

ORIGINAL ARTICLE

Intratympanic Steroids for Sudden Sensorineural Hearing Loss

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Background: Currently the treatment of sudden sensorineural hearing loss (SSNHL) by steroids is considered to be the most effective and common one. Nevertheless, there are many adverse effects of long-term systemic administration of steroids. Intratympanic administration of steroids, even in small quantities, results in higher concentration of the drug in the end organ, than in the case of systemic administration. Therefore, drugs that are used topically in low doses can be preferred.

Objective: Investigation of the efficiency of intratympanic route of steroid administration in treatment of SSNHL.

Materials and Methods: 73 patients with SSNHL were included into the study. 24 patients with SSNHL were treated with intratympanic dexamethasone (IT-Dex) over a period of 6 months. 24 patients were treated with standard systemic therapy (ST) and 25 patients were treated with intravenous dexamethasone (IV-Dex) over a period of 10 days. Pretreatment and 1-, 3-, 6-month posttreatment pure-tone audiograms were compared.

Results: Intratympanic and systemic therapy did not show any differences in the treatment efficiency during the first month. Further analysis demonstrated better results in high-frequency range in 1 month after the beginning of the treatment, which was due to a more expressed effect in the IT-Dex group compared with the ST group. Nevertheless, intratympanic steroid therapy results in higher efficacy after long treatment, i.e. 6 months.

Conclusions: Treatment efficacy of intratympanically administered steroids over 1 month did not differ from those of standard therapy and steroid monotherapy. IT therapy can be used as a primary method for treatment of patients with contraindications against systemic steroid therapy and for those with mainly high-frequency sensorineural hearing loss. Long-term IT steroid therapy over a period of 6 months showed a more noticeable efficacy than standard therapy and systemic steroid monotherapy. No differences were found between groups treated with standard and systemic steroid therapy. Further studies are needed to establish the availability of IT administered steroids as an additional method when standard or systemic steroid therapies are not or are partially effective.

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Introduction

Treatment of sudden sensorineural hearing loss (SSNHL) remains one of the most important and problematic issues of the contemporary otorhinolaryngology. Today steroid therapy is considered to be the most effective and common method for SSNHL treatment. At the same time a huge number of side effects appear to be associated with the long-term systemic use of steroids.

Neither the optimal dosage of systemic steroids nor the treatment duration has been precisely defined, so they are often picked up empirically and are far from being accurate.

Furthermore, a low dosage of systemic steroids cannot create an ideal therapeutic effect because of their limited capacity to penetrate through the hemato-perilymphatic barrier ^[1].

The latest pharmacokinetical studies show that the intratympanic (IT) administration of steroids, even in low dosage, enables direct penetration of the medication through the round window membrane (RWM) that leads to the high perilymph concentration of drug ^[2-11] without strong toxicity and systemic absorption of steroids ^[1].

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The IT administration of steroids is associated with a minimal rate of side effects [1, 12, 13]. When the systemic use is contra-indicated, the drug may be applied locally in low doses [14]. All the above-stated allows to apply the IT steroid therapy to those patients who have contraindications to the systemic steroid therapy.

We have studied 73 patients (75 ears) with SSNHL to evaluate the effectiveness of the IT application of steroid treatment on SSNHL patients and to compare the IT administration with the intravenous (IV) administration of steroids and the standard therapy of SSNHL.

The permission of ethical committee of the faculty of surgery of the Russian Medical Academy of

Postgraduate Education (N28, 10.04.2003) was obtained for our clinical research.

The objective of our study is to evaluate the effectiveness of the IT application of steroid treatment on SSNHL patients compared with the IV application of steroids and the standard therapy.

Materials and Methods

The analysis of the therapy efficacy was performed on 73 patients with SSNHL (mean age 43.4 ± 11.9 SD yr; range, 23-69 yr), 31 women and 42 men, without previous treatment ($n^p = 73$). Two of them demonstrated a bilateral SSNHL (the number of affected ears – $n^e = 75$) (Table 1).

Table 1. General data regarding SSNHL patients in 3 groups under study.

	Number of patients	Sex		Mean age, years old (median, 25 and 75 percentiles)	Vertigo		PTA _{ALL} before treatment, dB (mean \pm SD)
		male	female		+	–	
IT-Dex group	24	14	10	49 (35 – 52)	4	21	41.0 \pm 12.87
ST group	24	15	9	50 (30 – 53)	5	19	37.1 \pm 16.67
IV-Dex group	25	13	12	40 (32 – 53)	6	19	39.1 \pm 16.97
Total	73	42	31	46 (33 – 52)	15	59	39.1 \pm 15.49

PTA_{ALL} – pure tone average on all the frequencies (125-8000Hz).

