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Original Article

Predictive Factors for the Success of Intratympanic Dexamethasone Treatment of Acute Subjective Tinnitus

Hyeon Sik Oh, Eun Sub Lee, Yong-Hwi An, Hyun Joon Shim

Department of Otorhinolaryngology-Head and Neck Surgery, Eulji University School of Medicine, Nowon Eulji Medical Center, Seoul, Korea

ORCID IDs of the authors: H.S.O. 0000-0003-0018-0200; E.S.L. 0000-0002-7211-2074; Y.H.A. 0000-0001-8240-1673; H.J.S. 0000-0001-9719-6959.

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OBJECTIVES: The purpose of this study was to determine the factors predicting the success or failure of intratympanic dexamethasone (ITD) injection in the treatment of acute subjective tinnitus (AST).

MATERIALS and METHODS: We enrolled patients who were treated with ITD within 3 months of the onset of tinnitus, between 2013 and 2017. We compared the clinical characteristics and audiological data of the patients in the cured group (n=38, 45.6±13.3 years old) and the nonresponder group (n=40, 48.9±18.6 years old).

RESULTS: The cured group was predominantly female (p=0.002). The mean duration of tinnitus before ITD was shorter in the cured group than the nonresponder group (p=0.002). The pure-tone averages in both sides were lower in the cured group than in the nonresponder group (p=0.018). The time of tinnitus awareness was shorter in the cured group than in the nonresponder group (p=0.014). Multivariable analysis showed that the duration of tinnitus (odds ratio [OR]=1.045), a history of exposure to noise just before tinnitus development (OR=7.766), and distortion product otoacoustic emissions results (OR=4.580) predicted the outcome of ITD treatment in AST.

CONCLUSION: A short duration of tinnitus, no history of immediate noise exposure, and normal distortion product otoacoustic emissions could be favorable prognostic factors for AST treated with ITD injection.

KEYWORDS: Tinnitus, tympanic membrane, dexamethasone, injection

INTRODUCTION

Intratympanic (IT) dexamethasone (ITD) injection, rather than systemic steroid administration, is currently widely used for patients with sudden sensorineural hearing loss (SNHL), especially in those vulnerable to the adverse effects of systemic steroids, such as patients with diabetes. Several studies have demonstrated that ITD injection has the same effect as systemic steroid on sudden SNHL [1,2]. There are two main evidences that support the feasibility of ITD injections in the recovery from early-stage cochlear damage. First, steroid injected into the middle ear cavity can penetrate the round window membrane, allowing it to spread into the inner ear fluid [3,4]. Second, many steroid receptors are present in the inner ear structures [5-7].

There is much debate about the therapeutic effects of ITD on acute subjective tinnitus (AST), but we speculate that ITD is effective in the early stages of tinnitus on the basis of the rationale presented below. First, most tinnitus occurs because of cochlear damage, and there is a time window to repair that damage. Second, in many cases, the etiology of the AST might be same as that of sudden SNHL, including viral infection and microvascular obstruction. Third, ITD is a relatively easy and safe treatment with little concern for complications. Although several authors have recommended just observation or minimal evaluation for AST because acute tinnitus can resolve spontaneously [8, 9], it is unclear how much damage is reversed without intervention.

We previously reported a randomized controlled trial study of ITD for the treatment of AST that had developed within the previous 3 months, when not accompanied by sudden SNHL [10]. As for the overall improvement rate, including the cured case, ITD therapy

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Corresponding Address: Hyun Joon Shim E-mail: eardoc11@naver.com

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had a higher rate than alprazolam administration (75.8% vs. 40.3%, respectively), and the cure rate achieved with ITD therapy was higher than that achieved with alprazolam (25.8% vs. 9.8%, respectively). Because the injected steroid acts on the cochlea and cochlear damage cannot be reversed after 3 months, as shown in many animal studies, the indication for ITD should be restricted to acute tinnitus that develops within the preceding 3 months [11]. However, it is reasonable to assume that not all AST is caused by recent cochlear damage. If the cochlea has had subtle and continuous damage and tinnitus is only perceived when this damage reaches the limit, we cannot expect ITD to heal the damaged cochlea. Therefore, in the clinical field, the prognostic factors for the therapeutic effects of ITD for AST should be useful in determining the indications for ITD.

