**The Role of High Dose Intratympanic Dexamethasone as Salvage Therapy for Idiopathic Sudden Sensorineural Hearing Loss**

Špela Kordiš, Saba Battelino

Department of Otorhinolaringology, University Medical Centre Ljubljana, Ljubljana, Slovenia (SK)

University of Ljubljana Faculty of Medicine, Ljubljana, Slovenia (SB)

OBJECTIVE: The aim of this study was to assess the efficacy of a single high dose intratympanic (IT) dexamethasone (DEX) as salvage therapy for idiopathic sudden sensorineural hearing loss (ISSNHL) after unsuccessful treatment with oral corticosteroid (CS).

MATERIALS and METHODS: This was a prospective open-label study of 59 patients treated with IT DEX after systemic CS therapy has failed. All patients received high dose (24 mg/mL) IT DEX in a single injection through myringotomy.

RESULTS: Of the 59 patients, 40.7% showed improvement in their mean pure tone average (PTA) with IT DEX (p=0.005). The difference in the mean PTA after oral CS treatment only from baseline was not statistically significant (p=0.074). The time from onset of hearing loss to the start of therapy was significantly associated with the outcome (p=0.03).

CONCLUSION: We determined that high dose IT DEX as salvage therapy was beneficial when the primary treatment with oral CS had failed. An early start of the treatment significantly influenced the improvement of hearing.

KEYWORDS: Intratympanic, sudden sensorineural hearing loss, high dose dexamethasone, salvage therapy

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as sudden (<72 h) hearing loss (HL) of ≥30 dB over at least three contiguous frequencies [1]. Theories for the etiology of the disease include vascular, viral or autoimmune cause, and membrane brakes [1, 2]. Merchant and colleagues [3] did not find any evidence of vascular occlusion, viral cochleitis, or membrane breaks in their temporal bone histology, suggesting a new hypothesis of pathologic activation of cellular stress pathways involving nuclear factor kappa B leading to loss of hair cells and supporting cells of the organ of Corti [3]. However, it is most likely that there is a multifactorial etiology as clinical presentation varies from patient to patient.

Despite the various etiology theories, corticosteroids (CS) remain the preferred treatment. They can be applied as systemic (oral or intravenous) or as local intratympanic (IT) therapy. The mechanism of action of CS on hearing improvement remains unclear, whether it is the anti-inflammatory action of glucocorticoid activity or mineralocorticoid effect on the inner ear ion homeostasis [4].

In the last 20 years, IT steroids have become a popular treatment regimen for sudden deafness since they do not have systemic side effects [5]. They have also been used for acute idiopathic tinnitus, acute noise-induced tinnitus [6], and Meniere's disease [7]. IT steroids for ISSNHL were first reported by Silverstein in 1996 [8]. Since then different methods of administering IT have been described: injection through a myringotomy with or without tympanic tube, microcatheter, microwick implantation, and even application through Eustachian tube [9-12]. Both dexamethasone (DEX) and methylprednisolone (MET) have been used in IT application in different concentrations and number of applications (single injection or four-time injection). Intratympanic corticosteroids have been used as the primary and only treatment, concomitant with other remedies, or as salvage treatment when primary systemic therapy has failed. The aim of our study was to determine the efficacy of high dose DEX IT therapy as a salvage therapy.
MATERIALS and METHODS
We performed a prospective open-label study of patients treated for ISSNHL at University Medical Centre Ljubljana, Department of Otorhinolaryngology from September 2012 to March 2016. Out of 98 patients with ISSNHL who received oral steroids for 2 weeks, 75 (77%) did not respond to the therapy. These 75 patients were then offered IT DEX as a salvage therapy. The efficacy of IT DEX was determined in the second follow-up 14 days later. Inclusion criteria were patients with sudden sensorineural HL of ≥30 dB over at least three contiguous frequencies. We excluded patients with acute otitis media, conductive HL, head trauma, acoustic trauma, fluctuating HL, tumor of the internal auditory canal and cerebellopontine angle, pregnant or nursing women, and patients under 18 years old. Of the 75 patients, 59 had the first and second follow-up visit in the 14-day span and were included in the study.

