hz) before and after initial therapy ranged from 95 to 230 dB (median, 140 dB) and from 80 to 245 dB (median, 140 dB), respectively. There were no significant differences in these parameters among the groups.

Hearing outcomes in each group

Figure 1a, b, c depicts the rates of hearing loss recovery at 1 month, 1 year and 5 years after the completion of second-line therapy. Those at 1 month, 1 year and 5 years were 52.2% (47/90), 41.1% (37/90) and 28.2% (11/39) among the total subjects; 77.8% (21/27), 70.4% (19/27) and 33.3% (4/12) in the ITS group; 46.2% (18/39), 33.3% (13/39) and 26.7% (4/15) in the diuretic group; and 33.3% (8/24), 20.8% (5/24) and 25.0% (3/12) in the control group, respectively. The recovery rates at 1 month and 1 year in the ITS group were significantly higher than those in the diuretic ($p=0.012$, $p=0.006$) and control ($p=0.002$, $p<0.001$) groups. Meanwhile, there were no significant differences in the recovery rate at 5 years among the three groups. Although the diuretic alone treatment tended to produce better results than observed in the control group, there were no clinically significant differences between these two groups.

When we analyzed complete and partial recovery separately, no significant differences with regard to the rate of complete recovery were observed among the three groups. Meanwhile, the rate of partial recovery within 1 year in the ITS group was significantly higher than those in the diuretic ($p=0.014$) and control ($p=0.022$) groups.

Functional values in each group

Figure 2a, b, c shows the functional values for the sum of hearing levels at three low frequencies (125, 250 and 500 Hz) at 1 month, 1 year and 5 years after the completion of second-line therapy in the three patient groups. The mean values at 1 month, 1 year and 5 years were 53.3 dB (median, 45.0 dB; 95% confidence interval [CI], 0.0 to 120.0 dB), 50.4 dB (median, 45.0 dB; 95% CI, 0.0 to 120.0 dB) and 31.7 dB (median, 17.5 dB; 95% CI, 0.0 to 110.0 dB) in the ITS group, 24.1 dB (median, 20.0 dB; 95% CI, -10.0 to 70.0 dB), 18.9 dB (median, 5.0 dB; 95% CI, -10.0 to 70.0 dB) and 16.7 dB (median, 10.0 dB; 95% CI, -5.0 to 60.0 dB) in the diuretic group, and 17.7 dB (median, 5.0 dB; 95% CI, -10.0 to 87.5 dB), 15.0 dB (median, 5.0 dB; 95% CI, -10.0 to 87.5 dB) and 17.1 dB (median, 10.0 dB; 95% CI, -5.0 to 65.0 dB) in the control group, respectively. We found that the functional values at 1 month and 1 year in the ITS group were significantly higher than those in the diuretic ($p=0.001$, $p<0.001$) and the control ($p<0.001$, $p<0.001$) groups. However, there were no significant differences in the values at 5 years among the three groups.

Rates of recurrence in each group

Figure 3 demonstrates the recurrence rates of hearing loss. The 1-year and 5-years estimated recurrence rates were 7.4% and 27.6% in the ITS group, 12.8% and 22.3% in the diuretic group, and 16.7% and 26.1% in the control group, respectively. There were no significant differences in the recurrence rates among the three groups.

Rates of progression to definite Ménière's disease in each group

Figure 4 depicts the rates of progression to definite MD. The 1-year and 5-years estimated progression to MD rates were 0% and 13.3% in the ITS group, 0% and 12.1% in the diuretic group, and 0% and 12.5% in the control group, respectively. No statistical differences in the progression rates from ALHL to MD were observed among the three groups.

Figure 5 shows the rates of progression to definite MD in ALHL patients with nystagmus and dizziness at the initial examination. The 1-year and 5-years estimated progression rates were 0% and 50.0% in the ITS group, 0% and 57.1% in the diuretic group, and 0% and 50.0% in the control group, respectively. Whereas, no ALHL patients without nystagmus and dizziness developed definite MD. There were significant differences in the rates of progression to MD between those with and without nystagmus and dizziness at the initial examination in each of the three groups ($p<0.001$, $p<0.001$, $p<0.001$).

Complications

No patient in any group experienced severe side effects. However, 2 patients receiving ITS treatment experienced perforation of the tympanic membrane which persisted for more than 3 months. They underwent myringoplasty and the problem was resolved in both patients. A further 3 patients suffered from vertigo after intratympanic injection; however, this complaint was spontaneously resolved within 1 hour. In the diuretic group, epigastric discomfort was observed in 3 patients, and dry mouth in 1 patient.

However, these complaints disappeared in all cases without further treatment.

