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OTOLOGY

Systemic, intratympanic and combined administration of steroids for sudden hearing loss. A prospective randomized multicenter trial

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Abstract

Purpose The purpose of this prospective, randomized, multicenter clinical trial was to compare the therapeutic efficacy of systemic versus intratympanic versus combined administration of steroids in the treatment of idiopathic sudden sensorineural hearing loss.

Methods 102 patients with an up to 14 days history of idiopathic sudden sensorineural hearing loss were randomized to 1 of 3 arms and followed prospectively. Group A (35 patients) received prednisolone intravenously followed by methylprednisolone orally, whereas Group B (34 patients) were administered intratympanic methylprednisolone. Patients in Group C (33 patients) were administered the combination of the above-mentioned treatment modalities. The patients were followed-up with pure tone audiograms on days 1 (initiation of treatment), 3, 5, 10, 30 and 90.

Results The final mean hearing gain was 29.0 dB HL for Group A, 27.0 dB HL for Group B and 29.8 dB HL for Group C. The differences between the three groups were not statistically significant. When hearing improvement was assessed according to Siegel's criteria, no statistically significant difference was recorded either. Furthermore, patients younger than 60 years old achieved significantly better hearing outcomes.

Conclusions The results demonstrated that systemic, intratympanic and combined steroid administration have similar results in the primary treatment of idiopathic sudden hearing loss. Younger patients are more likely to achieve better hearing outcomes.

Keywords Sudden sensorineural hearing loss · Steroids · Intratympanic injection · Systemic · Combination · Audiogram

Introduction

Sudden sensorineural hearing loss (SSHL) was first reported in 1944 by De Kleyn [1]. It presents as rapid, most commonly unilateral hearing loss that is often accompanied by tinnitus, vertigo and aural fullness. Although SSHL has been the topic of many studies, it has not been feasible to reach a consensus on its definition up to now. The most widely used definition is the one that is proposed by the US National Institute on Deafness and Other Communication Disorders (NIDCD). According to this, SSHL is defined as greater than 30 dB HL of hearing loss in at least three consecutive audiometric frequencies occurring within 3 days or less [2]. It is an uncommon otologic condition and has a reported incidence of 5–20 per 100,000 population per year [3]. Despite extensive research, controversy remains in regards to the etiology of SSHL. The prevalent theories in literature include viral infection, vascular compromise, intralabyrinthine

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membrane rapture and immunologic disease. Nevertheless in 88% of cases no identifiable cause for hearing loss is found and these are, therefore, classified as 'Idiopathic Sudden Sensorineural Hearing Loss' (ISSHL) [4]. Although the treatment of these patients varies among otologic centers, administration of steroids orally or intravenously has been considered to be the treatment of choice for many years [5, 6]. Nevertheless, contraindications too, as well as potential side effects of systemic steroids, have motivated research for alternative ways of steroid administration directly into the cochlea. In 1996, Silverstein et al. introduced intratympanic steroid perfusion in the treatment of ISSHL [7]. Since then, several studies of this treatment modality appeared in the literature [8] whereas recently the combination of intratympanic and systemic steroids has gained interest among clinicians [9]. However, the diversity of the conclusions as well as the limited number of prospective randomized controlled studies, highlights the need for further research in this field. The objective of this study was to compare the therapeutic efficacy of systemic, intratympanic and combined administration of steroids in the primary treatment of ISSHL.

