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Original Article

A Comparison of Two Vasoactive/Vasodilative Agents in Combination with Corticosteroid for Treatment of Sudden Sensorineural Hearing Loss

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OBJECTIVE: Idiopathic sudden sensorineural hearing loss (ISSNHL) or sudden deafness is considered an otologic emergency. In spite of numerous investigations, its cause and treatment remain uncertain. Vascular hypothesis is one of the accepted etiologic theories, and vasodilator agents have been used to treat this medical condition.

MATERIALS and METHODS: We conducted a retrospective study in which we have compared the efficiency of two vasoactive/vasodilative agents-pentoxifylline and betahistine-separately and together for treatment of sudden deafness in 59 patients. Methylprednisolone was used in all three groups. Hearing threshold (HT) was measured, and pure tone average (PTA) was calculated on admission, after 1 week, and after 3 months.

RESULTS: Hearing improvement was noticed in 33 out of 59 patients (56%) at the second follow-up with a mean PTA improvement of 20 dB. The best recovery rate was seen in the pentoxifylline + steroid group (69%) versus the pentoxifylline + betahistine + steroid group (55%) and betahistine + steroid group (48%). There was no statistically significant difference in treatment outcome (p=0.433) between all three groups. Methylprednisolone dosage was 32, 48, or 64 mg/day. The amount of steroid given was not statistically significant for recovery of hearing loss (HL) (p=0.418).

CONCLUSION: The pentoxifylline with methylprednisolone group achieved the best results. In that group, 67% of patients improved at the first follow-up versus 69% after 3 months. Statistically, there was no significant difference in treatment outcome between all three groups (p=0.433). Greater PTA improvement was seen at higher doses of steroid. The amount of steroid given was not found to have a statistically significant influence on hearing recovery (p=0.418).

KEY WORDS: Sensorineural hearing loss, pentoxifylline, betahistine, methylprednisolone, treatment outcome

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSNHL) is an otologic emergency, and despite numerous investigations, it remains an unsolved medical issue [1]. It is defined as a rapid deterioration of hearing of 30 dB or more over at least three contiguous frequencies, in less than 72 hours [2]. In most cases, it is unilateral, affects both genders equally, and can be accompanied by tinnitus and/or vertigo [3]. It affects 5-20 per 100,000 people per year in the United States [3] and represents a frightening condition for the patient, with a strong impact on his/her quality of life.

Usually, the cause can not be identified; hence, it is called idiopathic. Although various theories have been suggested to explain the cause, no exact conclusion was made. Vascular disorders, viral infections, and autoimmune disorders are some of the most accepted hypotheses [3, 4, 5]. All of these hypotheses are likely but are most often proven in *in vitro* animal studies or *postmortem* human studies; so, it is very difficult to determine the actual cause in clinical practice [6, 7]. Since the etiology is uncertain, the problem of appropriate treatment appears. Vasoactive agents, steroids (oral, intravenous, or intratympanic injections), antivirals, and hyperbaric oxygen have already been used, but none of these treatments showed significantly better outcome than the placebo [5, 8-12]. A considerable spontaneous recovery rate has been reported (from 32% to 68%) [3, 4], so one can question not only which treatment would be the best option but also if it is required at all.

In the vascular hypothesis, the blood supply of the cochlea seems to be compromised [5, 13]. The cochlea receives blood from the labyrinthine artery, which is a small terminal artery and lacks collateral blood supply. Any ischemic effects (like vascular occlusion by emboli, vasospasm, acute vascular hemorrhage, or change in blood viscosity) can cause damage to the cochlea and thus hearing impairment [5, 13].

Vasoactive substances increase blood flow through changes in blood viscosity and vasodilators through dilation of blood vessels [9]. Pentoxifylline is a vasoactive agent that is otherwise used for treating peripheral vascular disease, cerebrovascular disease,

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and other disorders with dysfunctional regional microcirculation [14]. It reduces blood viscosity, platelet aggregation, and thus thrombus formation. Betahistine has a strong antagonist effect on histamine H_3 receptor and a weak agonist effect on histamine H_1 receptors [15]. By acting on local H_3 receptors, it causes an increase in vestibulocochlear blood flow, and through central H_3 receptors, it raises histamine synthesis and release. By acting on H_1 receptors on blood vessels of the inner ear, it causes local vasodilation. It is used for treatment of vestibular disorders, like Meniere's disease, and for tinnitus, as well [15, 16]. Laurikainen already reported that intravenous betahistine increases cochlear blood flow in animal models [17].