Discussion

The treatment of patients with ALHL continues to vary among otological centers with no standard protocol universally accepted. Steroids and/or mild diuretics have been administered to patients with ALHL based upon the assumption that the pathophysiology involves an autoimmune response of the endolymphatic sac that induces changes in fluid homeostasis within the cochlea and the development of EH [Fuse et al., 2003; McCabe, 1979]. However, it is difficult to determine whether any therapeutic intervention actually improves hearing impairment due to the natural history of ALHL [Fuse et al., 2002; Morita et al., 2010; Okada et al., 2012]. Salvage treatment for refractory ALHL, in particular, has not been well reported in contrast to that for ISSNHL or MD [Barrs et al., 2001; Li et al., 2015; Martin-Sanz et al., 2015; Selivanova et al., 2005]. We found that the rates of hearing loss recovery and the functional values within 1 year in the ITS group were significantly higher than those in the diuretic and control groups. The intratympanic application of dexamethasone resulted in significantly higher endolymph and perilymph concentrations than those achieved by systemic routes and exerted a stronger effect on hearing recovery [Barrs et al., 2001; Chandrasekhar et al., 2000; Li et al., 2015; Martin-Sanz et al., 2015; Parnes et al., 1999]. Dexamethasone have been shown to regulate inflammation, immune response, cochlear blood flow and the expression of active and passive Na/K channels and of aquaporins in the endolymph surrounding tissues to maintain ionic homeostasis in the cochlea, resulting in the reduction of EH [Fukushima et al., 2004; Pondugula et al., 2006; Pondugula

et al., 2004; Shirwany et al., 1998; Trune et al., 2006]. Meanwhile, the autoimmune response of the endolymphatic sac suggests that diuretic may not be effective for ALHL in the short-term, with long-term treatment required to improve EH.

The ideal treatment for ALHL should have a high rate of cure (complete recovery) as well as a high rate of response (partial recovery), as patients with ALHL might not feel a sense of satisfaction if their hearing level does not improve to a level close to that of the unaffected ear. In this analysis, there were no significant differences with regard to the rate of complete recovery among the three groups, whereas the rate of partial recovery within 1 year in the ITS group was significantly higher than those in the diuretic and control groups. One possible reason for this result might be the dosing schedule of the ITS administration. The pharmacokinetics of dexamethasone have demonstrated peak perilymph concentrations approximately 1 hour after ITS injection, with elimination from the perilymph approaches 6 hours and essentially no signal observed at 12 hours [Parnes et al., 1999; Salt, 2008; Yang et al., 2008]. As requirements for successful ITS treatment have been to maintain the concentration of the drug in the perilymph at a high level [Plontke et al., 2007], the weekly ITS injections administered in this study might not be as beneficial as a continuous infusion or sequential injections. Meanwhile, previous studies on cochlear pharmacokinetics with local ear drug delivery have revealed that the concentration in the basal turn of the cochlear is rapidly diffused into the apical turn after intratympanic injection [Plontke et al., 2007]. Therefore, ITS treatment, even if weekly, can

be expected to have a certain effect on hearing impairment at low-frequencies rather than at high-frequencies.

Although the short-term hearing outcomes are relatively good, the rates of recurrence and progression to MD in ALHL patients are estimated to be 27-47% and 9-11% during long-term follow-up [Fushiki et al., 2009; Junicho et al., 2008; Yamasoba et al., 1994]. In the current study, the 5-years estimated recurrence and progression rates were 24.7% and 12.3% among the total patients, and we did not find that ITS administration aided in the control of these incidents during long-term follow-up of at least 1 year. Due to pharmacokinetics of dexamethasone (i.e., the decline in drug concentration within cochlear), ITS administration might provide only transitory reductions in EH rather than a prolonged therapeutic effect. Thus, repeated ITS injections should be offered as a treatment choice once EH levels return.

We also demonstrated that the patients who developed MD had nystagmus at the initial presentation, whereas no ALHL patients without nystagmus and dizziness developed MD. This result suggested that the presence of nystagmus and dizziness with ALHL might be potential risk factor related to the progression to MD. It is interesting that patients with ALHL occasionally displayed nystagmus as a subclinical vestibular dysfunction even when they had no subjective vertigo. The presence of nystagmus is proposed to lead to the development of EH that spreads from the cochlea to the vestibule. If ALHL can be assumed to be the precursor stage of MD and a less-severe state of EH, evaluation of the severity and extent of EH within inner ear at

the initial presentation may be useful in predicting whether ALHL patients develop definite MD and present with recurrent hearing loss [Fuse et al., 2003; Fushiki et al., 2009; Shimono et al., 2013]. The value of using ECoG and VEMP in predicting the outcome of ALHL has also been reported [Yamasoba et al., 1993; Wang et al., 2010].

The primary advantages of ITS injection are the prevention of various adverse effects, such as immune suppression, gastric ulcers, glucose intolerance, avascular necrosis of the femur, endocrine problems, uncontrolled hypertension, facial flushing, mood changes, osteoporosis, and weight gain [Li et al., 2015]. On the other hand, the potential disadvantages of ITS injection include pain, tympanic membrane perforation, acute otitis media, otorrhea, vertigo, and the potential for further HL. Although the incidence of tympanic membrane perforation after ITS is 4.8-17.6%, cases of permanent perforation are rare and perforation is frequently resolved spontaneously or with paper-patch myringoplasty in the clinical setting [Barrs et al., 2001; Rutt et al., 2011]. In the current study, perforation of tympanic membrane was observed in 2 patients, but it was curable in both cases. As dexamethasone causes no histological or functional changes in the inner ear [Shirwany et al., 1998], ITS administration seems to be a sufficiently safe procedure.