We have already conducted a retrospective study to investigate the favorable prognostic factors in 114 subjects treated with ITD for AST with a symptomatic period lasting £3 months [12]. We anticipated that the response rate of bilateral tinnitus would be lower than that of unilateral tinnitus because acute cochlear injury is more likely to develop on one side. However, the improvement rate in both groups was about the same. Moreover, we predicted that patients with tinnitus and symmetric hearing loss would be less responsive to the treatment than patients with tinnitus and asymmetric hearing loss, but the results did not differ between the two groups. The only factor associated with the cure rate of ITD for AST was symptom duration. Therefore, we could not identify any prognostic factors effective enough to determine the inclusion criteria for the use of ITD for AST, except early intervention and tinnitus duration.

Because the treatment outcome for tinnitus should be based on subjective symptom changes, which can vary with daily conditions or other factors, the judgment of improvement could be erroneous. Therefore, we designed this study to compare the clinical characteristics and audiological data of wholly cured patients and wholly nonresponsive patients, excluding any gray zone. With this comparative analysis, we aimed to determine the predictive factors for the success or failure of ITD treatment for AST.

MATERIALS AND METHODS

Study Design and Subjects

We retrospectively analyzed the medical records of patients who were treated with ITD within 3 months of the onset of tinnitus between 2014 and 2017 and who completed follow-up questionnaires at least 3 months after treatment. Patients with unilateral tinnitus were injected into the affected side, and patients with bilateral tinnitus were injected into the side with the stronger tinnitus. Subjects were excluded when they met the following criteria: 1) bilateral tinnitus with the same tinnitus intensity on both sides; 2) history of past otological disease; 3) familial history of hearing loss; 4) history of ototoxic drug use; 5) accompanying recurrent vertigo; 6) history of temporomandibular joint or cervical problems; 7) the presence of Meniere's disease or retrocochlear lesion; or 8) tinnitus combined with sudden hearing loss or acute low-tone hearing loss. We excluded patients with suspected objective tinnitus or somatic tinnitus using a careful physical examination of the head and neck. The study protocol was approved by the Institutional Review Board (2019-03-008).

MAIN POINTS

- We determined the prognostic factors of intratympanic dexamethasone for acute tinnitus.
- A short duration of tinnitus was a favorable prognostic factor.
- No history of immediate noise exposure was another favorable prognostic factor.
- Normal distortion product otoacoustic emissions might be the other prognostic factor.

ITD Injection Procedure

After confirmation that the tympanic membrane was intact, local anesthesia was induced with 10% lidocaine spray for 10 minutes. Then, 0.4-0.6 mL of dexamethasone (5 mg/mL; Yuhan, Seoul, Korea) was injected while the patient was in the supine position with his/her head turned approximately 45° toward the unaffected side. The patients were kept in the same position, without swallowing or speaking, for approximately 20 minutes to prevent the steroid from escaping through the eustachian tube. ITD was injected four times on 4 consecutive days.

Audiological Evaluations

The pure-tone thresholds at frequencies of 0.5, 1, 2, 3, 4, and 8 kHz were measured using an audiometer (AC40; Interacoustics, Middelfart, Denmark) and headphone (TDH-39P; Telephonics, New York, NY, USA) in a sound attenuating booth. Distortion product otoacoustic emissions (DPOAEs) were collected with a Navigator Pro (Bio-logic, New York, NY, USA). DPOAEs corresponding to frequency 2f1-f2 were recorded as DP-grams: f1=65 dB sound pressure level, f2=55 dB sound pressure level, f2/f1=1.22.

Outcome Measures

The improvement of tinnitus was investigated by comparing the response to questionnaires that patients submitted before treatment and again at 3 months after treatment, in terms of the following measures: tinnitus handicap inventory (THI), visual analogue scale (VAS) of tinnitus loudness (10-point scale), and tinnitus awareness score (percentage of time the patient was aware of tinnitus within one day). We defined the cured group as those patients with reduction in the loudness of tinnitus and the period of tinnitus awareness to 0 after treatment. The nonresponder group was defined as those patients who reported 1) an increase or a £2 point reduction in the VAS of tinnitus loudness or 2) an increase or a £10% reduction in the tinnitus awareness score. In this analysis, patients who did not meet the criteria for the cured or nonresponder group were excluded. Data from patients who completed the study were used to analyze the differences between the cured group and the nonresponder group.