Glucocorticoids, like methylprednisolone, are the most commonly prescribed drug for ISSNHL. Its mechanism of action in sudden hearing loss is not thoroughly understood. It is known to reduce inflammation and edema, but its role on mineralocorticoid receptors and regulation of ion homeostasis of inner ear fluids might be even more significant [18]. Mineralocorticoids regulate ion homeostasis in endolymph, which is required for endocochlear membrane potential and thus normal cochlear function [19]. Glucocorticoids help to restore ion homeostasis, since they have a strong affinity to mineralocorticoid receptors in the inner ear [18].

MATERIALS and METHODS

We conducted a retrospective study of 59 patients that were hospitalized at our clinic for treatment of ISSNHL in 2011 and 2012. The youngest patient was 20 years old, and the oldest was 82; the mean age was 57 years. After clinical examination, pure tone audiometry with tympanometry was carried out, and pure tone average (PTA) was calculated. We calculated PTA as the arithmetic mean of the hearing thresholds (HT) at 500, 1000, 2000, 4000, and 6000 Hz. Patients with hearing loss (HL) of 20 dB or more in at least 3 subsequent frequencies, which developed in less than 3 days, were included in the study. Exclusion criteria were any known reasons of sensorineural or conductive hearing loss, like acute otitis media, previously impaired hearing, history of fluctuating hearing loss, previous ear surgery, and vestibular schwannoma of the affected ear.

We compared the efficiency of three treatment schemes: a vasoactive agent, pentoxifylline (Pentilin; Krka d.d., Novo mesto, Slovenia), and a vasodilator, betahistine, (Betaserc; Abbott Laboratories, Abbott Park, Illinois, USA) separately and combined. All groups received the corticosteroid methylprednisolone (Medrol; Pfizer, New York, USA), as well. The patients were divided into three groups, since we changed the treatment scheme from pentoxifylline to betahistine and lowered the dosage of corticosteroid. The first group received pentoxifylline intravenously in increasing doses from 100 mg up to 400 mg per day for 7 days and 64 mg of methylprednisolone. In the transitional period, some of the patients received both pentoxifylline and betahistine with 64 mg of methylprednisolone (group 2). The third group received betahistine with 48 mg of methylprednisolone. All patients in group 3 received 24 mg of betahistine twice a day orally, which was continued for up to 6-8 weeks. Corticosteroid was given orally for 7 days, followed by a taper of the dosage every 2 days. Patients that were at risk by taking corticosteroids (like disordered diabetes) were given 32 mg of methylprednisolone.

The first follow-up audiometry was usually made 7 days after the start of treatment and second follow-up after 2–4 months (mean time 3 months). We therefore compared frequency-specific and mean HT. Seventeen patients did not come for a second follow-up (either due to the normalization of hearing already at the first follow-up or because of the patient's poor compliance). For patients who had not done a second follow-up, the first follow-up PTA was used (we presumed that no change in PTA occurred). Improvement was considered an increase in hearing threshold of at least 10 dB. More than 30 dB of improvement of PTA was labeled as significant.

Patients were informed about treatment scheme, its efficiency and risks and consented to it. They were able to withdraw the treatment at any time on their wish. The protocol of this retrospective study was approved by the National Medical Ethics Committee.

Statistical Analysis

Statistical data were processed in Microsoft Excel (Microsoft Corporation; Redmond, Washington, USA) and the SPSS program (SPSS for Windows 21.0; IBM, Armonk, New York, USA).

Fisher's exact test was used to evaluate the influence of treatment scheme, amount of steroid, sex, age, time to therapy, presence of tinnitus, and vertigo on hearing recovery. A statistically significance difference was defined when the p value was less than 0.05.

RESULTS

In the study, we included 59 patients with ISSNHL; 30 (51%) of them were male and 29 (49%) were female. All of them had sudden unilateral hearing loss, with the left ear being slightly more frequently affected (32 patients, 54%). Thirty-three patients (56%) also complained of tinnitus and 27 (46%) complained of vertigo. Mean time from onset of hearing loss to treatment start was 4 days (the earliest on day 0 to maximum day 30, median time 2 days) (Table 1).

Sixteen patients received treatment with pentoxifylline and methylprednisolone (group 1) (27%). A combination of pentoxifylline, betahistine, and methylprednisolone (group 2) was given to 22 patients (37%). Betahistine and methylprednisolone alone (group 3) was used for 21 patients (36%) (Figure 1).