In conclusion, salvage ITS therapy appears to be effective in improving hearing loss in patients with ALHL who have persistent symptoms despite conventional treatment. However, its efficacy for the treatment of hearing impairment was limited to the short-term, indicating that salvage ITS

therapy is not expected to provide good long-term hearing outcomes. Furthermore, we demonstrated that the recurrence and progression to MD after ITS treatment were not uncommon during a long-term observation at least 1 year. In particular, the presence of nystagmus and dizziness has been shown to be a potential prognostic factor of progression to MD. Although the kind, dose, and optimum concentration of the steroid as well as the number and frequency of intratympanically administered treatments remain to be undetermined, repeated ITS injections may be necessary in the cases with recurrence or progression to MD.

Limitations

Due to the retrospective nature of this study, the presence of bias caused by loss of subjects from follow-up, the selection criteria of patients and treatment protocols (non-randomized analysis) cannot be completely ruled out. However, retrospective chart review is an important method for gathering clinical data on outcomes and aiding clinical decision-making, as well as in generating hypotheses for future research.

Other limitations might be the dosing schedule applied, and whether the overall response to the treatment was simply a picture of the natural history of ALHL or not. In particular, the weekly ITS injections might not be as beneficial as a continuous infusion or daily injections with regard to maintaining a high drug concentration or extending the duration of the drug in the perilymph. The clinical benefits of ITS treatment for patients with refractory ALHL should be confirmed in well-designed prospective,

randomized, double-blind trials.

Disclosure Statement

We have no conflicts of financial interest to declare.

References

Barrs DM, Keyser JS, Stallworth C, McElveen JT Jr: Intratympanic steroid injections for intractable Ménière's disease. *Laryngoscope* 2001;111:2100-2104.

Chandrasekhar SS, Rubinstein RY, Kwartler JA, Gatz M, Connelly PE, Huang E, Baredes S: Dexamethasone pharmacokinetics in the inner ear: comparison of route of administration and use of facilitating agents. *Otolaryngol Head Neck Surg* 2000;122:521-528.

Fukushima M, Kitahara T, Fuse Y, Uno Y, Doi K, Kubo T: Changes in aquaporin expression in the inner ear of the rat after i.p. injection of steroids. *Acta Otolaryngol Suppl* 2004;553:13-18.

Fuse T, Aoyagi M, Funakubo T, Sakakibara A, Yoshida S: Short-term outcome and prognosis of acute low-tone sensorineural hearing loss by administration of steroid. *ORL J Otorhinolaryngol Relat Spec* 2002;64:6-10.

Fuse T, Hayashi T, Oota N, Fukase S, Asano S, Kato T, Aoyagi M: Immunological responses in acute low-tone sensorineural hearing loss and Ménière's disease. *Acta Otolaryngol* 2003;123:26-31.

Fushiki H, Junicho M, Aso S, Watanabe Y: Recurrence rate of idiopathic sudden low-tone sensorineural hearing loss without vertigo: a long-term follow-up study. *Otol Neurotol* 2009;30:295-298.

Govaerts PJ, Somers T, Offeciers FE: Box and whisker plots for graphic presentation of audiometric results of conductive hearing loss treatment. *Otolaryngol Head Neck Surg* 1998;118:892-895.

Imamura S, Nozawa I, Imamura M, Murakami Y: Clinical observations on acute low-tone sensorineural hearing loss. Survey and analysis of 137 patients. *Ann Otol Rhinol Laryngol* 1997;106:746-750.

Junicho M, Aso S, Fujisaka M, Watanabe Y: Prognosis of low-tone sudden deafness. Does it inevitably progress to Meniere's disease? *Acta Otolaryngol* 2008;128:304-308.

Li H, Feng G, Wang H, Feng Y: Intratympanic steroid therapy as a salvage treatment for sudden sensorineural hearing loss after failure of conventional therapy: a meta-analysis of randomized, controlled trials. *Clin Ther* 2015;37:178-187.

Martin-Sanz E, Esteban-Sanchez J, Rodrigañez-Riesco L, Sanz-Fernández R: Transitory effect on endolymphatic hydrops of the intratympanic steroids for Ménière's disease. *Laryngoscope* 2015;125:1183-1188.

McCabe BF: Autoimmune sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 1979;88:585-590.

Monsell EM, Balkany TA, Gates GA, Goldenberg RA, Meyerhoff WL, House JW: Committee on hearing and equilibrium guidelines for the diagnosis and evaluation of therapy in Ménière's disease. *Otolaryngol Head Neck Surg* 1995;113:181-185.

Morita S, Suzuki M, Iizuka K: A comparison of the short-term outcome in patients with acute low-tone sensorineural hearing loss. *ORL J Otorhinolaryngol Relat Spec* 2010;72:295-299.

Noguchi Y, Nishida H, Tokano H, Kawashima Y, Kitamura K: Comparison of acute low-tone sensorineural hearing loss versus Meniere's disease by electrocochleography. *Ann Otol Rhinol Laryngol* 2004;113:194-199.

Nozawa I, Imamura S, Mizukoshi A, Honda H, Okamoto Y: Clinical study of acute low-tone sensorineural hearing loss: survey and analysis of glycerol test and orthostatic test. *Ann Otol Rhinol Laryngol* 2002;111:160-164.