Hearing was evaluated as pure tone average (PTA) of 125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 6000 Hz, and 8000 Hz. We evaluated tinnitus according to pitch, frequency, and left or right side. Patients with vertigo were also examined for nystagmus and neurologic deficits.

All patients with ISSNHL were initially treated with 48 mg of MET (metilprednizolon Medrol; Pfizer SARL, Luxembourg; Grand Duchy of Luxembourg) orally for 1 week, followed by a tapered dose every 2 days. We applied IT DEX as salvage therapy to the patients who did not respond to systemic CS.

We performed a single injection of high dose (24 mg/mL) IT DEX (dexamethasone; Krka d.d., Novo mesto, Slovenia) with the patient in a supine position and the head rotated 45° to the contralateral ear. Approximately 0.5-1 mL DEX was injected through a myringotomy. Patients were instructed to remain recumbent for 30 min.

The improvement of hearing was considered as an improvement of the PTA of >10 dB.

Statistical Analysis
The mean difference in PTA was analyzed using mixed analysis of covariance (ANCOVA), where p<0.05 was considered significant. Time, sex, tinnitus, vertigo, time until first visit (baseline visit), and age were between-subject factors. The dependent variable was PTA. All statistical analyses were performed using the Statistical Package for Social Sciences version 23, (IBM Corp.; Armonk, NY, USA).

Ethical Considerations
Informed consent was obtained from all participants. The study was approved by the National Medical Ethics Committee No. 60/02/14.

RESULTS
Of the 59 patients included in the analysis, 38 (64.4%) were males and 21 (35.6%) were females. The mean age of the study group was 55.9 years (standard deviation [SD] 12.7), the youngest patient was aged 26 years and the oldest was 80 years; 53 of the 59 patients (89.9%) had accompanying tinnitus, and 35 (59.3%) had concomitant vertigo. The mean time from HL and first visit to the doctor was 10.2 days (median time, 3 days, SD, 14.7; Table 1).

Table 1. Group characteristics

| Characteristic     | (n=59) |
|--------------------|--------|
| Mean age (SD) [years] | 55.9 (12.7) |
| Sex (%)            |        |
| Male               | 38 (64.4) |
| Female             | 21 (35.6) |
| Tinnitus (%)       |        |
| No                 | 6 (10.2) |
| Yes                | 53 (89.8) |
| Vertigo (%)        |        |
| No                 | 24 (40.7) |
| Yes                | 35 (59.3) |
| Mean no. of days to the baseline visit (SD) | 10.2 (14.7)a |
| Mean no. of days to the first follow-up (SD) | 15 (1.7) |
| Mean no. of days to the second follow-up (SD) | 32.9 (5.3) |
| Mean PTA on baseline visit (SD) [dB] | 71.4 (30.9) |
| Mean PTA on first follow-up (SD) [dB] | 61.1 (26.6) |
| Mean PTA on second follow-up (SD) [dB] | 56.1 (25.8) |

A: missing data for one patient; SD: standard deviation; PTA: pure tone average; dB: decibel

Table 2. Relationship between time, possible confounders, and mean PTA (results of repeated measures ANOVA)

|          | MS       | df      | F         | p       |
|----------|----------|---------|-----------|---------|
| Time     | 281.268  | 1.256   | 1.557     | 0.220   |
| Time * Sex | 265.197  | 1.256   | 1.468     | 0.235   |
| Time * Tinnitus | 122.264  | 1.256   | .677      | 0.446   |
| Time * Vertigo | 11.752   | 1.256   | .065      | 0.853   |
| Time * Time to first visit | 803.643  | 1.256   | 4.449     | 0.030   |
| Time * Age | 5.059    | 1.256   | .028      | 0.913   |

*MS: mean square; df: degrees of freedom; F: F

The mean PTA on the first visit was 71.4 dB. We distributed patients according to the severity of HL on admission and at the end of treatment in five groups: normal (≤20 dB), mild HL (21-40 dB), moderate HL (41–70 dB), severe HL (71-90 dB), and profound HL (>90 dB). On admission, 10 patients (16.9%) had mild HL, 22 (37.3%) had moderate HL, 8 (13.6%) had severe deterioration of hearing, and 19 (32.2%) had profound HL (Figure 1).