Materials and methods

Study design and patients

This study was conducted between September 2013 and September 2016 at the 1st Department of Otorhinolaryngology of Aristotle University of Thessaloniki and at the Department of Otorhinolaryngology of Konstantopouleio Hospital of Nea Ionia Athens. Eligible subjects were adults aged 18 years or older both male and female with minimum 30 dB HL hearing loss in three consecutive octaves that had occurred within a course of 3 days. The hearing thresholds were calculated at 500, 1000, 2000 and 4000 Hz. Since according to Goodman's criteria a threshold of up to 25 dB HL is normal, the hearing thresholds of the affected frequencies must have been 55 dB HL or higher. Moreover, the affected ear must have been at least 30 dB HL worse than the contralateral ear in at least 1 of the affected frequencies. To the best of the participant's knowledge, hearing must have been symmetric prior to onset of sensorineural hearing loss. Exclusion criteria for the study included any recognized cause of SSHL such as Meniere's disease, any previous treatment for the specific episode of ISSHL, interval of more than 14 days from the onset of the disease to initiation of the treatment and any contraindication to the use of systemic steroids, such as uncontrolled diabetes mellitus or hypertension. All patients underwent medical history, physical and laboratory examinations as well as audiologic evaluations that included tympanometry and pure tone audiometry before initiation of treatment. A GSI 33 middle ear analyzer was used in both centers to perform the tympanometric tests. Tympanograms were evaluated according to Jerger's classification [10] as modified by Stollman [11]. Only patients with a type A tympanogram were included in the study. Patients with conductive or mixed hearing loss were excluded per se. 30 days after the initiation of treatment, every patient underwent MRI scan of the internal acoustic canal to rule out acoustic neuroma or other retrocochlear lesions. In case such a lesion was identified, the patient was automatically excluded from the study.

Measurement of auditory function

Auditory function was determined by pure tone audiometry and pure tone averages (PTAs) were measured by taking the 4-frequency average of the threshold value at 500, 1000, 2000 and 4000 Hz. Thresholds that were not measurable because of the limit of the audiometric equipment were coded with the maximum level of the audiometer that was set at 120 dB HL. Audiograms in both centers were performed in soundproofed chambers with audiometers Interacoustics AC5 and headphones Telephonics TDH–50. Air and bone conduction threshold audiometry as well as masking were performed according to the guidelines of the British Society of Audiology [12]. Auditory measurements were performed before initiation of treatment as well as 3, 5, 10, 30 and 90 days after initiation of treatment. In the groups where intratympanic injections were involved, audiograms were performed before each injection. The primary end point of the study was the final mean hearing gain, which was defined as the difference between initial and final PTA at day 90. Secondary outcome measures included final hearing improvement as evaluated at day 90 using Siegel's criteria and prognostic value of age, time to onset of treatment and severity of initial hearing loss. The prognostic value of the above-mentioned parameters was assessed in regards to final mean hearing gain at day 90. According to Siegel's criteria, "complete recovery" was defined as final hearing better than 25 dB HL, "partial recovery" as more than 15 dB HL hearing gain and final hearing between 25 and 45 dB HL, "slight improvement" as more than 15 dB HL gain and final hearing poorer than 45 dB HL, and "no improvement" as less than 15 dB HL gain.

Treatment protocol

After screening for eligibility, patients consenting to enroll were randomized to 1 of 3 groups. Randomization was accomplished by generating sequential random numbers (sequential randomization) using a computer-based software. The random numbers were placed in closed envelopes and were given sequentially to every patient that was recruited. Treating physicians and patients were aware of the allocated

arm. The physicians that performed the audiologic assessment and data analysis were kept blinded to the allocation. The matching of the random numbers to the type of treatment was revealed to them after completion of the statistical analysis. Subjects were administered treatment as follows:

Group A (systemic steroids)

The patients that were recruited in this group were hospitalized and treated with intravenous 1 mg/kg of body weight prednisolone per day for 7 days followed by 0.5 mg/kg of body weight prednisolone per day for another 3 days. After completing this course, patients were discharged and continued their treatment with oral methylprednisolone 32 mg/day for 4 days followed by oral methylprednisolone 16 mg/day for another 3 days. In case complete recovery was confirmed by a pure tone audiogram the treatment was interrupted without tapering.

Group B (intratympanic steroids)

The patients that were enrolled in this group were not hospitalized but instead they were visiting the outpatient clinics regularly to receive intratympanic methylprednisolone injections. 1 h before each injection, every patient received orally 1 tablet that contained 500 mg paracetamol (Depon, Bristol-Myers Squibb, Athens, Greece) together with 1 tablet that contained 400 mg paracetamol in combination with 10 mg codeine and 50 mg caffeine (Lonarid-N, Boehringer Ingelheim, Athens, Greece) for purposes of analgesia. Intact tympanic membrane and middle ear status were confirmed by the surgeon. While the patient lay in the supine position with the head tilted 45° to the healthy side a 25-gauge spinal needle was introduced into the posterior–inferior quadrant of the tympanic membrane, and 0.4–0.6 ml of 62.5 mg/ml methylprednisolone were slowly instilled intratympanically into the middle ear cleft. Patients were then instructed to avoid moving or swallowing for 20 min to create the optimal conditions for the solution to fill the round window niche. Intratympanic methylprednisolone injections were performed on the day of presentation, 3, 5 and 10 days after presentation (total of 4 times). In case complete recovery was confirmed by a pure tone audiogram the treatment was interrupted.