Mean PTA on admission was 81 dB (79 dB in the first group, 81 dB in second, and 82 dB in the third group). Twenty patients (34%) had mild to moderate loss with PTA less than 60 dB, 17 patients (29%) had moderately severe to severe hearing loss (PTA between 60-90 dB), and 22 (37%) patients were deaf (PTA >90 dB). Most of the patients (38%) in the first group had mild HL; the distribution of moderately severe or deaf patients was equal (31% and 31%, respectively). In the second group, 41% had the most severe HL, 36% had mild HL, and 23% had moderately severe HL. More than one-third (38%) of patients in the last group were deaf, one-third (33%) had moderately severe HL, and a little less than one-third (29%) had mild HL. Mean PTA improvement in patients with mild to moderate HL was 9 dB, while in the moderately severe to severe group, the mean PTA change was 27 dB. Even in the most debilitating group, we noticed a substantial PTA improvement of 26 dB.

At the first follow-up audiometry, 26 of 54 patients (48%) showed improvement, and 12 patients (22%) improved significantly. Mean PTA in all three groups was 63 dB. Ten patients (67%) in group 1 improved

Table 1. Baseline characteristics. Influence of each factor on improvement rate (IMP rate), statistically significant when p value <0.05

	All	Scheme 1	Scheme 2	Scheme 3	p value (IMP rate)
Sex					
Male: Female (%)	30:29 (51:49)	7:9 (44:56)	13:9 (59:41)	10:11 (48:52)	0.299
Age					
Mean years (min - max)	57 (20-82)	57 (25-80)	58 (20-77)	57 (30-82)	0.601
Treatment delay time					
Mean days (min - max)	4 (0-30)	3 (0-14)	3 (0-14)	6 (0-30)	0.050
Medrol					
32mg: 48mg: 64mg (%)	13:15:31 (22:25:53)	4:1:11 (25:6:69)	7:0:15 (32:0:68)	2:15:5 (9:68:23)	0.418
Tinnitus					
No: Yes (%)	26: 33 (44:56)	8:8 (50:50)	8:14 (36:64)	10:11 (48:52)	0.071
Vertigo					
No: Yes (%)	32:27 (54:46)	9:7 (56:44)	12:10 (55:45)	11:10 (52:48)	0.607

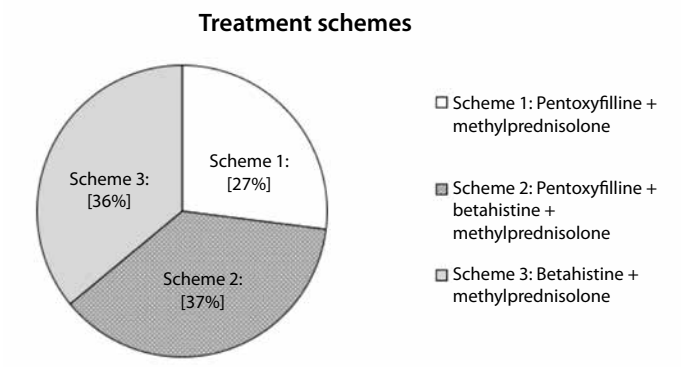


Figure 1. Treatment schemes (percentage of patient treated with the scheme)

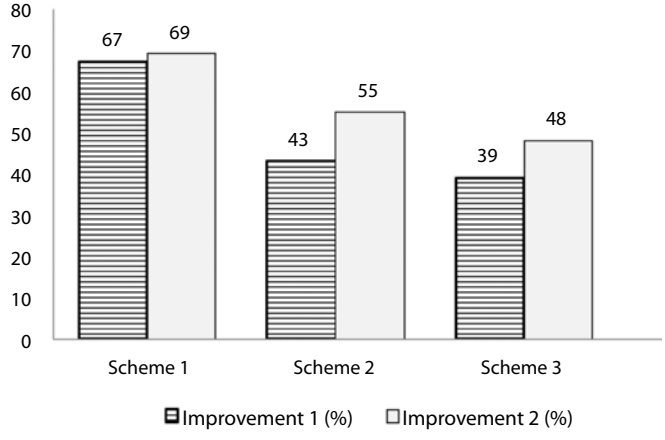


Figure 2. Hearing improvement (%) at first and second follow up in different treatment schemes

in HT; 27% (4 patients) showed significant improvement. Mean PTA in this group was 60 dB. Nine patients (43%) in group 2 had a difference in PTA, only 5 patients (24%) significantly better. In the last group, 39% (7 patients), improvement was noticed; 3 patients (17%) recovered significantly. Mean PTA was 65 dB and 62 dB in these two groups, respectively (Figure 2, Figure 3).