The first follow-up averaged 15 days (SD, 1.7), and the second follow-up averaged 32.9 days (SD, 5.3) after the initial visit. After oral CS, the hearing threshold improved on an average by 10.3 dB, which was considered a clinically poor result; 24 of 59 patients (40.7%) improved their hearing by >10 dB and 18 (30.5%) by >20 dB after IT DEX. We observed a 15.3 dB improvement after IT DEX treatment from the initial visit (mean PTA, 56.1 dB). The distribution of patients regarding their hearing threshold after IT DEX was as follows: 19 patients (32.2%) had mild HL, 26 (44.1%) had moderate HL, 7 (11.9%) experienced severe HL, and 7 had (11.9%) profound HL (Figure 1).

Hearing loss occurred primarily at high frequencies at 8000 Hz (average threshold at 8000 Hz=86.4 dB) and lowest at 125 Hz (average...
A delayed start of the treatment and age was considered when studying the PTA improvement (ANCOVA). The difference in mean PTA after systemic MET treatment from baseline was not statistically significant (p=0.074). The difference after receiving IT DEX treatment from baseline was statistically significant (p=0.005). Analyses of the time of treatment start and patients’ age and mean PTA after DEX treatment on an average decreased from baseline by 13.6 dB (95% confidence interval [CI]: 3.4-23.7. The difference in mean PTA was also statistically significant between the first and second follow-up (p=0.01). On an average, PTA after treatment with MET and introducing treatment with DEX decreased further by 5.1 dB (95% CI: 1-9.3; Figure 2). Mixed ANCOVA showed that interaction between the time (hearing threshold through time) and time to first clinic visit from HL was statistically and significantly associated with mean PTA (p=0.03; Table 2). After loss of hearing, patients who waited a longer time to start treatment had worse prognosis than those who started early. Interactions between time and sex, tinnitus, and vertigo were not statistically and significantly associated with mean PTA. The mean differences in PTA between visits with 95% CI adjusted for multiple comparisons and controlled for possible confounders are shown in Figure 2.

**DISCUSSION**

Oral CS is the preferred treatment for ISSNHL. Efficacy has been reported by Wilson [1] as 61% recovery in the systemic steroid-treated groups over 32% in the placebo group. However, cases of spontaneous recovery with no therapy have been reported as high as 65% [2]. Clinical practice guidelines from the American Academy of Otorhinolaryngology-Head and Neck Surgery (AAO-HNS) advise clinicians using systemic CS as primary and IT CS as salvage treatment for ISSNHL [13].

The two most common CS in IT treatment are DEX and MET. Parnes [14] and Chandrasekhar [15] showed that IT administration of steroids results in higher penetration to the inner ear fluids than does systemic steroids. The highest concentration and longest duration in the endolymph and perilymph was noticed after IT administration of MET compared to DEX and hydrocortisone, but resulted in increased pain and burning sensation in the ear and the throat [14]. A meta-analysis of Ng et al. [16] showed better outcomes using DEX compared to MET. The concentration used in treatment is often associated with availability and approval of each country or medical center and ranged from 4 mg/mL to 24 mg/mL for DEX. A higher concentration was found to be more effective [17]. The number of applications from single injection to four injections over several days has been reported. The diversity of CS use, concentration, and the number of applications contribute to the difficult comparison of CS treatments [18]. Studies use various measurements of hearing and criteria of improvement that add to the controversy of best practice [18]. A larger randomized controlled trial investigating the efficacy of the IT DEX would be more appropriate; however, as the Slovene National ENT Association Assembly recommended IT DEX as a standard therapy, we were not able to perform it [13].

In our study, we chose to evaluate the efficacy of a single application of the maximal concentration of IT DEX as salvage treatment after failure of systemic CS. The time of onset of HL to baseline visit and age was considered when analyzing PTA improvement. Speech discrimination score (SDS) defines hearing better than does pure tone audiometry. At the time of our study, we were still developing a new Slovene national speech discrimination test and could not apply it in this study. We found that the difference in PTA after systemic treatment was not statistically significant (p=0.074). The difference in PTA after receiving IT DEX was statistically significant (p=0.005) from baseline.