Group C (combined treatment)

The patients that were recruited in this group were hospitalized and treated with intravenous 1 mg/kg of body weight prednisolone per day for 7 days followed by 0.5 mg/kg of body weight prednisolone per day for another 3 days. In combination with intravenous prednisolone, patients underwent intratympanic injections of 62.5 mg/ml methylprednisolone on the day of presentation, 3, 5 and 10 days after presentation (total of 4 times). After completing this course, patients were discharged and continued their treatment with oral methylprednisolone 32 mg/day for 4 days followed by oral methylprednisolone 16 mg/day for another 3 days. In case complete recovery was confirmed by a pure tone audiogram, systemic and intratympanic steroids were both discontinued.

Statistical analysis

The statistical analysis was performed using the SPSS software package (version 17). The graphs were created using Microsoft Excel software package (version 2013). Categorial variables were compared with Chi-square test, whereas the means of metric variables between two groups were compared with independent samples *t* test. To determine whether there were significant differences between the means of the three groups one way analysis of variance (ANOVA) was used. The means of quantitative variables within the same group at different points in time were compared with paired samples *t* test. Pearson product–moment correlation coefficient was used to measure the linear dependence between two variables. A difference was considered to be statistically significant when the *p* value was less than 0.05.

The power of the statistical test was defined as equal to 80% ($P = 1-b = 0.8$). The level of statistical significance alpha was defined as equal to 0.025. According to these parameters the number of randomized participants needed was at least 25 per group for a total of 75.

Ethics

All patients receiving intratympanic steroids were informed about the procedure and the possible risks, including transient dizziness, otitis media and residual tympanic membrane perforation. They all agreed to take part in the study and signed an informed consent form. The study protocol was approved by the Ethical Committee of the Atristotle University of Thessaloniki and by the international scientific database Australian New Zealand Clinical Trials Registry (ANZCTR, ID: ACTRN12613001032741).

Results

A total of 137 patients were screened. There were 12 patients excluded for not meeting eligibility criteria, whereas 5 declined to participate. The rest 120 patients that consented to participate were randomized and included in the intention to treat analysis. Of the 120 participants included, 18 withdrew from the study. Reasons for study withdrawal were withdrawal of consent (4 patients), loss of contact (12 patients) and detection of acoustic neuroma in the MRI