Okada K, Ishimoto S, Fujimaki Y, Yamasoba T: Trial of Chinese medicine Wu-Ling-San for acute low-tone hearing loss. *ORL J Otorhinolaryngol Relat Spec* 2012;74:158-163.

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.

Plontke SK, Siedow N, Wegener R, Zenner HP, Salt AN: Cochlear pharmacokinetics with local inner ear drug delivery using a three-dimensional finite-element computer model. *Audiol Neurotol* 2007;12:37-48.

Pondugula SR, Raveendran NN, Ergonul Z, Deng Y, Chen J, Sanneman JD, Palmer LG, Marcus DC: Glucocorticoid regulation of genes in the amiloride-sensitive sodium transport pathway by semicircular canal duct epithelium of neonatal rat. *Physiol Genomics* 2006;24:114-123.

Pondugula SR, Sanneman JD, Wangemann P, Milhaud PG, Marcus DC: Glucocorticoids stimulate cation absorption by semicircular canal duct epithelium via epithelial sodium channel. *Am J Physiol Renal Physiol* 2004;286:F1127-1135.

Rutt AL, Hawkshaw MJ, Sataloff RT: Incidence of tympanic membrane perforation after intratympanic steroid treatment through myringotomy tubes. *Ear Nose Throat J* 2011;90:E21.

Salt AN: Dexamethasone concentration gradients along scala tympani after application to the round window membrane. *Otol Neurotol* 2008;29:401-406.

Selivanova OA, Gouveris H, Victor A, Amedee RG, Mann W: Intratympanic dexamethasone and hyaluronic acid in patients with low-frequency and Ménière's-associated sudden sensorineural hearing loss. *Otol Neurotol* 2005;26:890-895.

Shimono M, Teranishi M, Yoshida T, Kato M, Sano R, Otake H, Kato K, Sone M, Ohmiya N, Naganawa S, Nakashima T: Endolymphatic hydrops revealed by magnetic resonance imaging in patients with acute low-tone sensorineural hearing loss. *Otol Neurotol* 2013;34:1241-1246.

Shirwany A, Seidman MD, Tang W: Effect of transtympanic injection of steroids on cochlear blood flow, auditory sensitivity, and histology in the guinea pig. *Am J Otol* 1998;19:230-235.

Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM, Brown SR, Fife TD, Ford P, Ganiats TG, Hollingsworth DB, Lewandowski CA, Montano JJ, Saunders JE, Tucci DL, Valente M, Warren BE, Yaremchuk KL, Robertson PJ; American Academy of Otolaryngology-Head and Neck Surgery: Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg* 2012;146(3 Suppl):S1-35.

Trune DR, Kempton JB, Gross ND: Mineralocorticoid receptor mediates glucocorticoid treatment effects in the autoimmune mouse ear. *Hear Res* 2006;212:22-32.

Wang CT, Fang KM, Young YH, Cheng PW: Vestibular-evoked myogenic potential in the prediction of recovery from acute low-tone sensorineural hearing loss. *Ear Hear* 2010;31:289-295.

Yamasoba T, Kikuchi S, Sugasawa M, Yagi M, Harada T: Acute low-tone sensorineural hearing loss without vertigo. *Arch Otolaryngol Head Neck Surg* 1994;120:532-535.

Yamasoba T, Sugasawa M, Kikuchi S, Yagi M, Harada T: An electrocochleographic study of acute low-tone sensorineural hearing loss. *Eur Arch Otorhinolaryngol* 1993;250:418-422.

Yang J, Wu H, Zhang P, Hou DM, Chen J, Zhang SG: The pharmacokinetic profiles of dexamethasone and methylprednisolone concentration in perilymph and plasma following systemic and local administration. *Acta Otolaryngol* 2008;128:496-504.

Table headings

Table 1. Characteristics of subjects with “definite” acute low-tone sensorineural hearing loss by group

Figure legends

Fig. 1. The rates of hearing loss recovery at 1 month (a), 1 year (b) and 5 years (c) after second-line therapy in the ITS, diuretic and control groups. Statistical differences were analyzed using the Mann-Whitney U-test and Kruskal-Wallis test.

ITS; intratympanic steroids

Fig. 2. The functional values at 1 month (a), 1 year (b) and 5 years (c) after second-line therapy in the ITS, diuretic and control groups. Statistical differences were analyzed using the Mann-Whitney U-test and Kruskal-Wallis test.

ITS; intratympanic steroids

Fig. 3. Kaplan-Meier plots indicating the percentage of subjects who experienced recurrence of hearing loss after second-line therapy in the ITS, diuretic and control groups. Statistical differences were analyzed using the log-rank test.

ITS; intratympanic steroids

Fig. 4. Kaplan-Meier plots indicating the percentage of subjects who experienced progression to definite Ménière's disease after second-line therapy in the ITS, diuretic and control groups. Statistical differences were analyzed using the log-rank test.

ITS; intratympanic steroids

Fig. 5. Kaplan-Meier plots indicating the rates of progression to definite Ménière's disease in subjects with and without nystagmus and dizziness after second-line therapy in the ITS, diuretic and control groups. Statistical differences were analyzed using the log-rank test.