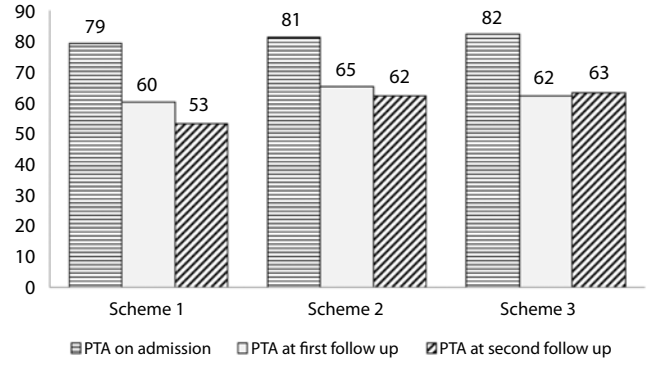


Figure 3. Average PTA (dB) on admission, at first and second follow up

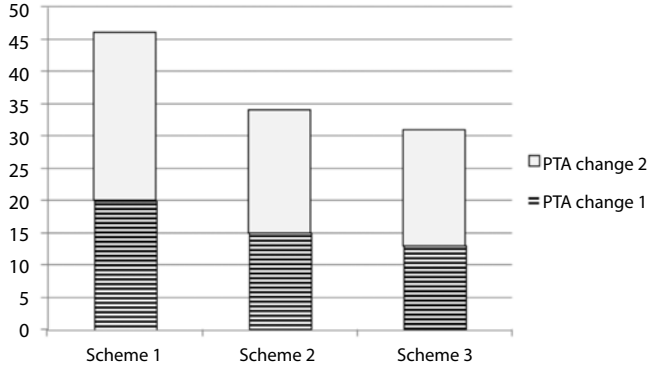
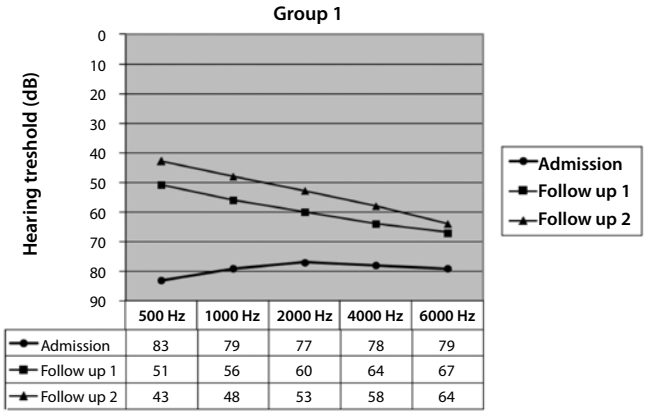


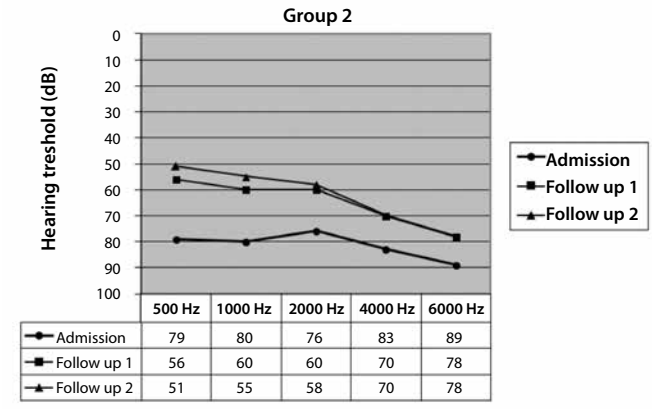
Figure 4. Mean PTA change (dB) at first and second follow up

At the second audiometry, 33 patients (56%) showed improvement in HT. Mean PTA at the second follow-up was 60 dB. Eleven patients (69%) in the first group, 12 patients (55%) in group 2, and 10 patients (48%) in the last group. Altogether, 11 patients (19%) recovered to HT of 30 dB or less. Mean PTA improvement in group 1 was 26 dB, 19 dB in the second group, and 18 dB in the third group (Figure 4). There was no statistically significant difference in HL improvement between the treatment groups (p=0.433).