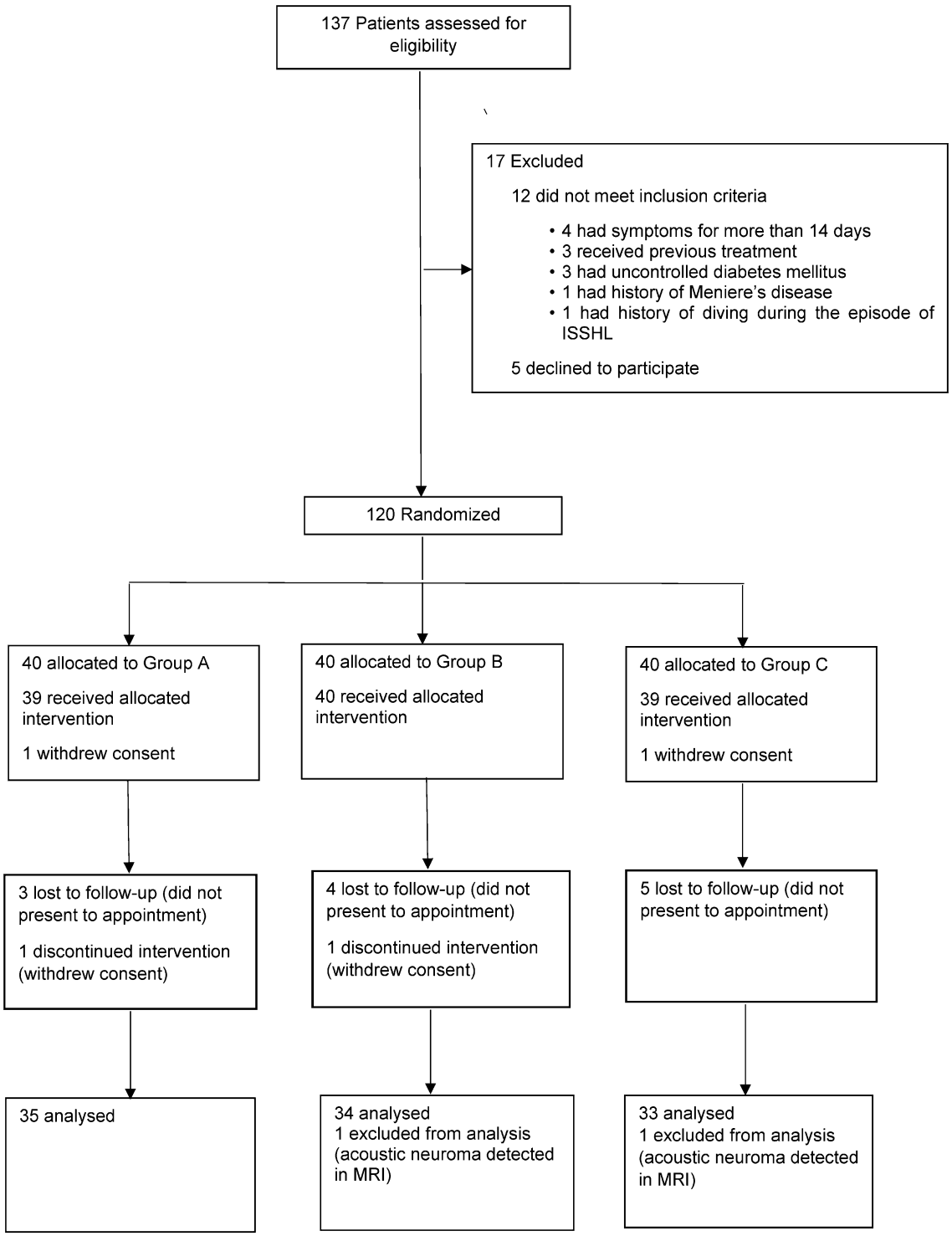

Fig. 1 Study flowchart

scan (2 patients). Overall 102 participants were included in the per-protocol analysis (Fig. 1). 59 of them had been recruited at the 1st Department of Otorhinolaryngology of Aristotle University of Thessaloniki and 43 at the Department of Otorhinolaryngology of Konstantopouleio Hospital of Nea Ionia Athens. There were 54.9% male ($N=56$) and 45.1% female ($N=46$) with an average age of 54.4 years (SD = 16.1, range: 18–80, median: 56.5). 35 (34.3%) patients had been randomized to Group A, 34 (33.3%) to Group B and 33 (32.4%) to Group C. The mean severity of initial

hearing loss was 80.7 dB HL (SD = 26.0, range: 38–120, median: 77.5) and the mean time to initiation of treatment was 4.0 days (SD = 3.7, range: 0–14, median: 3.0). There were no statistically significant differences between the 3 groups with regard to age, sex, site of ISSHL, initial PTA, dizziness, tinnitus and interval from hearing loss to onset of therapy (Table 1).

The mean PTA gains of groups A, B and C on the 10th, 30th and 90th day from onset of treatment are shown in Fig. 2. No statistically significant differences were detected.

