The Outcome of Prompt Concomitant Single-Dose High-Concentration Intratympanic and Tapered Low-Dose Oral Systemic Corticosteroid Treatment for Sudden Deafness

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OBJECTIVES: To investigate the efficacy of prompt concomitant corticosteroid treatment with single application of high-concentration intratympanic (IT) dexamethasone and tapered low-dose systemic methylprednisolone of an idiopathic sudden sensorineural hearing loss (ISSNHL).

MATERIALS and METHODS: Between September 2017 and September 2019, 86 adult patients met the criteria for the diagnosis of ISSNHL at baseline evaluation. The patients received immediate concomitant treatment with single high-concentration (24 mg/mL) IT dexamethasone and low-dose (48 mg) oral methylprednisolone for 1 week followed by tapered doses. Improvement in pure-tone average (PTA) and word recognition score (WRS) was determined after 1 and 6 months.

RESULTS: A total of 63 patients met the requirements for the analysis. PTA improved in 71% and WRS improved in 59% of patients with ISSNHL. PTA and WRS were statistically significantly different at different time points during the intervention (p<0.0005). Hearing improved in all measured frequencies from 125 to 8000 Hz until the second follow-up. In 65.4% of patients with tinnitus, the WRS has improved compared with 27.3% without tinnitus (p<0.05). In 69.2% of patients without vertigo, the WRS has improved compared with 41.7% with vertigo (p<0.05).

CONCLUSION: Prompt concomitant single high-concentration IT and low-dose systemic corticosteroid treatment is efficient in recovering hearing loss and speech discrimination in ISSNHL. Tinnitus positively predicts hearing outcome. Vertigo negatively predicts speech discrimination recovery.

KEYWORDS: Audiometry, speech, dexamethasone, tinnitus, vertigo, sudden deafness

INTRODUCTION
Corticosteroids (CSs) are the main treatment option for an idiopathic sudden sensorineural hearing loss (ISSNHL). Although their use has been widely investigated for the treatment of ISSNHL, there is no definite conclusion on their efficacy. Compared with systemic CSs, intratympanic (IT) CSs offer several advantages, such as delivering a higher concentration of CSs to the inner ear fluids and causing less adverse effects. According to the American Academy of Otorhinolaryngology-Head and Neck Surgery (AAO-HNS) guidelines, an IT CS should be offered to a patient whose hearing fails to recover after initial systemic CS treatment [1]. The AAO-HNS guidelines [1] and other studies [2] recommend low-dose systemic CS treatment (i.e., methylprednisolone 48 mg/d), whereas the German guidelines recommend high-dose treatment (i.e., methylprednisolone 200 mg/d) [3]. Low-dose systemic CS treatment can be considered as superior due to the less frequent side effects [4].

Because the treatment delay negatively affects the hearing outcome [5-7], we aimed to determine the efficacy of prompt concomitant single high-concentration IT and low-dose systemic CS treatment for ISSNHL in a prospective clinical study.
MATERIALS AND METHODS

Patients
The study approved by the Republic of Slovenia National Medical Ethics Committee (No. 0120-475/2017-4) was performed at our tertiary referral center from September 2017 to September 2019. The procedures followed in the study were in accordance with the ethical standards of the Republic of Slovenia National Medical Ethics Committee on human experimentation and with the Helsinki declaration. Written informed consent was obtained from the patients following a detailed explanation of the procedures.

We prospectively recruited adult patients with ISSNHL for the treatment according to our protocol. ISSNHL was defined as ≥30 dB hearing loss (HL) over ≥3 contiguous frequencies that developed in ≤3 days without other identifiable causes of sudden HL (e.g., Meniere’s disease and fluctuating HL). Patients with diabetes, history of peptic ulcer, immune dysfunction, and thyroid gland abnormalities were excluded from the study. The presence of these conditions was screened at each subsequent follow-up because some causes of sudden HL become identifiable later, during the diagnostic work-up, e.g., magnetic resonance imaging (MRI) for vestibular schwannoma.