The inclusion criteria during this study were as follows: patients with SSNHL with hearing loss in 3 contiguous frequencies of at least 30 dB, who had not previously been treated and were at least 18 years old. The time between the onset and the beginning of the therapy was less than 1 month.

The following exclusion criteria were adopted:

1. Patients with somatic pathology (such as diabetes, hypertension, gastric ulcer, tuberculosis, glaucoma, and so on), for whom systemic steroids were contra-indicated;
2. Oncology patients;
3. Patients with autoimmune diseases or those who were constantly or periodically taking steroids;
4. Patients who were or have been taking ototoxic agents;

5. Patients with acoustic neurinoma;
6. Pregnant and nursing women;
7. Patients with middle ear diseases, abnormal type of tympanometric curves or barotrauma in their anamnesis;
8. Those who had intolerance for any component of treatment;
9. Those who had SSNHL in the only hearing ear.

All patients ($n_p = 73$, $n_e = 75$) were divided into 3 groups depending on the method of therapy. The division into groups was based on mechanical randomization.

The IT-Dex group, 24 patients with SSNHL (25 ears), was treated with dexamethasone (Dex) administered intratympanically. Dex was injected through a tympanostomy tube fixed in the posteroinferior

quadrant of the tympanic membrane (TM). Dex was given according to the following dosage regimen: 4 mg/cc every day during 10 days, 4 mg every other day over 20 days and then 4 mg 2 times a week over 5 months by injecting the drug in the tympanic cavity through the tympanostomy tube, we oriented patient's head in a specific position to be sure the RWM was covered with the solution for 30 minutes. We asked the patient to avoid swallowing to reduce the drug leaking through the eustachian tube.

The ST group included 24 patients with SSNHL (25 ears) who received standard systemic therapy, (Dexamethasone (0.1 mg/kg) in 200 ml of isotonic solution intravenously; Pentoxifylline, Cocarboxylase, Potassium and magnesium aspartate intravenously and vitamin B-complexe intramuscularly. All these were given to the patients daily over 10 days.

The last, IV-Dex group consisted of 25 patients (25 ears) with SSNHL who were treated with intravenous administration of Dexamethasone(0.1 mg/kg) daily over 10 days.

In the ST and IV-Dex groups, all patients received a steroid medication Dex (as indicated above) over 10 days with a following dose declining over the next 5 days and therapy cessation on the fifth day.

The evaluation of the efficacy was based on the pure-tone audiograms before and after treatment. Hearing evaluation relied on the following criteria: a hearing restoration within 15 dB from the normal rate was defined as a complete recovery, an improvement of the average hearing of 50% or more from the initial test results – as a partial recovery, a reduction of hearing thresholds of 15 dB or more - as a hearing improvement. The average hearing levels (PTA) were determined by 4 frequencies (500, 1,000, 2,000 and 4,000 Hz).

All patients had a follow-up period of 6 months. They were observed before the treatment, 10 days after, and then 1, 3 and 6 months after the beginning of the therapy.

Only patients with idiopathic sudden sensorineural hearing loss were included in the study.

Statistical data processing was performed with the software Statistica (StatSoft Inc., release 6.1) and Biostatistics, Version 4.03, by Stanton A. Glantz, USA 1998. The statistical analysis included the following methods: descriptive statistics, analysis of variance

(One-Way ANOVA), repeated measures analysis of variance, Newman-Keuls test, pared t-test, Kruskal-Wallis test, Dunn test, Chi-Squared test, Fisher exact test (one-tailed version), factor analysis of variance, analysis of covariance (ANCOVA), logistic regression, polynomial regression.

Results

There were no significant differences in sex, age, PTA (including low-, mid- and high-frequency ranges) before treatment, duration between onset and treatment of the disease, association with vertigo or hearing loss degree between the three groups ($p < 0.05$).

The efficacy of the treatment was evaluated 1 and 6 months after the beginning. The affected ear was considered control. At the first stage of our study, the results were divided into 2 subgroups depending on presence or absence of treatment response: with positive effect («effect+» subgroup) and without positive effect («effect-» subgroup). «Effect+» subgroup included cases of complete recovery, partial recovery and hearing improvement, whereas «effect-» subgroup enclosed cases without changes or with hearing loss (Table 2).