ITS; intratympanic steroids

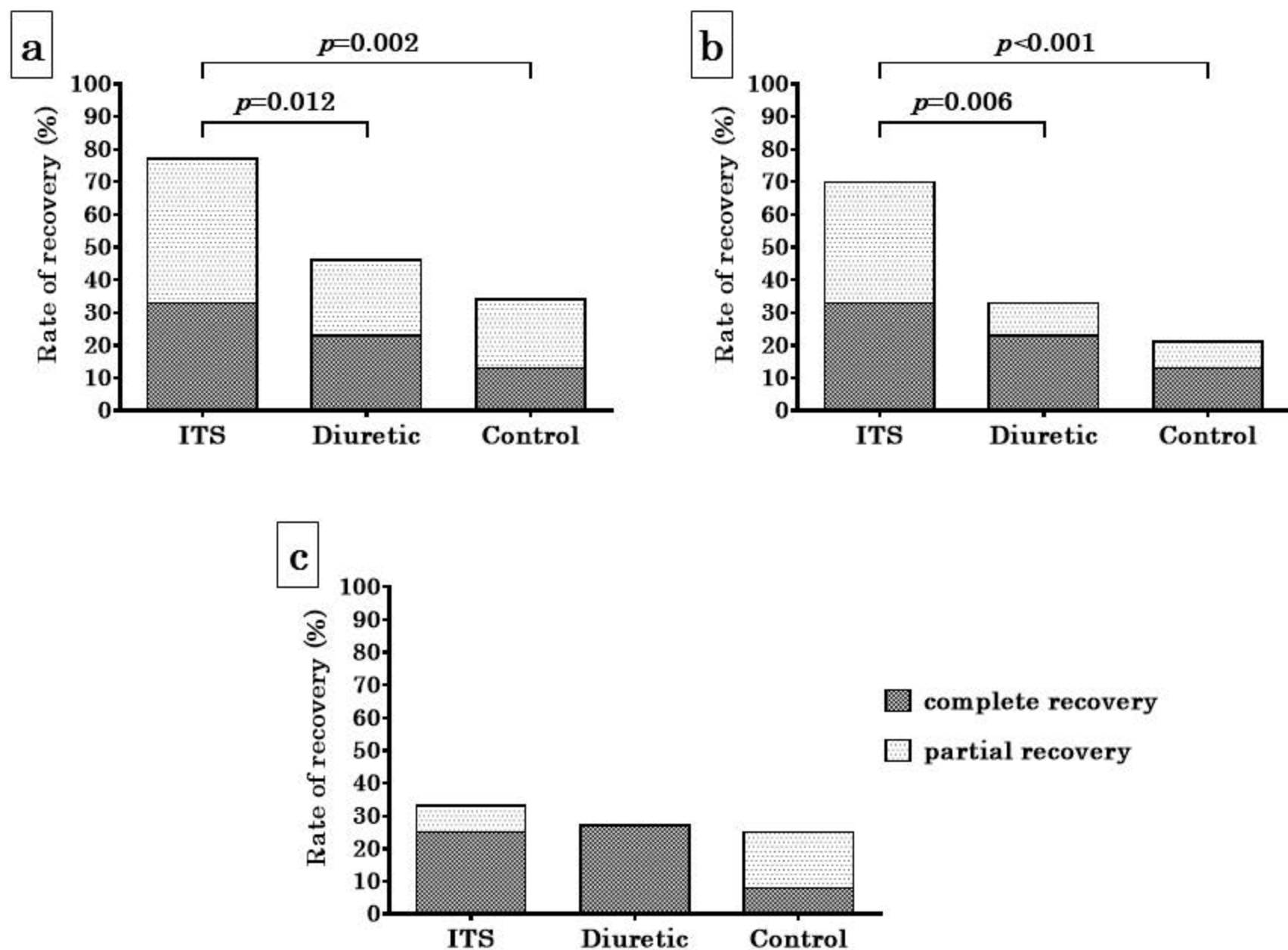


Fig. 1

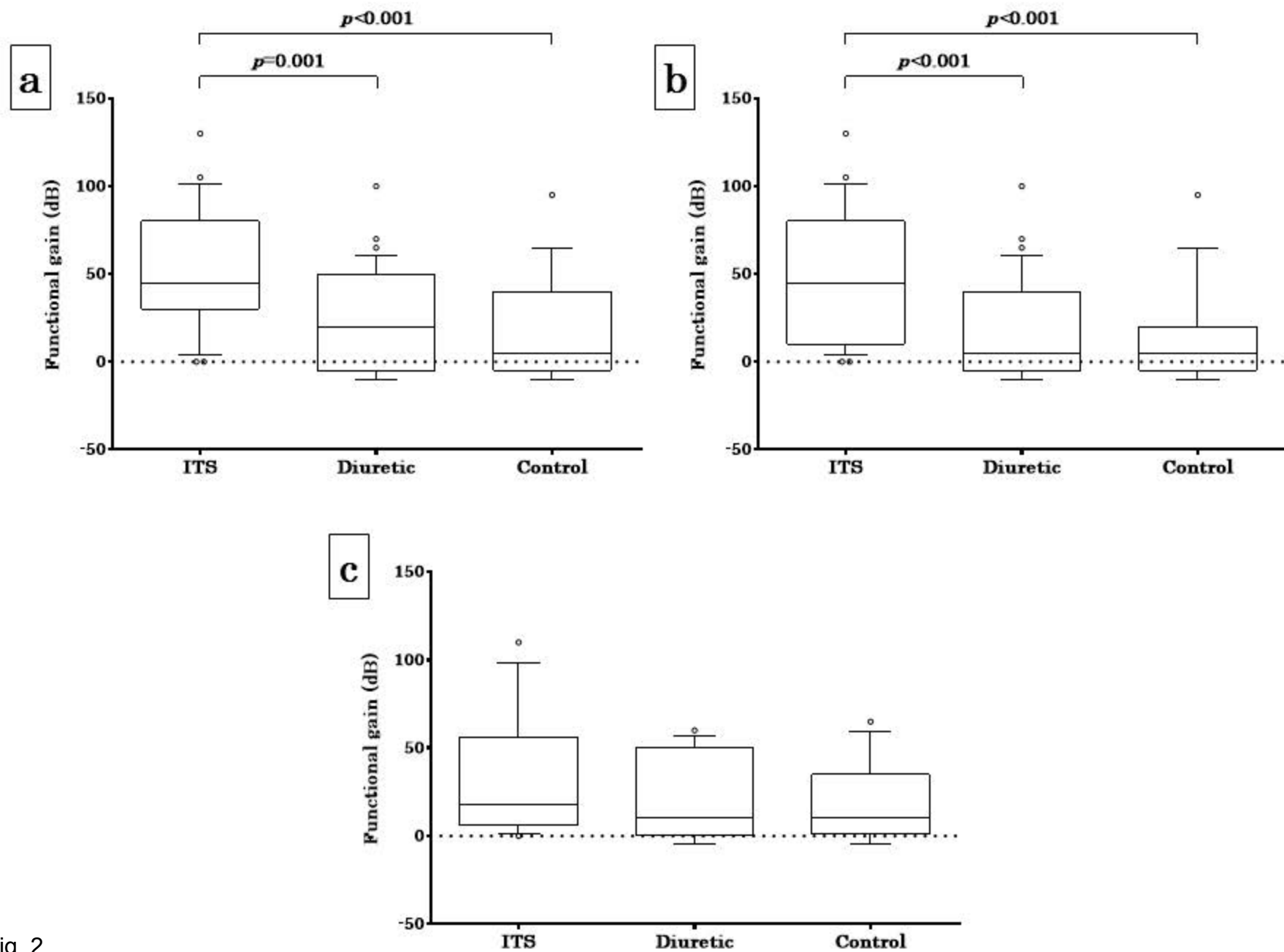


Fig. 2

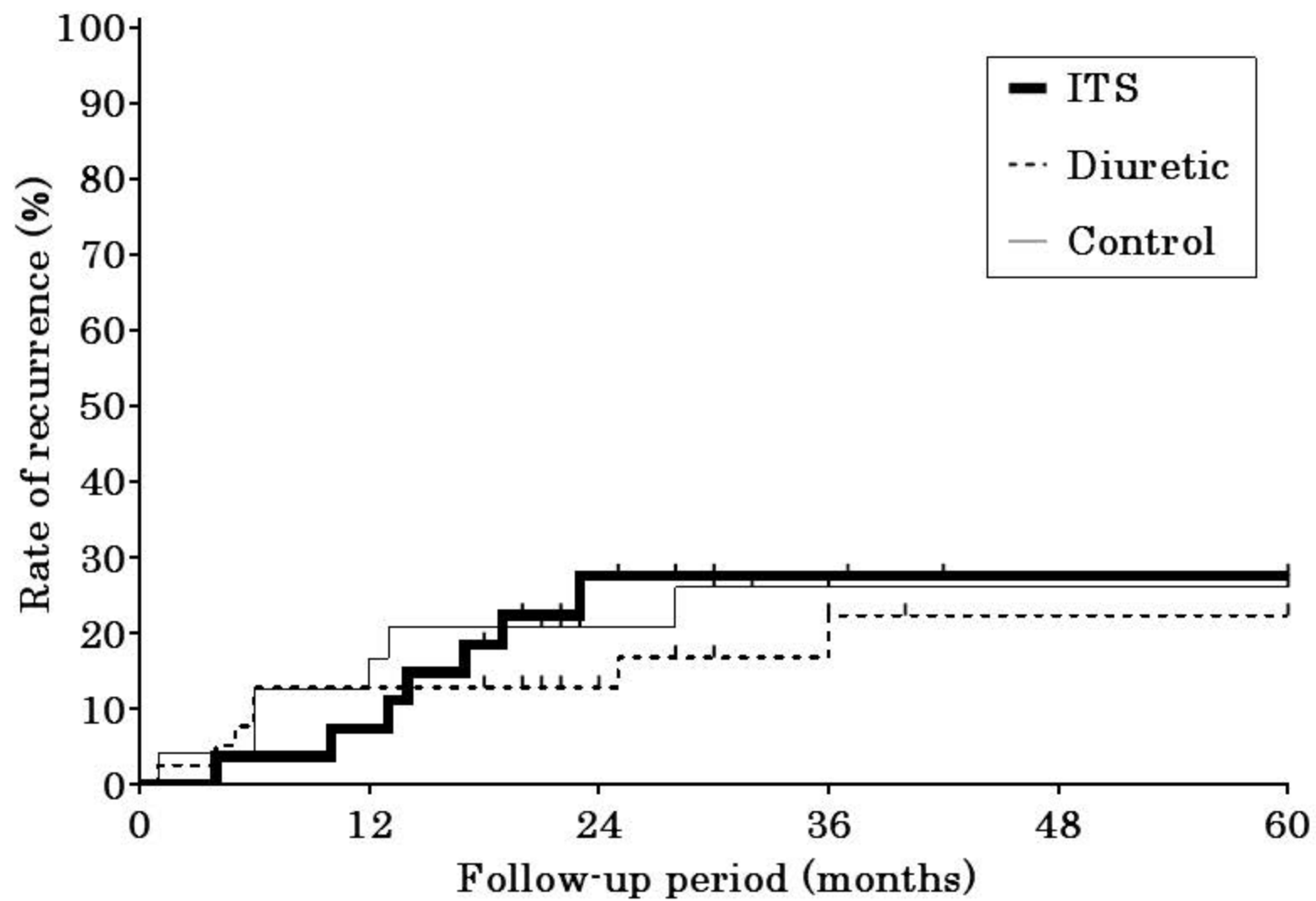


Fig. 3

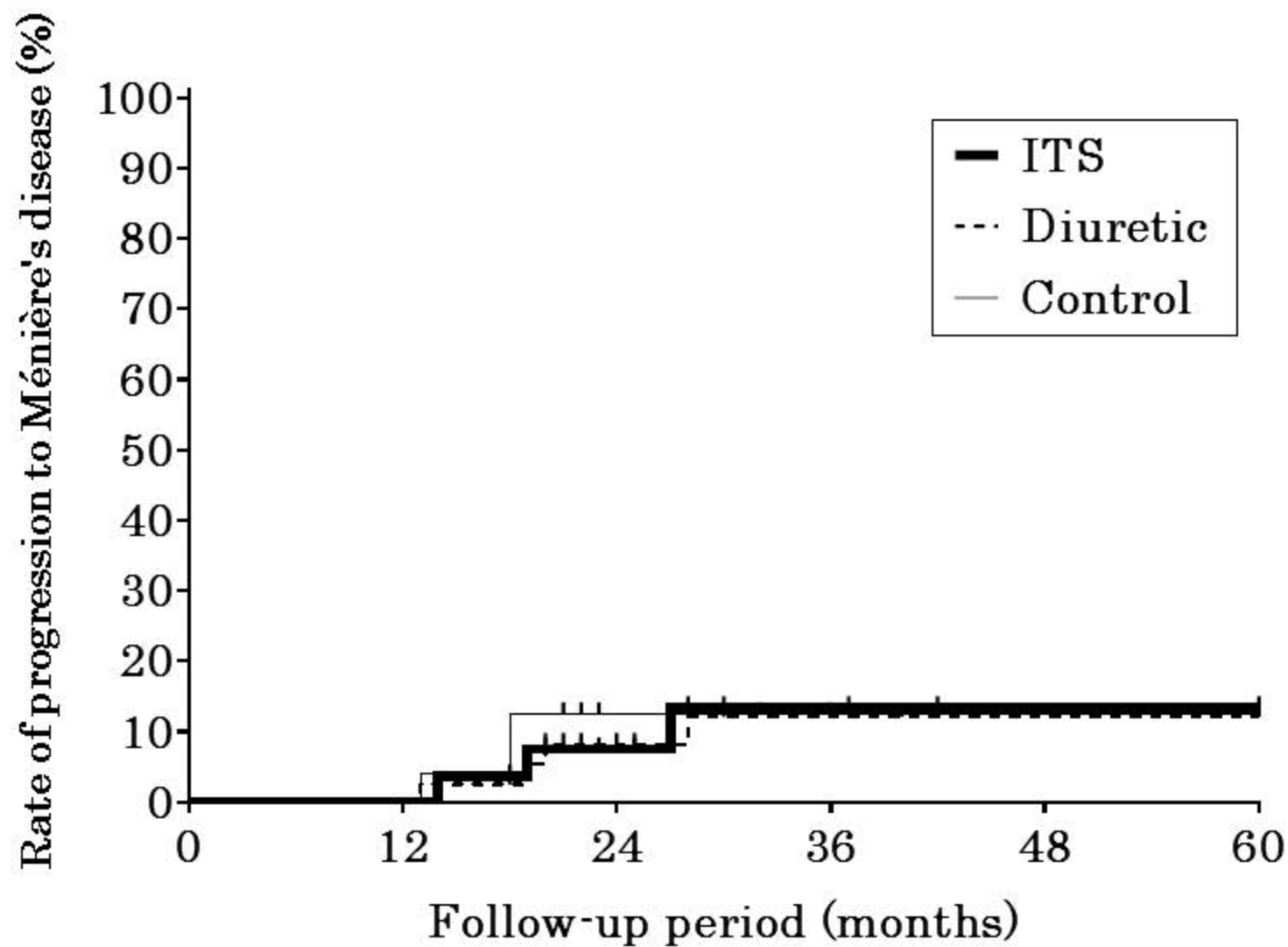


Fig. 4

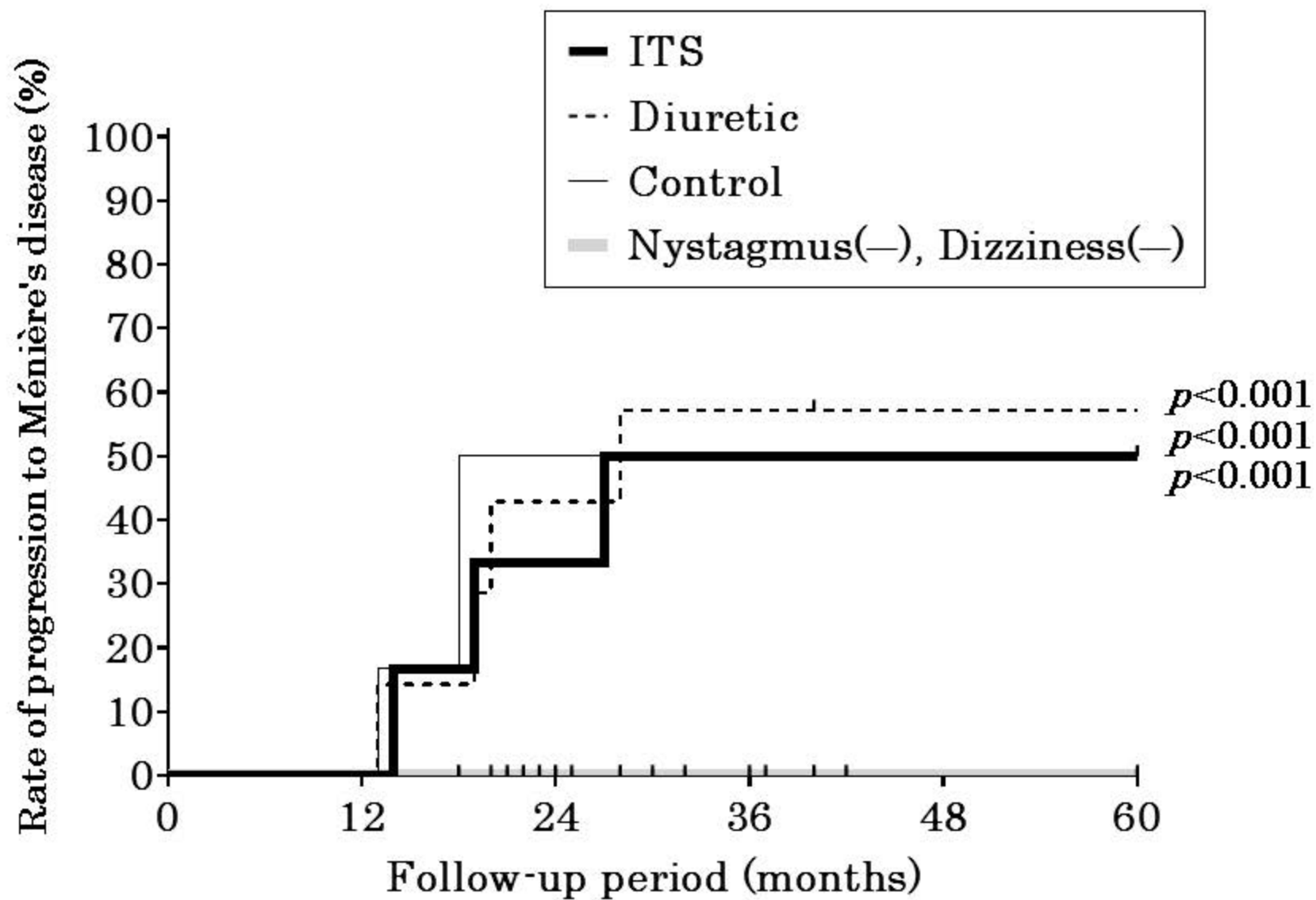


Fig. 5

Table 1. Characteristics of subjects with “definite” acute low-tone sensorineural hearing loss by group