Audiometry and vestibular function tests
Standardized tympanometry, pure-tone audiometry, and word recognition score (WRS) test were performed to assess hearing at admission, 1 month (i.e., first follow-up), and 6 months (i.e., second follow-up) after the start of the treatment.

Because HL can occur at different frequencies, assessing only the speech frequencies from 500 to 4000 Hz could cause bias. Therefore, a wide range of frequencies (125, 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz) was used to calculate the pure-tone average (PTA) up to 120 dB. The patients were classified in five grades according to the severity of HL: normal (≤25 dB), mild (26-40 dB), moderate (41-60 dB), severe (61-80 dB), and profound (>80 dB) Hls. WRS test was carried out in silence with the nonaffected and non-afflicted ear masked. We used the Freiburg monosyllabic word test, adapted for Slovenian language [4]. Improvement of PTA >10 dB or improvement of WRS >15% was considered as clinically significant improvement. The intensity, frequency, and laterality of tinnitus were evaluated. The patients were asked if they had vertigo. The vestibular function was assessed with a bithermal caloric test (Variotherm plus, Atmos Medizintechnik, Lenzkirch, Germany) or video head-impulse test (EyeSeeCam vHIT 1.2.0 and Otoaccess 1.4.0, Interacoustics, Middelfart, Denmark).

Treatment Protocol
All patients received a single high-dose IT dexamethasone (DEX) and low-dose systemic methylprednisolone immediately after admission. Approximately 0.5-1 mL of filtered IT DEX (dexamethasone sodium phosphate; 24 mg/mL; Krka d.d., Novo mesto, Slovenia), previously warmed in a bottle to body temperature, was given as a single injection through a myringotomy under topical anesthesia. A 5-cm-long sterile cotton wick prepared from 1 cm x 10 m tamponade gauze (ref: 9190, Tosama d.o.o., Domžale, Slovenia) was inserted in the outer ear canal for 1-2 days. The patients were instructed to protect the ear against water and to avoid significant pressure changes (e.g., forceful nose blowing). They had to stay recumbent for 30 min after the IT CS application with the affected ear turned upward.

Methylprednisolone (Medrol; Pfizer SARL, Luxembourg; Grand Duchy of Luxembourg) was administered orally at a dose of 48 mg daily for 1 week, followed by a taper of 32, 16, and 8 mg each for 2 days. To prevent gastric upset, a proton pump inhibitor was administered orally at a dose of 40 mg daily while administering methylprednisolone.

Adverse Effects
At the beginning of the treatment and at each follow-up, adverse events were looked for. Adverse events attributed to IT CS treatment could be persistent tympanic membrane perforation following myringotomy, vertigo, dizziness or nausea after IT CS application, signs or symptoms of middle ear infection, more severe HL, tinnitus reported within 24 hours of IT CS treatment, and disturbed sense of taste. Momentary vertigo and dizziness or nausea during the injection were not considered as adverse effects. Because patients were covered sterile over the head, we could not observe nystagmus.

Adverse events attributed to our systemic CS treatment protocol could be sleeplessness, mood swings, psychotic reactions, anxiety, a sense of well-being, a sense of fullness, weight gain, gastric upset, blood pressure elevation, ocular hypertension, glaucoma, and blood glucose elevation [10].

Statistical Analysis
Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23, (IBM Corp., Armonk, NY, USA) and Microsoft Excel for Mac (version 16 and later, Microsoft corporation, Redmond, Washington). Specific statistical tests were used depending on the group characteristics as shown in Table 1. p<0.05 was considered as statistically significant.

RESULTS
At baseline evaluation, 86 adult patients met the criteria for the diagnosis of ISSNHL. During follow-up, 23 patients were excluded from the study because of lack of data for the analysis (13 patients did not perform all the tests and 6 missed the follow-up), vestibular schwannoma diagnosed with MRI (2 patients), and additional hyperbaric oxygen treatment administration (2 patients). Patients who had other identifiable causes of HL (e.g., enlarged vestibular aqueduct) were excluded. Thus, the final analysis included 63 patients.
Relationships of baseline demographic and clinical characteristics with an improvement in PTA and WRS are shown in Table 1.