Table 1 Demographic, clinical and audiological features of patients in Groups A, B and C

	Group A ($n=35$)	Group B ($n=34$)	Group C ($n=33$)	p value
Age (years) (mean + SD)	50.1 ± 17.3	53.2 ± 12.0	51.7 ± 15.8	0.74
Gender (male/female)	20:15	18:16	18:15	0.94
Ear (right/left)	18:17	20:14	17:16	0.78
Initial PTA (dB Hl) (mean + *SD*)	81.1 ± 28.8	81.4 ± 23.3	79.1 ± 25.1	0.71
Dizziness (%)	45.7 (16)	38.2 (13)	24.2 (8)	0.18
Tinnitus (%)	91.4 (32)	91.2 (31)	93.9 (31)	0.90
Time interval to initiation of treatment (days) (mean + SD)	3.1 ± 3.0	4.6 ± 3.0	4,.0 ± 3.9	0.44

PTA pure tone average at 500, 1000, 2000 and 4000 Hz hearing thresholds. *SD* standard deviation. *Group A* patients that were treated with systemic steroids. *Group B* Patients that were treated with intratympanic steroids. *Group C* Patients that were treated with combination therapy

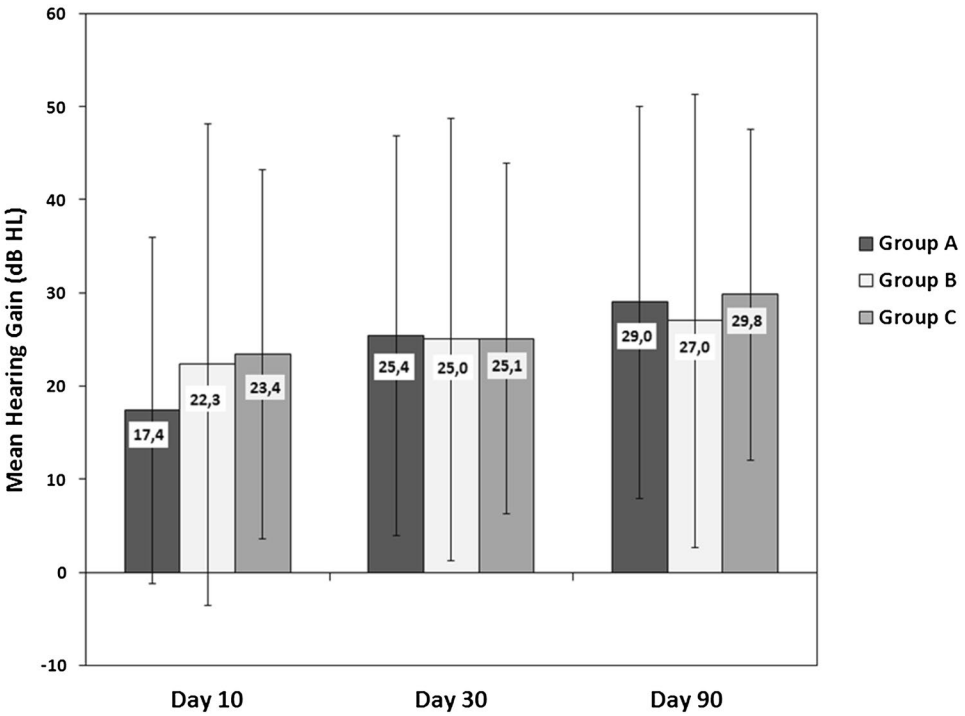

Fig. 2 Hearing gain profile of ISSNHL patients in each group on the 10th, 30th and 90th day after initiation of treatment

Table 2 Hearing improvements based on Siegel's criteria

	Group A ($n=35$)	Group B ($n=34$)	Group C ($n=33$)
Complete recovery (%)	14 (40.0%)	6 (17.6%)	12 (36.4%)
Partial recovery (%)	4 (11.4%)	10 (29.4%)	7 (21.2%)
Slight improvement (%)	9 (25.7%)	8 (23.5%)	7 (21.2%)
No improvement (%)	8 (22.9%)	10 (29.4%)	7 (21.2%)

Group A Patients that were treated with systemic steroids. *Group B* Patients that were treated with intratympanic steroids. *Group C* Patients that were treated with combination therapy

Table 3 Distribution of patients to treatment arms according to age, time to onset of treatment and initial PTA

	Age (years)			Time to onset (days)		Initial PTA (dB HL)	
	< 40	40–60	> 60	0–7	8–14	< 70	≥ 70
Group A	11 (31.4%)	13 (37.1%)	11 (31.4%)	27 (77.1%)	8 (22.6%)	12 (34.3%)	23 (65.7%)
Group B	10 (29.4%)	12 (35.3%)	12 (35.3%)	25 (73.5%)	9 (26.5%)	11 (32.4%)	23 (67.6%)
Group C	10 (30.3%)	12 (36.4%)	11 (33.3%)	25 (75.8%)	8 (24.2%)	12 (36.4%)	21 (63.6%)

PTA pure tone average at 500, 1000, 2000 and 4000 Hz hearing thresholds

The final mean PTA was 52.1 dB HL, 54.4 dB HL and 51.3 dB HL for Groups A, B and C, respectively.