	ITS group	Diuretic group	Control group	<i>p</i> value
Number (n)	27	39	24	
Age (years)				0.54
range	13-60	14-61	30-61	
median	46	50	50.5	
Gender (n)				0.32
male	10	8	6	
female	17	31	18	
Dizziness (n)	2	3	2	0.99
Nystagmus (n)	6	7	6	0.79
Duration from the onset of cochlear symptoms to the beginning of initial therapy (days)				0.68
range	1-26	1-28	1-28	
median	8	9	9.5	
Duration from the onset of cochlear symptoms to the beginning of second-line therapy (days)				0.75

range	15-40	16-42	15-42	
median	22	23	23.5	
Follow up period (months)				0.29
range	18-92	18-72	21-108	
median	37	36	36	
Sum of hearing levels at 3 low frequencies (125, 250 and 500 Hz) before initial therapy (dB)				0.74
range	100-230	95-205	105-205	
median	140	145	137.5	
Sum of hearing levels at 3 low frequencies (125, 250 and 500 Hz) after initial therapy (dB)				0.43
range	105-245	80-210	90-230	
median	150	125	132.5	
ITS; intratympanic steroids, ALHL; acute low-tone sensorineural hearing loss, Hz; hertz, dB; decibel				
Statistical differences were analyzed using the Kruskal-Wallis test.				