Statistical Analysis

An independent *t*-test was used to compare the hearing thresholds, the pure-tone averages, the changes in the THI score, ages, initial VAS of tinnitus loudness, initial tinnitus awareness score, and the psychoacoustic measurements of tinnitus in the two groups. Pearson's χ^2 test was used to compare affected sides, sex, noise events, accompanying symptoms, and DPOAE in the two groups. A multivariable

logistic regression analysis was performed to identify the independent contributions of different factors to a poor outcome. The Statistical Packages for the Social Sciences (SPSS) for Windows version 18.0 (IBM Corp.; Armonk, NY, USA) was used for all data analyses. Values of $p<0.05$ were considered to indicate statistical significance.

RESULTS

Of the 165 patients enrolled in the study, tinnitus was cured in 38 patients (23.0%) and did not improve in 40 patients (24.2%). Patients with partial improvement (n=87) after ITD treatment were excluded from the analysis.

Table 1. Comparison of age, sex, laterality, and PTA, DPOAE in the cured and nonresponder groups

	Cured group (N=38)	Nonresponder group (N=40)	p
Age (years)	45.6±13.3	48.9±18.6	ns
Sex (M:F)	9:29	23:17	0.002
Mean duration of tinnitus (d)	25.4±24.1	45.3±29.7	0.002
Laterality (R/L)	15:23	18:22	ns
Initial PTA (dB) of injected ears	17.3±11.8	25.6±18.0	0.018
Initial PTA (dB) of noninjected ears	16.0±11.3	25.2±16.3	0.050
Ratio of reduced DPOAE amplitude	15/29	25/35	ns

PTA: pure-tone average; DPOAE: distortion product otoacoustic emissions; ns: not significant; M: male; F: female; R: right; L: left ($p>0.05$).

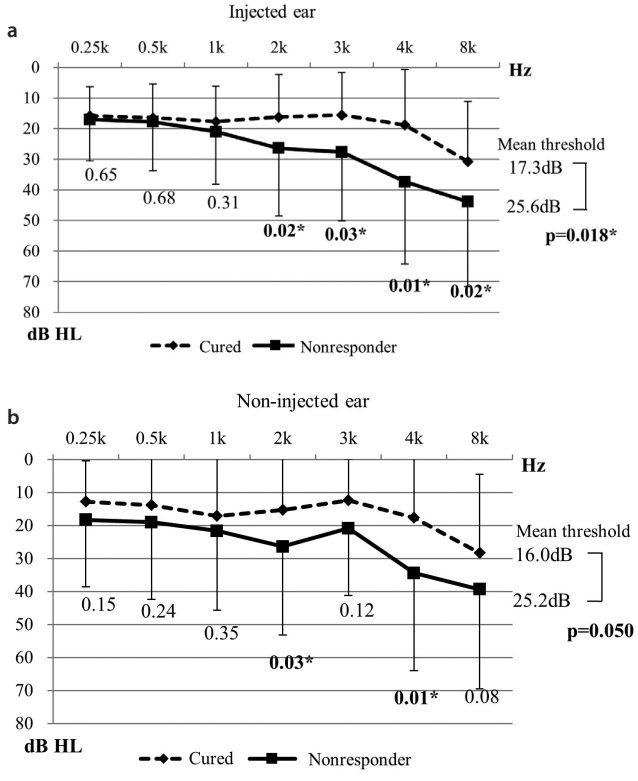

Figure 1. a, b. Initial average pure-tone thresholds in the (a) injected ears and (b) noninjected ears of the cured group and nonresponder group. The cured group shows lower PTA in the injected ear ($p<0.05$) and lower hearing thresholds at frequencies of 2, 3, 4, and 8 kHz in the injected ear and 2 and 4 kHz in the noninjected ear than that in the nonresponder group (*$p<0.05$). PTA: pure-tone average

Patient Characteristics

The mean age did not differ significantly between the cured and nonresponder groups (45.6±13.3 vs. 48.9±18.6 years, $p>0.05$), but the cured group showed female dominance, whereas the nonresponder group did not (male:female=9:29 vs. male:female=23:17, $p=0.002$). The mean duration of symptoms was shorter in the cured group than in the nonresponder group (25.4±24.1 vs. 45.3±29.7 days, $p=0.002$), but there was no significant difference in the laterality in the two groups (Table 1).