HL grade according to PTA at admission and at the first (Avg=33, SD=7 days) and second follow-ups (Avg=183, SD=30 days) is depicted in Figure 1. PTA improved in 71% of patients after 6 months. By that time, in 37% of patients, hearing regained to the normal level, in 11% of patients, hearing improved to mild HL, in 29% of patients, hearing improved to moderate HL, and in 14% patients, HL was severe. Furthermore, 9% of patients remained deaf. After the treatment, hearing improved in all patients with mild HL, in 63% of patients with moderate HL, in 79% of patients with severe HL, and in 58% of patients with profound HL at admission. However, a Cochran-Armitage test of trend did not show a linear trend between the HL grade at admission and PTA improvement (p=0.235).

A Friedman test was performed to determine the differences in PTA and WRS at admission, first follow-up, and second follow-up because of nonnormal distributions of data. To perform pairwise comparisons, a Bonferroni correction for multiple comparisons was applied.

PTA was statistically significantly different between admission, first follow-up, and second follow-up, $\chi^2(2)=53.696$, $p<0.0005$ (Figure 2).

### Table 1. Descriptive statistics and relationships of demographical and clinical characteristics.

| Outcome                      | Descriptive statistics | Improvement | No improvement | Improvement | No improvement |
|------------------------------|------------------------|-------------|----------------|-------------|----------------|
| Age (years)                  | 54.79 (15.633)         | 53.31 (16.923) | 58.50 (11.388) | 55.08 (2.539) | 54.38 (3.176) |
| Gender                       |                        |             |                |             |                |
| Male                         | 35 (55.6)              | 27 (77.1)   | 8 (22.9)       | 20 (57.1)   | 15 (42.9)      |
| Female                       | 28 (44.4)              | 18 (64.3)   | 10 (35.7)      | 17 (60.7)   | 11 (39.3)      |
| Tinnitus                     |                        |             |                |             |                |
| Yes                          | 49 (77.8)              | 35 (71.4)   | 14 (28.6)      | 34 (65.4)   | 18 (34.6)      |
| No                           | 14 (22.2)              | 10 (71.4)   | 4 (28.6)       | 3 (27.3)    | 8 (72.7)       |
| Vertigo                      |                        |             |                |             |                |
| Yes                          | 24 (38.1)              | 14 (58.3)   | 10 (41.7)      | 10 (41.7)   | 14 (58.3)      |
| No                           | 39 (61.9)              | 31 (79.5)   | 8 (20.5)       | 27 (69.2)   | 12 (30.8)      |
| Caloric test and/or vHIT     |                        |             |                |             |                |
| Normal                       | 54 (85.7)              | 41 (75.9)   | 13 (24.1)      | 31 (57.4)   | 23 (42.6)      |
| Pathological                 | 9 (14.3)               | 4 (44.4)    | 5 (55.6)       | 6 (66.7)    | 3 (33.3)       |
| Time to th (days)            | 4 (2-7)                | 0.510 $^c$, $r_s = -0.085$ | 0.976 $^c$, $r_s = -0.04$ |               |                |

PTA: pure-tone average; WRS: word recognition score; +: improvement; -: no improvement; vHIT: video head-impulse test; th: therapy; p: p-value; $\tau$: Kendall’s tau-b; $r_p$: point-biserial correlation coefficient; $r_s$: Spearman rank-order correlation coefficient; $\Delta%$: difference in proportions; $^a$: data are given as mean (SD) for continuous variables with normal distribution; $^b$: data are given as number (percentage) for categorical variables; $^c$: data are given as median (Q1-Q3) for continuous variables without normal distribution; $^*: $ Kendall’s tau-b; $^%*: $ Point-biserial correlation; $^&*: $ Chi-square test of homogeneity; $^!: $ Fisher’s exact test; $^\circ$: Spearman’s rank-order correlation. Shapiro-Wilk test was initially used to determine group distributions. $p<0.05$ was considered as statistically significant.
2). A post hoc analysis revealed statistically significant differences between PTA at admission (Mdn=60 dB) and PTA at first follow-up (Mdn=44 dB) (p<0.0005) and between PTA at admission and PTA at the second follow-up (Mdn=43 dB) (p<0.0005). There was no statistically significant difference between PTA at the first and PTA at the second follow-up (p=1.000).