Moreover, when Siegel's criteria were used for the assessment of final hearing improvement, no statistically significant differences among Groups A, B and C were detected ($p = 0.54$) (Table 2).

In a post hoc subgroup analysis, the predictive value of age, time to onset of treatment and severity of initial hearing loss were tested. For this purpose, the population was divided into three groups according to patients' age: (a) patients aged less than 40 years (b) patients aged between 40 and 60 years and (c) patients aged more than 60 years. The distribution of the age groups between the treatment arms is shown in Table 3 (χ^2 test, $p = 0.998$). The respective mean hearing gain for each group was 34.3 dB HL (SD = 25.4, range 0.0–88.8 median 31.9), 30.8 dB HL (SD = 15.5, range 0.0–62.0, median 27.5) and 21.9 dB HL (SD = 20.6, range −27.5 to 61.6, median 18.8). The mean hearing gain of patients older than 60 years was significantly lower when compared to the hearing gain of other age groups ($p = 0.02$). The correlation between age and mean hearing gain was also significant (Pearson's correlation coefficient, −0.291, $p = 0.008$).

As a separate analysis, patients were divided into two groups according to the days to initiation of treatment: (a) patients that started their treatment within 7 days from onset of ISSHL and (b) patients that started their treatment from 8 to 14 days from onset of ISSHL. The distribution of patients between the treatment arms according to time to onset of treatment is shown in Table 3. No statistically significant difference was detected (χ^2 test, $p = 0.94$). The mean hearing gain was 27.9 dB HL (SD = 20.6, range −27.5 to 88.8, median 26.3) for the first group and 28.5 dB HL (SD = 22.8, range 0.0–67.5, median 22.5) for the second group. The differences were not statistically significant ($p = 0.824$) There was also no significant correlation between time to onset of treatment and mean hearing gain (Pearson's correlation coefficient, −0.025, $p = 0.827$).

The severity of initial hearing loss was the last prognostic factor to be evaluated. According to Goodman's criteria "mild" hearing loss was defined as initial PTA between 26 and 40 dB HL, "moderate" as PTA between 41 and 55 dB HL, "moderate to severe" as hearing between 56 and 70 dB HL, "severe" as PTA between 71 and 90 dB HL and finally "profound" as PTA higher than 91 dB HL. Patients were divided into 2 groups. The first one consisted of subjects that had a PTA between 26 and 70 dB HL thus suffering from mild, moderate or moderate to severe hearing loss and the second one of patients that their initial PTA was 70 dB HL or higher thus presenting with severe or profound hearing loss. The distribution of patients between the treatment arms according to their initial hearing level are shown in Table 3 (χ^2 test, $p = 0.998$). The mean hearing gain for the first group was 27 dB HL (SD = 13.8, range −2.5 to 55.0, median 28.6), whereas for the second group was 28.6 dB HL (SD = 24.2, range −27.50 to 88.25, median 25.0). The statistical difference between the two groups was not significant ($p = 0.748$). There was no significant correlation between the severity of initial hearing loss and mean hearing gain (Pearson's correlation coefficient, −0.135, $p = 0.227$).

Adverse events

There were no significant complications during the intratympanic injections or the follow-up period. Only one patient experienced transient dizziness as a result of caloric stimulation from the injected steroid solution directly after the first injection. The symptoms resolved completely within 15 min and there was no need to discontinue the treatment. The injections that followed caused no further side effect.

Discussion

The treatment of ISSHL remains one of the most controversial aspects. Many treatments have been tested till now. These include antivirals, vasodilators, agents that decrease blood viscosity (dextran, pentoxifylline, procaine, histamine), diuretics, hyperbaric oxygen, carbogen inhalation and even surgical interventions [13]. Currently, steroid therapy is the most commonly used modality.