Comparison of Hearing Results

The initial average pure-tone threshold (0.5, 1, 2, and 4 kHz) was lower in the injected ears of the cured group than that in the nonresponder group (17.3±11.8 vs. 25.6±18.0 dB hearing level (HL), $p=0.018$), and the threshold in the noninjected ears revealed a borderline significant difference in both the groups (16.0±11.3 vs. 25.2±16.3 dB HL, $p=0.050$) (Figure 1). The cured group showed lower hearing thresholds on initial audiometry than the nonresponder group at frequencies of 2, 3, 4, and 8 kHz in the injected ear and at frequencies of 2 and 4 kHz in the noninjected ear ($p<0.05$). When the symmetry of audiometry was defined as a discrepancy of less than 10 dB HL at any frequency, the cured group produced 17 symmetric and 21 asymmetric audiograms, and the nonresponder group produced 17 symmetric and 23 asymmetric audiograms. Therefore, there was no difference in the ratio of symmetry between the two groups ($p>0.05$). Twenty of the 38 patients in the cured group and 34 of the 40 patients in the nonresponder group were tested with pure-tone audiometry again 3 months after the ITD treatment. There were no differences in the average pure-tone thresholds before and af-

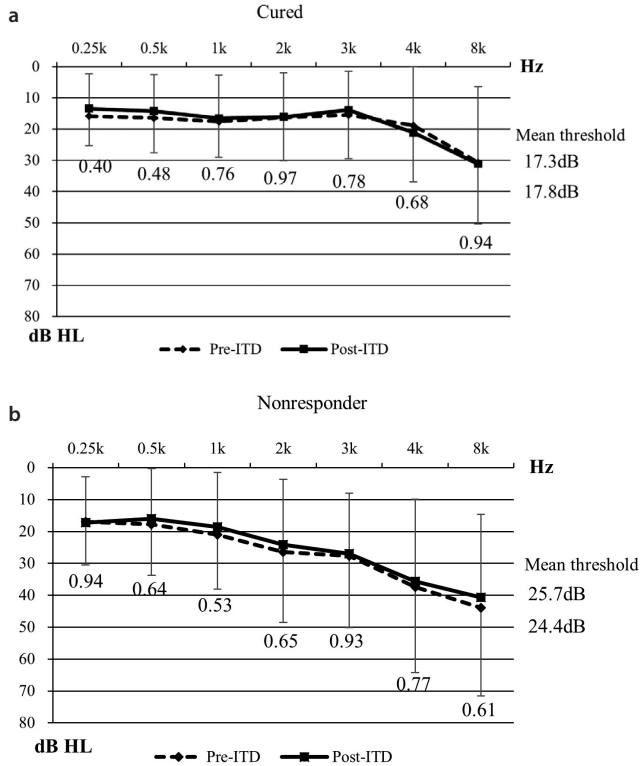

Figure 2. a, b. Mean pure-tone thresholds in the (a) cured group and (b) nonresponder group before and after treatment with ITD. There was no difference in the pure-tone thresholds beforehand after treatment in either group. ITD: intratympanic dexamethasone.

Table 2. Pure-tone threshold data for audiometric responders who showed a hearing threshold recovery of ≥15 dB at more than two frequencies