WRS improved in 59% of patients after 6 months. In 50% of patients with mild HL, in 58% with moderate HL, in 74% with severe HL, and in 42% with profound HL at admission, hearing improved after 6 months. WRS was statistically significantly different between admission, first follow-up, and second follow-up, \( \chi^2(2)=80.983, p<0.0005 \) (Figure 3). A post hoc analysis revealed statistically significant differences between WRS at admission (Mdn=38%) and WRS at the first follow-up (Mdn=80%) (p<0.0005) and between WRS at admission and WRS at the second follow-up (Mdn=80%) (p<0.0005) but not between the follow-ups (p=1.000).

Figures 4 and 5 represent WRS and PTA at admission and follow-ups in accordance with the AAO-HNS guidelines [9]. Figure 5 shows data plotted up to 100 dB, therefore, seven patients are not presented because of a higher PTA.

Hearing improved in all frequencies according to differences in median pure-tone hearing thresholds. The hearing threshold at admission
Age did not consider hearing is improved when PTA improves for Assessment of hearing improvement differs in the literature. Some Alexander therapy be more effective than systemic CSs combined with hyperbaric oxygen concern, our study was not placebo controlled similar to few other stud enforcement concerning our study was that the PTA improvement rate increased to 71% and WRS to 59% of patients after 6 months, the difference between the follow-ups was not statistically significant. In 37% of patients, the hearing level regained to normal, and in 11% of patients, hearing improved to the mild HL grade. Furthermore, 9% of patients remained deaf. Patients with serviceable hearing levels (43%), i.e., moderate (29%) and severe HLs (14%) were offered a hearing aid. However, there was no linear trend between the HL grade and PTA improvement. Patients with mild HL recovered better and those with profound HL recovered worse, which is consistent with the results of other studies.

Our study confirms that the hearing thresholds at low frequencies improved better than at high frequencies. Age did not have a statistically significant influence on the hearing outcome, which is consistent with the results of other studies.

Patients with associated tinnitus had a better prognosis for improvement of WRS but not PTA. This is because word recognition is impaired by tinnitus in addition to HL. When tinnitus subsides, WRS improves although PTA does not improve. Therefore, tinnitus, especially of short duration, is considered a good prognostic sign, as already described.

Vertigo was associated with statistically significantly worse hearing improvement compared with patients without vertigo, which is consistent with the results of other studies. Therefore, vertigo is considered a poor prognostic sign.

According to published studies, statistically significant better hearing improvement is achieved if IT CS treatment is prompt. Our results show that patients in our study received treatment earlier than the time to therapy reported by Alexander et al. (Avg=9.2 days, SE=1.3) and Battaglia et al. (Avg=7.2 days, SD=7.6 days). The majority (75%) of our patients received treatment within 7 days. For that reason, we did not detect a statistically significant high correlation between the time to therapy and PTA or WRS improvement.

Although our study lacked a control group, a randomized placebo-controlled clinical study by Filipo et al. confirmed the efficacy of IT CS treatment for sudden HL. Because of possible ethical concerns, our study was not placebo controlled similar to few other studies.

CONCLUSION
Prompt concomitant single high-concentration IT and low-dose systemic CSs are efficient for the treatment of ISSNHL, especially in

![Figure 6. Median pure-tone hearing thresholds with 95% confidence intervals (i.e., error bars) due to nonnormal distributions at admission and at first and second follow-ups.](image)
patients with associated tinnitus or absent vertigo. More than one-third of the patients recovered their normal hearing. Our treatment regimen yielded hearing improvement without adverse side effects.

Ethics Committee Approval: The study was approved by the Republic of Slovenia National Medical Ethics Committee (No. 0120-475/2017-4). The procedures followed in this study were in accordance with the ethical standards of the Republic of Slovenia National Medical Ethics Committee on human experimentation and with the Helsinki Declaration.

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

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