The mechanism of action of steroids in the inner ear is not completely understood. They are believed to have local effects by directly influencing inner ear tissues as well as systemic effects. When injected intratympanically, steroids enter the inner ear through the round window membrane

[14], the annular ligament of the oval window [15] and possibly through the otic capsule [16]. Glucocorticoid receptors of the inner ear are thought to mediate the local actions of steroids [17]. These include ion homeostasis, antioxidant action, inhibition of apoptosis, down-regulation of local pro-inflammatory cytokines and promotion of cochlear blood-flow [18–21]. Mineralocorticoid receptors also bind steroids, contributing thus to ion homeostasis [22]. On the other hand, systemic actions of steroids include decrease in the number of circulating leucocytes and inhibition of the formation and liberation of inflammatory mediators [23]. One could assume that the combination of intratympanic and systemic steroids would achieve the maximum therapeutic effect.

Although intratympanic steroids have achieved good results when used as a salvage treatment after the failure of systemic steroids [24–27], their efficacy as initial therapy for ISSHL has not been proven yet [24, 25, 28, 29]. According to our study's results, the difference in the therapeutic efficacy of intratympanic and systemic steroids is not significant. Additionally, intratympanic steroid administration has been applied as an adjunctive treatment given concomitantly with systemic steroids. However, reports regarding the efficacy of combination therapy for ISSHL remain controversial. In 2013 a prospective, randomized, multicenter clinical trial concluded that the addition of intratympanic steroids to the conventional systemic steroid therapy may provide a safe and potentially more effective therapeutic option in patients with mild-to-severe ISSHL [30]. On the other hand, studies like Ahn's et al. [31] and Bae's et al. [32] concluded that combined treatment did not have additional benefits compared with systemic or intratympanic steroids alone. The diversity in the results of these studies can be partially due to the relatively small number of patients that they enroll as well as to the different criteria that they use. In our study, there was no statistically significant difference between the systemic, intratympanic and combined administration of steroids in regards to hearing gain as well as to hearing recovery according to Siegel's criteria. The authors have chosen to analyze their data without excluding any patient regardless of the severity of their initial hearing loss. Nevertheless, it has been shown that exclusion of patients with complete anacusis, i.e., a non-measurable hearing threshold might change the outcome of the analysis [33]. In addition, it has been noted that inclusion of patients with an initial PTA better than 60 dB HL may impose the so called 'statistical floor effect'. This 'floor effect' arises from the fact that the amount of possible recovery is related to the initial severity of the presentation. That is, a patient with a PTA 30 dB HL can only recover (approach 0 dB HL) by about that amount, while a person with a presenting PTA of 60 dB HL can recover 'twice as much' [34]. As a result, the fact that our analysis was based on all the patients without any exclusion imposes a possible risk of bias as well as a risk of the above mentioned statistical issue. Another important element of research on ISSHL is to identify prognostic factors for this disease. As mentioned above, the predictive value of age, time to onset of treatment and severity of initial hearing loss were tested in this study. Patients older than 60 years showed significantly less favorable response to the treatment when compared with younger patients. Recent studies confirm our results and correlate younger age with higher rates of hearing recovery [35, 36]. Despite reports in the literature which show that the initiation of treatment within 7 days from onset of hearing loss results in better prognosis [36], our study did not confirm such a correlation. This is possibly due to the fact that our study included subjects that started their treatment within 14 days after onset of hearing loss the latest, thus excluding patients with delayed treatment. Although initial hearing level has been found to have stronger or weaker correlation to the final hearing outcome, our study demonstrates that the severity of initial hearing loss is not a significant prognostic factor in the treatment of ISSHL [35, 37].

Conclusion

The results of the present study suggest that treatment of ISSHL with systemic, intratympanic or combined administration of steroids result in similar rates of hearing improvement. Patients who start their treatment within the first week after onset of hearing loss have similar prognosis with those who start their treatment within the second week. Younger patients are more likely to achieve better hearing outcomes, whereas the severity of initial hearing loss does not affect significantly the prognosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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