Following one month there were no significant differences between the groups however 6 months later, we found a significant difference (χ^2 , $p < 0.05$).

The IT-Dex group represented the major component of positive clinical results (88%), whereas the ST and the IV-Dex groups differed slightly (48% and 56% respectively), which was considered to be nonsignificant. The difference between the IT-Dex group and the two others overall was significant (χ^2 , $p < 0.05$).

At the second stage the analysis of previously revealed differences and further evaluation of the significance of differences between groups was performed. The comparative analysis of rates of complete recoveries, partial recoveries, hearing improvements («effect+» subgroup) and of cases without changes or with hearing loss («effect-» subgroup) in all groups 6 months after the therapy beginning revealed the greatest differences within the complete recovery rates between groups – in the IT-Dex group, 60% of patients demonstrated complete recovery, while in the ST group, as well as the IV-Dex group only 20% of patients recovered completely (Table 3).

Table 2. Therapy efficacy in the groups at different time points after the treatment beginning.

Time after the treatment beginning	Groups	Treatment response				Total	
		®effect+/-		®effect-/-			
		Abs.	%	Abs.	%	Abs.	%
1 month	IT-Dex group	17	68.0	8	32.0	25	100
	ST group	12	48.0	13	52.0	25	100
	IV-Dex group	15	60.0	10	40.0	25	100
6 months	IT-Dex group	22	88.0	3	12.0	25	100
	ST group	12	48.0	13	52.0	25	100
	IV-Dex group	14	56.0	11	44.0	25	100

Abs. – absolute value.

Table 3. Treatment results at different time points after the beginning of the therapy.

Groups	Time after the beginning of the therapy	Total		Complete recovery		Partial recovery		Improve ment		Without changes		Decrement	
		Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
IT-Dex	1 month	25	100	6	24.0	6	24.0	5	20.0	8	32.0	0	0.0
ST		25	100	5	20.0	3	12.0	4	16.0	12	48.0	1	4.0
IV-Dex		25	100	5	20.0	4	16.0	6	24.0	10	40.0	0	0.0
IT-Dex	6 months	25	100	15	60.0	5	20.0	2	8.0	3	12.0	0	0.0
ST		25	100	5	20.0	3	12.0	4	16.0	12	48.0	1	4.0
IV-Dex		25	100	5	20.0	4	16.0	5	20.0	11	44.0	0	0.0

Abs. – absolute value.

Six months after the treatment beginning the following results were obtained:

1. Differences of complete recoveries rates between groups were significant (χ^2 , $p < 0.05$).
2. Differences of complete recoveries rates between IT-Dex group and ST group were significant (χ^2 , $p < 0.05$).
3. Differences of complete recoveries rates between IT-Dex group and IV-Dex group were significant (χ^2 , $p < 0.05$).
4. No significant differences of complete recoveries rates were seen between ST and IV-Dex groups.

Thus, 6 months after the beginning of the therapy the highest efficacy was observed in the group of patients treated with IT steroids (the maximal rate of complete and partial recoveries and of hearing improvements) compared to the group of patients who had received standard therapy and only systemic steroid therapy. The number of patients with complete recovery in the IT group was significantly more than in the two other groups 6 months after the treatment beginning (Fig. 1).

Moreover, the effect of the therapy on different frequencies (low, middle and high) was evaluated. Frequency range of 125 and 250 Hz was defined as low frequencies; 500, 1.000, 2.000 Hz – as medium