Several others studies have supported IT DEX as salvage therapy, while other lack sufficient evidence of success [9, 12, 17, 19, 20-23]. Among the factors that could influence hearing outcome, time from onset of HL to the baseline visit was found to be statistically significant (p=0.030). Our study confirms other reports that delaying treatment has negative influence on hearing improvement [5, 17]. Other factors, such as age, presence of tinnitus or vertigo, did not impact the hearing threshold in our study.

Higher frequencies were found to be most severely affected and had the lowest PTA improvement. In contrast, lower frequencies were least impaired and had the greatest response in pure tone average.
which is in accordance to some studies in the literature [2, 21, 24]. Based on the known basal-apical concentration gradient of DEX through the round window [25], we would expect that higher frequencies would recover better than lower frequencies. Sha et al. [26] reported that basal outer hair cells are more vulnerable to free radicals than are apical hair cells and that in the apical turn, hair cells may recover better due to higher antioxidant concentration. The limitation of our study is the relatively small number of included patients and no control group.

CONCLUSION
A 40.7% improvement and an average of 13.6 dB recovery of PTA demonstrated in the present study is clinically significant for the patient. There was a 20% reduction in the number of patients with profound hearing loss after therapy. At the end of the treatment, majority of the patients had mild to moderate residual HL. Based on the results of our study, we conclude that high dose IT DEX is efficient as salvage treatment of ISSNHL and therefore worth considering if the primary therapy has failed. Patients waiting longer time from onset of HL until visiting the doctor have worse prognosis. Age and presence of tinnitus and vertigo did not have a prognostic impact on hearing outcome.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the National Medical Ethics Committee No. 60/02/14.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.B.; Design - S.B., Š.K.; Supervision - S.B.; Resources - S.B., Š.K.; Materials - S.B., Š.K.; Data Collection and/or Processing - Š.K.; Analysis and/or Interpretation - S.B., Š.K.; Literature Search - S.B., Š.K.; Writing Manuscript - S.B., Š.K. Critical Review - S.B., Š.K