Subject Number	Injected side		Threshold of injected ear (kHz)						Threshold of noninjected ear (kHz)					
			0.25	0.5	1	2	4	8	0.25	0.5	1	2	4	8
Cured group														
2	L	Pre-ITD	20	25	15	20	30	15	0	10	15	20	15	20
		Post-ITD	10	**10**	5	**5**	**5**	10	10	10	5	5	5	5
3	L	Pre-ITD	30	30	20	0	10	15	10	15	10	20	45	65
		Post-ITD	**15**	**10**	10	10	15	15	5	10	10	20	40	65
5	L	Pre-ITD	30	35	25	20	30	35	5	10	10	5	30	45
		Post-ITD	**0**	**10**	**10**	10	25	**15**	5	15	15	10	30	45
13	L	Pre-ITD	30	20	15	10	10	25	15	15	10	15	10	50
		Post-ITD	**5**	10	5	5	0	**10**	5	**0**	10	15	5	**35**
33	R	Pre-ITD	25	40	50	50	55	35	25	35	45	50	20	15
		Post-ITD	10	30	**35**	40	**30**	**15**	15	30	45	55	20	15
Nonresponder group														
39	L	Pre-ITD	20	35	40	50	55	70	15	20	30	30	30	80
		Post-ITD	25	**20**	**20**	**20**	**35**	**50**	20	30	30	25	25	70
41	L	Pre-ITD	15	25	25	15	35	25	5	10	20	20	35	30
		Post-ITD	25	15	15	5	**10**	**10**	15	10	15	10	**15**	**15**
47	L	Pre-ITD	35	40	30	60	80	80	10	20	25	40	75	70
		Post-ITD	45	40	25	**45**	**65**	**50**	20	20	20	30	65	55
59	L	Pre-ITD	0	5	10	15	20	45	20	25	20	10	15	15
		Post-ITD	10	0	5	**0**	**0**	**30**	20	20	15	5	0	0
70	R	Pre-ITD	50	50	40	35	15	30	20	20	35	20	25	25
		Post-ITD	**35**	**30**	**25**	25	20	30	20	15	35	15	25	20
73	R	Pre-ITD	20	30	50	40	55	70	15	20	30	40	55	65
		Post-ITD	10	**15**	**30**	50	55	**50**	15	25	30	40	70	80
74	R	Pre-ITD	30	35	30	35	50	60	20	20	15	35	40	60
		Post-ITD	**10**	**15**	20	35	40	55	5	10	10	30	40	50

Bold type indicates a reduced hearing threshold of ≥15 dB
L: left; R: right; ITD: intratympanic dexamethasone.

Table 3. Comparison of the psychoacoustic measurements of tinnitus (loudness, pitch, and level of discomfort) in the cured and nonresponder groups

	Cured group	Nonresponder group	p
Loudness (dB sensation level)	6.0±3.5	8.4±9.3	ns
Pitch (kHz)	3.7±4.5	4.4±4.4	ns
Loudness discomfort level, 0.5 kHz	109.6±11.4	106.7±13.8	ns
Loudness discomfort level, 3 kHz	104.0±12.9	104.0±10.6	ns

ns: not significant (p>0.05).

ter treatment in either group (cured group, 17.3±11.8 vs. 17.8±13.1 dB HL, respectively, p>0.05; nonresponder group 25.7±18.0 vs. 24.4±17.1 dB HL, respectively, p>0.05) (Figure 2). An audiometric response was defined as a hearing threshold recovery of greater than or equal to 15 dB at more than two frequencies on the pure-tone audiogram. In 20 cured patients who underwent follow-up audiometry, five had an audiometric response in the injected ear (25.0%), and in 34 nonresponders who underwent follow-up audiometry, seven had an audiometric response in the injected ear (20.6%); the ratios of the audiometric responses did not differ between the two groups (p>0.05) (Table 2). The ratio of patients with normal amplitude to those with reduced amplitude in the DPOAE results was 15:29 in the cured group and 25:35 in the nonresponder group, which did not differ significantly (p=0.105) (Table 1).

Comparison of Tinnitus Characteristics, Subjective Severity, and Accompanying Symptoms

The psychoacoustic measurements of tinnitus, including the loudness, pitch, and loudness discomfort level, did not differ between the

Table 4. Comparison of the quantitative assessment of tinnitus severity determined with the initial questionnaires in the cured and nonresponder groups

	Cured group	Nonresponder group	p
Mean VAS of tinnitus loudness	4.3±1.7	4.9±1.6	ns
Mean tinnitus awareness score (%)	51.6±30.4	69.0±30.8	0.014
Mean THI score	34.2±22.7	38.8±26.0	ns

VAS: visual analogue scale; THI: tinnitus handicap inventory; ns: not significant (p>0.05).

Table 5. Multivariable logistic regression analysis of the failure of ITD in AST

Variables	OR	95% CI	p
Sex	0.286	0.058–1.411	ns
Age	1.015	0.949–1.085	ns
Duration of tinnitus	1.045	1.016–1.075	0.002
History of noise exposure	7.766	1.693–35.616	0.008
Ear fullness	0.943	0.242–3.679	ns
Vertigo	0.813	0.172–3.679	ns
Hyperacusis	2.669	0.410–17.366	ns
VAS of tinnitus loudness	0.990	0.580–1.692	ns
THI score	1.002	0.966–1.040	ns
Tinnitus awareness score	1.011	0.985-1.037	ns
BDI score	0.991	0.895-1.098	ns
Reduced DPOAE amplitude	4.580	1.282–16.366	0.019
Initial PTA (injected ear)	1.014	0.937–1.098	ns

ITD: intratympanic dexamethasone treatment; AST: acute subjective tinnitus; OR: odds ratio; CI: confidence interval; VAS: visual analogue scale; THI: tinnitus handicap inventory; BDI, Beck Depression Inventory; DPOAE, distortion product otoacoustic emissions; PTA, pure-tone average; ns, not significant (p>0.05).