	500 Hz	1000 Hz	2000 Hz	4000 Hz	6000 Hz
Admission	83	79	77	78	79
Follow up 1	51	56	60	64	67
Follow up 2	43	48	53	58	64

Figure 5. Hearing threshold (in dB) at each frequency on admission, at first and second follow up in Group 1



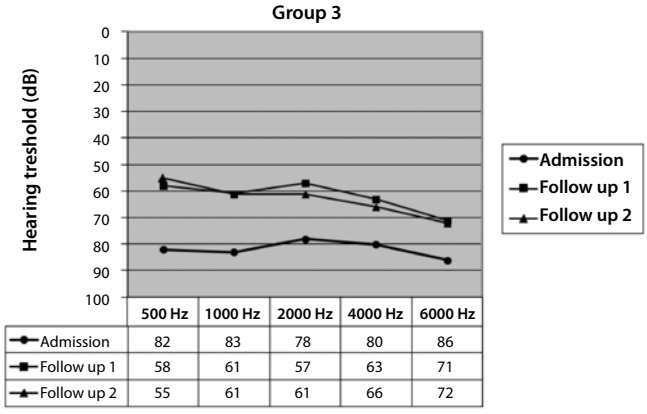
	500 Hz	1000 Hz	2000 Hz	4000 Hz	6000 Hz
Admission	79	80	76	83	89
Follow up 1	56	60	60	70	78
Follow up 2	51	55	58	70	78

Figure 6. Hearing threshold (in dB) at each frequency on admission, at first and second follow up in Group 2

Frequency-specific HT on admission was best at 2000 Hz in all three groups and worst at 6000 Hz in groups 2 and 3, while the worst HT on admission in group 1 was at 500 Hz. At the second follow-up, HT was best at 500 Hz and worst at 6000 Hz in all three groups. Comparing schemes, group 1 had best results at the second follow-up in all frequencies, while the worst results at 500-2000 Hz were found in group 3 and at 4000 Hz-6000 Hz in group 2. A thorough review of the improvement at different frequencies is described in Figures 5-7.

We also tested if methylprednisolone had some effect on the treatment outcome. The high dosage (64 mg) of methylprednisolone was given to 31 patents (53%), mostly in group 2 (15 patients) and group 1 (11 patients). Twenty of 33 patients (61%) whose hearing improved received 64 mg of methylprednisolone, 7 patients (21%) got 48 mg of steroid, and 6 patients (18%) received 32 mg. The difference was not found to be statistically significant (p=0.418). Patients who received 64 mg of steroid also had greater PTA improvement (mean PTA change was 27 dB) than those who received 48 mg or 32 mg (mean PTA change was 15 dB and 12 dB, respectively) (Figure 8).

Patient's sex, age, and presence of vertigo had no statistically significant influence on hearing improvement. Treatment delay time and tinnitus were more likely to influence hearing outcome. Patients who started therapy within 4 days of sudden deafness had better results that those who started therapy later (p=0.050). Presence of tinnitus



	500 Hz	1000 Hz	2000 Hz	4000 Hz	6000 Hz
Admission	82	83	78	80	86
Follow up 1	58	61	57	63	71
Follow up 2	55	61	61	66	72

Figure 7. Hearing threshold (in dB) at each frequency on admission, at first and second follow up in Group 3

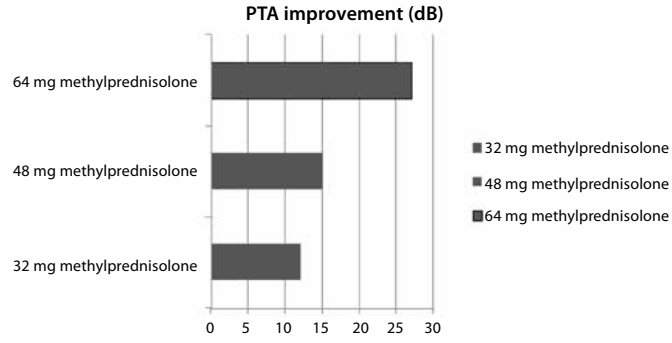


Figure 8. Mean PTA improvement (dB) at different dosage of methylprednisolone

seemed to have a better influence on hearing improvement, as well (p=0.071) (Table 1).

DISCUSSION

Although the definition of ISSNHL requires a reduction of at least 30 dB in 3 subsequent frequencies, we also hospitalized patients with less than 30 dB of hearing deficit if they complained of serious debilitation of everyday life because of the hearing loss [2]. In the study, we therefore included patients with a hearing loss of 20 dB or more in at least 3 subsequent frequencies, which developed in less than 3 days.