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES
1. Wilson WR, Byal FM, Laird N. The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study. Arch Otolaryngol 1980; 106: 772-6. [CrossRef]
2. Mattox DE, Simmons FB. Natural history of sudden sensorineural hearing loss. Ann Otol Rhinol Laryngol 1977; 86: 463-80. [CrossRef]
3. Merchant SN, Adams JC, Nadol JB Jr. Pathology and pathophysiology of idiopathic sudden sensorineural hearing loss. Otol Neurotol 2005; 26: 151-60. [CrossRef]
4. Trune DR, Canlon B. Corticosteroid therapy for hearing and balance disorders. Anat Rec 2012; 295: 1928-43. [CrossRef]
5. Novoa E, Gartner M, Henzen C. Systemic effects of intratympanic dexamethasone therapy. Endocrin Connect 2014; 3: 127-31. [CrossRef]
6. Shim HJ, Lee ES, An YH, Kim DH. Comparison of Long-Term Outcome of Intratympanic Dexamethasone Therapy between Acute Noise-Induced Tinnitus and Acute Idiopathic Tinnitus. J Int Adv Otol 2017; 13: 53-60. [CrossRef]
7. Attrache Al Âtratche N, Krstulovic C, Pérez Guillen V, Moreira Pérez C, Pérez Garrigues H. Response Over Time of Vertigo Spells to Intratympanic Dexamethasone Treatment in Meniere’s Disease Patients. J Int Adv Otol 2016; 12: 92-7. [CrossRef]
8. Silverstein H, Choo D, Rosenberg SI, Kuhn J, Seidman M, Stein I. Intratympanic steroid treatment of inner ear disease and tinnitus (preliminary report). Ear Nose Throat J 1996; 75: 468-71.
9. Lee HS, Kim JM, Kim YJ, Chung DH, Seo BS, Kim SH. Results of intratympanic dexamethasone injection as salvage treatment in idiopathic sudden hearing loss. Otolaryngol Head Neck Surg 2008; 37: 263-8.
10. Gianoli GJ, Li JC. Trans tympanic steroids for treatment of sudden hearing loss. Otolaryngol Head Neck Surg 2001; 125: 142-6. [CrossRef]
11. Herr BD, Marzo SJ. Intratympanic steroid perfusion for refractory sensorineural hearing loss. Otolaryngol Head Neck Surg 2005; 132: 527-31. [CrossRef]
12. Zhang Q, Song H, Peng H, Yang X, Zhou J, Huang W. Noninvasive intratympanic dexamethasone treatment for sudden sensorineural hearing loss. Acta OtoLaryngologica 2012; 132: 583-9. [CrossRef]
13. Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM, et al. Clinical practice guideline: sudden hearing loss. Otolaryngol Head Neck Surg 2012; 146: S1-35. [CrossRef]
14. Barnes LS, Sun AH, Freeman DJ. Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. Laryngoscope 1999; 109: 1-17. [CrossRef]
15. Chandrasekhar SS. Intratympanic dexamethasone for sudden sensorineural hearing loss: clinical and laboratory evaluation. Otol Neurotol 2001; 22: 18-23. [CrossRef]
16. Ng JH, Ho RC, Cheong CS, Ng A, Yuen HW, Ngo RY. Intratympanic steroids as a salvage treatment for sudden sensorineural hearing loss? A meta-analysis. Eur Arch Otorhinolaryngol 2015; 272: 2777-82. [CrossRef]
17. Alexander TH, Harris JP, Nguyen QT, Vorasubin N. Dose effect of intratympanic dexamethasone for idiopathic sudden sensorineural hearing loss: 24 mg/ml is superior to 10 mg/ml. Otol Neurotol 2015; 36: 1321-7. [CrossRef]
18. Plontke SK, Bauer M and Meisner C. Comparison of pure-tone audiometry analysis in sudden hearing loss studies: lack of agreement for different outcome measures. Otol Neurotol 2007; 28: 753-63. [CrossRef]
19. Choung YH, Park K, Shin YR, Cho MJ. Intratympanic dexamethasone injection for refractory sudden sensorineural hearing loss. Laryngoscope 2006; 116: 747-52. [CrossRef]
20. Xenellis J, Papadimitriou N, Nikolopoulous T, Maragoudakis P, Segas J, Tzagarakoulakis A, et al. Intratympanic steroid treatment in idiopathic sudden sensorineural hearing loss: a control study. Otolaryngol Head Neck Surg 2006; 134: 940-5. [CrossRef]
21. Lee JB, Choi SJ, Park K, Park HY, Choo OS, Choung YH. The efficiency of intratympanic dexamethasone injection as a sequential treatment after initial systemic steroid therapy for sudden sensorineural hearing loss. Eur Arch Otorhinolaryngol 2011; 268: 833-9. [CrossRef]
22. Günel C, Başal Y, Toka A, Eryilmaz A, Kurt Ömürli U. Efficacy of low-dose intratympanic dexamethasone for sudden hearing loss. Auris Nasus Larynx 2015; 42: 284-7. [CrossRef]
23. Plontke SK, Löwenheim H, Mertens J, Engel C, Meisner C, Weidner A, 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 hearing loss after failure of systemic therapy. Laryngoscope 2009; 119: 359-69. [CrossRef]
24. Ahn JH, Han MW, Kim JH, Chung JW, Yoon TH. Therapeutic effectiveness over time of intratympanic dexamethasone as salvage treatment of sudden deafness. Acta OtoLaryngol 2008; 128: 128-31. [CrossRef]
25. Plontke SK, Bieger T, Kammerer B, Delabar U, Salt AN. Dexamethasone concentration gradients along scala tympani after application to the round window membrane. Otol Neurotol 2008; 29: 401-6. [CrossRef]
26. Sha SH, Taylor R, Forge A, Schacht J. Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals. Hear Res 2001; 155: 1-8. [CrossRef]