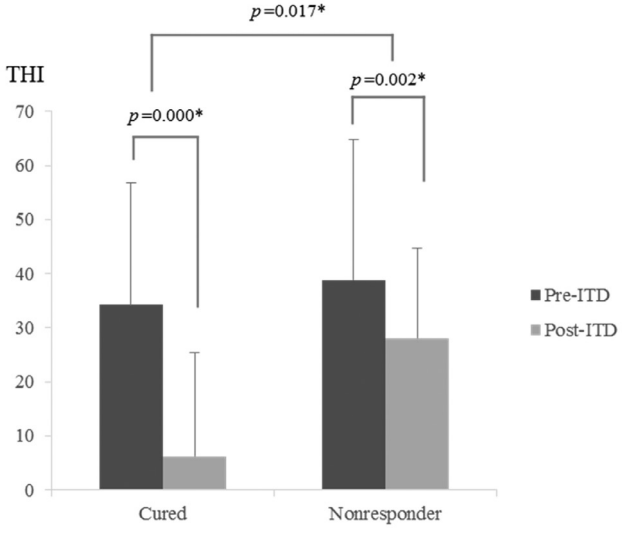

Figure 3. Mean change in the THI score from baseline to 3 months after treatment. The mean change in the THI score was greater in the cured group than in the nonresponder group (*p<0.05). THI: tinnitus handicap inventory.

cured and nonresponder groups (Table 3). The VAS of tinnitus loudness and THI score determined with the initial questionnaires did not differ between the cured and nonresponder groups, whereas the subjective period of daily tinnitus awareness determined with the initial questionnaires (tinnitus awareness score) was shorter in the cured group than in the nonresponder group (51.6±30.4% vs. 69.0±30.8%, p=0.014) (Table 4). The mean THI score in the cured group decreased significantly from 34.2±22.7 before treatment to 4.4±5.5 after treatment and that of the nonresponder group also decreased significantly from 38.8±26.0 to 26.3±16.8 (p<0.001 and p=0.002, respectively). However, the mean change in the THI score was greater in the cured group than in the nonresponder group (p=0.017) (Figure 3)

The two groups showed no differences in the accompanying symptoms, including vertigo, hyperacusis, and ear fullness (Figures 4a–c). A history of noise exposure just before the development of tinnitus was less common in the cured group than in the nonresponder group (6:38 vs. 15:40, p=0.031) (Figure 4d). Of the total 78 patients in the combined cured and nonresponder groups, the proportion with a history of noise exposure in male patients (14 of 32) was greater than the proportion in female patients (7 of 46) (p=0.005) (Figure 4e).

Multivariable Analysis of Prognostic Factors

The various factors investigated were included as independent variables in a stepwise multiple logistic regression analysis to identify the independent predictors of outcome after ITD treatment for AST. In the final model, a longer period of tinnitus (OR=1.045, 95% confidence interval [CI]=1.016–1.075, p=0.002), a history of exposure to noise just before the development of tinnitus (OR=7.766, 95% CI=1.693–35.616, p=0.008), and abnormal DPOAE (OR=4.580, 95% CI=1.282–16.366, p=0.019) were independently associated with a poor prognosis for recovery from tinnitus (Table 5).

DISCUSSION

Several previous studies using IT saline as a placebo failed to show any significant beneficial effects of IT steroid over the placebo [13–16]. However, those studies did not take into account the duration of the symptoms and included many patients with tinnitus lasting for more than a year. In a recent study [17], 54 adults reporting the onset of acute unilateral tinnitus within the preceding month were treated with either ITD injection (n=27) or IT normal saline injection (n=27), and there was no difference in the treatment effects. The main difference between that study and our previous study, which showed a therapeutic effect of ITD [10], was the protocol used for steroid injection. In the study by Lee et al. [17], 3-5 injections were administered as two injections per week, whereas our protocol involved a daily ITD injection on 4 consecutive days, on the basis of the pharmacokinetic properties reported by Parnes et al. [4], which showed that the concentration of dexamethasone in the inner ear fluid drops to zero within 1 day of injection.