Within treatment schemes, group 1 had a better outcome in percentage of patients that recovered hearing, as well as in PTA improvement. But, the number of patients with improved hearing was almost equal between all three groups. There was no statistically significant difference in hearing outcome between all three groups (p=0.433). Probst and colleagues compared pentoxifylline, dextran, and placebo for treating sudden hearing loss and acute acoustic trauma but also found no difference between groups in hearing gains [20]. Conlin and Parnes reviewed different research on vasoactive and hemodilution agents (including pentoxifylline, dextran, *Ginkgo biloba*, nifedipine, and their combinations), but also, no significant difference from the control group was noticed [21]. Hearing improvement at the second follow-up (3 months after the start of treatment) was not much better as at the first follow-up (1 week after the start of treatment). We can assume that most of the recovery happens in the first days after sudden deafness.

Our results revealed the most severe HL at 6000 Hz and a worse recovery of hearing in higher frequencies, as well. The best improvement of hearing was seen at lower frequencies: 500 Hz and 1000 Hz. Other authors also reported better improvement at lower frequencies [22, 23], but it has not yet been clarified why.

We tested whether the amount of orally given steroid had influenced hearing recovery. We found that patients who had received a high dosage of steroid had better outcomes than the ones with low dosage, but the difference was not statistically significant (p=0.418). Standard treatment of ISSNHL usually involves steroids, although the results of efficacy are opposing [10]. Different ways of application of steroids are under investigation, with some promising results of intratympanic application of steroids, especially as addition to systemic steroid therapy [24, 25].

Treatment delay time was found to be statistically significant (p=0.050). Late onset of treatment resulted in less recovery. Byl already reported treatment delay time as a poor prognostic factor [3]. The presence of tinnitus was correlated with higher recovery rate, and the difference was close to statistical significance (p=0.071). Uri also reported better hearing outcome if tinnitus was present and worse outcome if vertigo was accompanied [13]. Although vertigo is considered a poor prognostic factor [1], we did not notice any difference on hearing gain if vertigo was present. Chin-Saeng Cho's research on prognostic factors showed no direct effect of vertigo on hearing improvement but found close correlations between vertigo and initial hearing level, which also predicts the prognosis of the disease [26]. The age and sex of the patient did not influence treatment outcome.

Since it was a retrospective study we could only compare different therapy schemes with each other. There was no control group; so, it is hard to say whether the improvement was due to the medication itself or due spontaneous recovery, which is known to be substantial [3, 4]. As in the Cochrane review in 2009, the effectiveness of different vasodilators for treatment of ISSNHL was not proven [9].The question of the right treatment is obviously still open to debate. New therapies are therefore encouraged to be developed, and new diagnostic tools should be proposed. To determine the actual cause of sudden hearing loss would aid immensely in finding the cure.

In a retrospective study of 59 patients hospitalized for ISSNHL, we compared the efficiency of two vasoactive/vasodilator agents, pentoxifylline and betahistine, combined with steroid. The pentoxifylline with methylprednisolone group achieved the best results. In that group, 67% of patients improved at the first follow-up and 69% improved after 3 months. A combination of pentoxifylline, betahistine, and steroid was less effective; improvement of HT at the first follow-up was seen in 43% of patients and in 55% at the second follow-up. The betahistine with methylprednisolone scheme showed an improvement of HT in 39% of patients at the first follow-up and in 48% at the second. Although we noticed better results in the first group, there was no statistically significant difference (p=0.433) between all three groups. No therapy was better or more appropriate for treatment of ISSNHL. Lower frequencies were usually less affected and improved much better than higher frequencies. Methylprednisolone, as an anti-inflammatory agent, as well as an endolymph ion homeostasis regulator, helps to restore hearing in ISSNHL. Greater PTA improvement was seen at higher doses of steroid. The amount of steroid given was not found to have a statistically significant influence on hearing recovery (p=0.418). The research has been continued with an emphasis on the efficiency between intratympanic and per os application of corticosteroids.

Ethics Committee Approval: Ethics committee approval was received for this study from Božidar Voljč, MD, PhD.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.B., S.K.; Design - S.B, S.K; Supervision - S.B; Funding - S.B.; Materials - S.K.,S.B.; Data Collection and/or Processing - S.K.; Analysis and/or Interpretation - S.B., S.K.; Literature Review - S.K., S.B.; Writer - S.K., S.B.; Critical Review - S.B.

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