From the simple comparisons of the cured group with the nonresponder group, the short-term duration of tinnitus, a low hearing threshold, female sex, a short period of tinnitus awareness, and no history of immediate noise exposure were candidates of favorable prognostic factors for ITD treatment for AST. However, in the multivariable logistic regression analysis, the duration of tinnitus and a history of exposure to noise just before the development of tinnitus

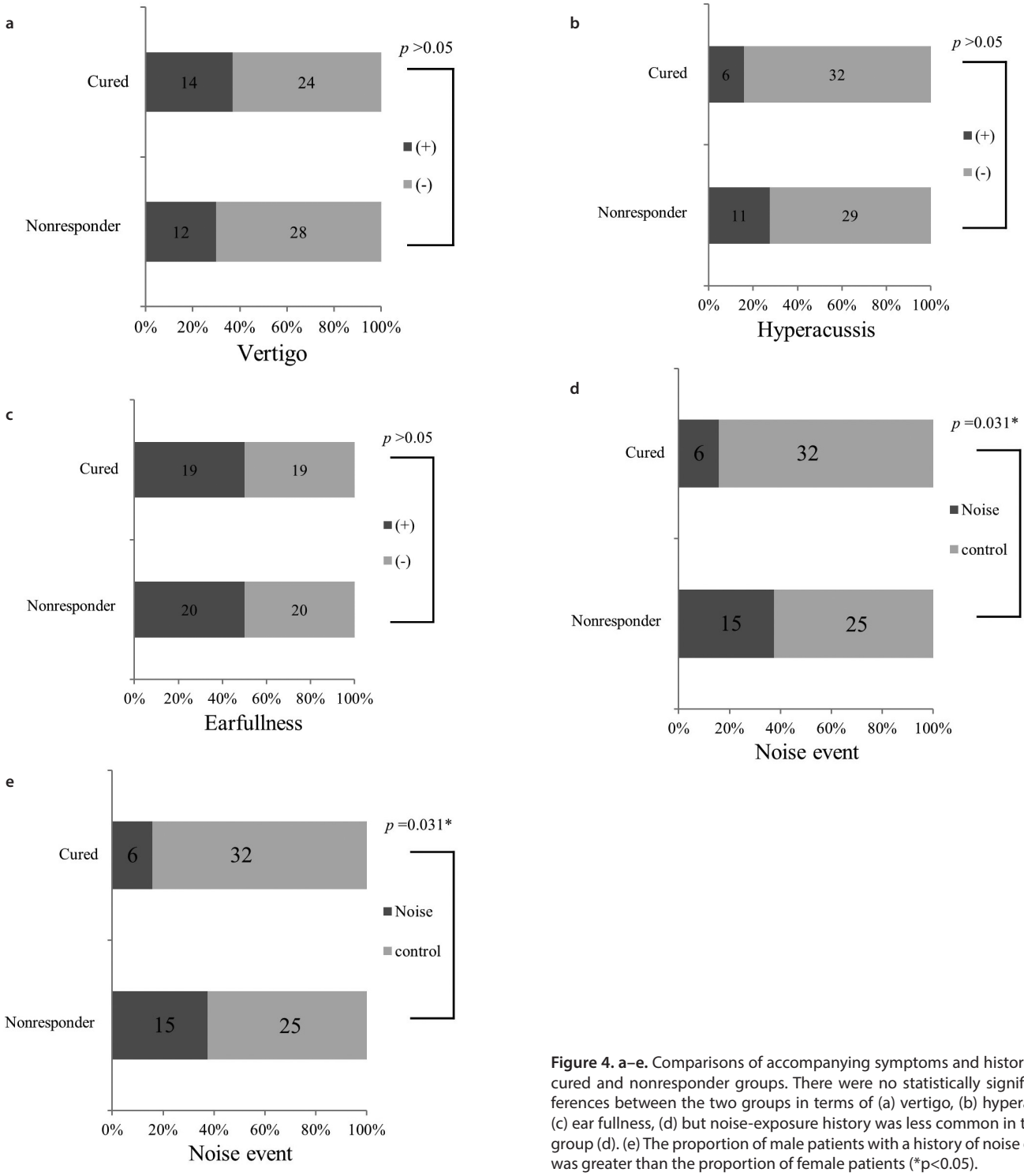

Figure 4. a–e. Comparisons of accompanying symptoms and histories in the cured and nonresponder groups. There were no statistically significant differences between the two groups in terms of (a) vertigo, (b) hyperacusis, or (c) ear fullness, (d) but noise-exposure history was less common in the cured group (d). (e) The proportion of male patients with a history of noise exposure was greater than the proportion of female patients (*p<0.05).

were meaningful factors predicting the outcome of ITD treatment for AST, and DPOAE was included as a new prognostic factor.

A lower cure rate, as the period from symptom onset to treatment increases, has also been observed in previous studies that used the same treatment protocol [10, 12]. Because the rationale of administering ITD for AST is the repair of reversible cochlear damage, it is not surprising that short symptom duration or a short time from onset to treatment are the definite and most important factors in curing acute tinnitus.

In this study, the cured group showed lower hearing thresholds on initial audiometry than the nonresponder group. However, when we controlled for the other variables with a logistic regression analysis, the initial hearing threshold was not associated with the prognosis of ITD treatment for AST. The higher mean hearing threshold in the nonresponder group on the initial audiograms (especially at high frequencies) might be attributable to their more frequent history of noise exposure. Several studies have shown a clear correlation between the tinnitus pitch and the frequency of the max-

imum hearing loss [18, 19] or the edge frequency [20, 21]. However, in some patients the tinnitus pitch does not correlate to their maximum hearing loss [22], and some patients with tinnitus have normal audiograms. Therefore, the relationship between the site or the degree of cochlear damage and the development of tinnitus remains unclear. In this respect, it is understandable that the initial hearing threshold is not a reliable predictor of the success or failure of ITD in the treatment of AST.

The audiometric response on the follow-up audiogram did not seem to be associated with the success of ITD for AST because the ratios of the audiometric responses did not differ between the cured and nonresponser groups. The majority of patients in both groups showed no change in audiometry after ITD, which is understandable, given that in many cases the tinnitus was accompanied by the patient's perception of no change in hearing, and no threshold shift was documented with audiometry. In contrast, several patients showed audiometric improvement even though there was no change in the quality of their tinnitus (i.e., nonresponders). One possible explanation of this result is that the partial recovery of the cochlear damage improved the hearing threshold, although the existing maladaptive plasticity of the central auditory pathway or nonauditory pathway still sustained the tinnitus. These results are consistent with the notion that the plasticity in the central auditory system induced by reduced input signal, rather than the cochlear damage itself, might be crucial for the development of tinnitus [23].

Subnormal DPOAE indicates obvious outer-hair-cell damage, and it can be assumed that this damage has little chance of recovery and that the likelihood that the central auditory system will adapt to the tinnitus is low. Several investigators have shown that subtle damage confined to the outer hair cells that alters otoacoustic emission can cause tinnitus even without a documented threshold shift on audiometry [24-27].

In this study, noise-induced tinnitus showed a poorer response to ITD treatment than other forms of idiopathic tinnitus. The advantage of female sex in the treatment outcome could be strongly related to the more frequent history of immediate noise exposure observed in the male patients. Males are usually considered to be more frequently exposed to noise events than females for occupational and environmental reasons. The predominance of males with a noise-exposure history may also explain why the cured group contained a higher proportion of females than the nonresponder group. In the same vein, the higher mean hearing threshold in the nonresponder group on initial audiograms (especially at high frequencies) might be attributable to greater noise exposure.

The limitations of this study included the lack of a control group to exclude any possible placebo effect and a relatively short follow-up period for outcome assessment. Randomized controlled trials of ITD injection for AST will be required in the future to clarify the prognostic factors.

CONCLUSION

In this study, a short duration of tinnitus, no history of immediate noise exposure, and normal DPOAE may be favorable prognostic factors predicting the success of ITD in the treatment of AST.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Nowon Eulji Medical Center.

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Author Contributions: Conception - H.J.S.; Design - H.J.S.; Supervision - H.J.S., Y.A.; Materials - H.J.S., Y. A.; Data Collection and/or Processing - H.S.O., E.S.L.; Analysis and/or Interpretation - H.S.O., E.S.L.; Literature Search - H.J.S., H.S.O.; Writing - H.S.O., H.J.S.; Critical Review - H.J.S.

Conflict of Interest: The authors have no conflict of interest to declare.

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