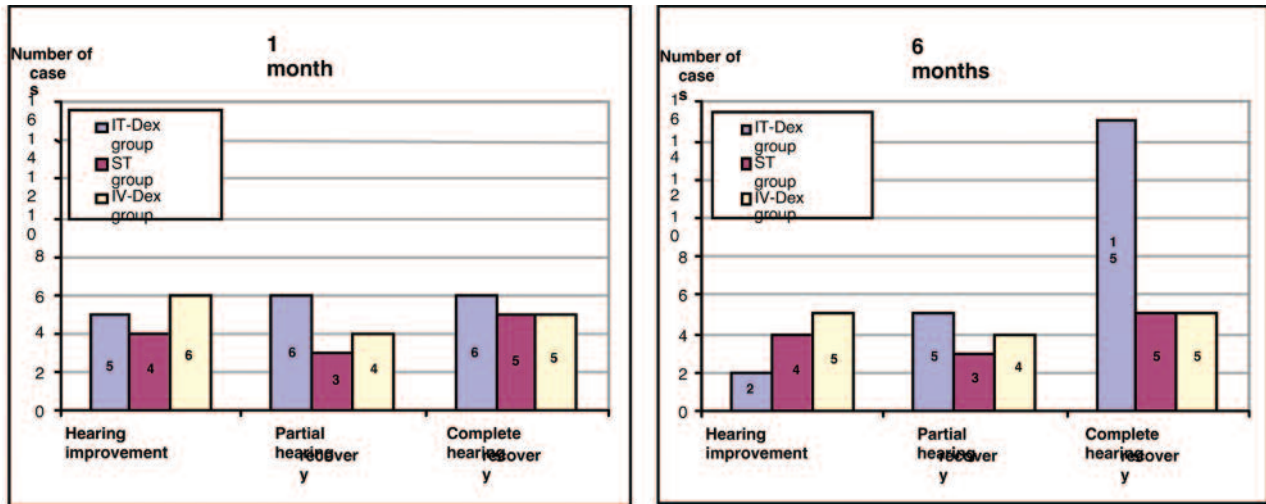


Figure 1. Treatment response 1 and 6 months after the beginning of the therapy.

frequencies and 4000, 8000 Hz – as high frequencies. Pure tone averages on low frequencies (PTA_{LF}), medium frequencies (PTA_{MF}), high frequencies (PTA_{HF})

and on all the frequencies being studied (PTA_{ALL}) before and at different moments after treatment beginning are presented in the Table 4.

Table 4. Hearing changes at different periods within different frequency ranges.

Measurement time	IT-Dex group				ST group				IV-Dex group			
	PTA_{ALL} $\pm \sigma$, dB	PTA_{LF} $\pm \sigma$, dB	PTA_{MF} $\pm \sigma$, dB	PTA_{HF} $\pm \sigma$, dB	PTA_{ALL} $\pm \sigma$, dB	PTA_{LF} $\pm \sigma$, dB	PTA_{MF} $\pm \sigma$, dB	PTA_{HF} $\pm \sigma$, dB	PTA_{ALL} $\pm \sigma$, dB	PTA_{LF} $\pm \sigma$, dB	PTA_{MF} $\pm \sigma$, dB	PTA_{HF} $\pm \sigma$, dB
Before the treatment	41.0 ± 12.9	35.1 ± 19.6	38.5 ± 16.1	50.1 ± 15.0	37.1 ± 16.7	32.9 ± 22.0	35.2 ± 17.0	44.3 ± 18.4	39.1 ± 17.0	33.1 ± 21.3	38.4 ± 22.0	45.8 ± 18.5
1 month after	25.1 ± 12.2	21.3 ± 12.1	31.1 ± 12.2	27.7 ± 17.3	24.6 ± 17.0	23.4 ± 18.6	25.7 ± 17.2	35.5 ± 20.2	24.8 ± 15.3	19.6 ± 13.4	23.3 ± 17.5	32.5 ± 21.5
6 months after	16.1 ± 8.5	11.5 ± 6.2	14.9 ± 9.6	23.0 ± 13.4	28.0 ± 17.0	24.1 ± 18.8	25.4 ± 17.4	36.2 ± 20.0	25.1 ± 15.3	20.2 ± 13.6	32.7 ± 17.5	23.3 ± 21.5

PTA_{ALL} – pure tone average on all the frequencies;

PTA_{LF} - pure tone average on low frequencies;

PTA_{MF} - pure tone average on medium frequencies;

PTA_{HF} - pure tone average on high frequencies.

The PTA_{ALL} decrease in the different phases of treatment is presented in the Table 5. In the IT-Dex group the maximal effect was observed 10 days after the beginning of the treatment. The PTA_{ALL} decrease 10 days after the therapy's beginning and later (1, 3 and 6 months after) in comparison with the initial hearing

level was significant ($p < 0.05$). The PTA_{ALL} decrease 6 months after the treatment's beginning compared to the PTA_{ALL} one month after the treatment beginning was also significant ($p < 0.05$). The maximal effect in the ST group was also observed 10 days after the beginning of the treatment. The following changes of

PTA_{ALL} during the period from the 10th day to the 6th month of therapy were not significant. In the IV-Dex group, as well as in the ST group, the maximal effect was observed 10 days after the beginning of the treatment and the following changes of PTA_{ALL} during the period from the 10th day to the 6th month of therapy were not significant.

Thus, in the IT-Dex group improvement was registered during all the treatment (6 months), whereas in the two other groups patients had an improvement only during the first 10 days of the therapy (Fig. 2).

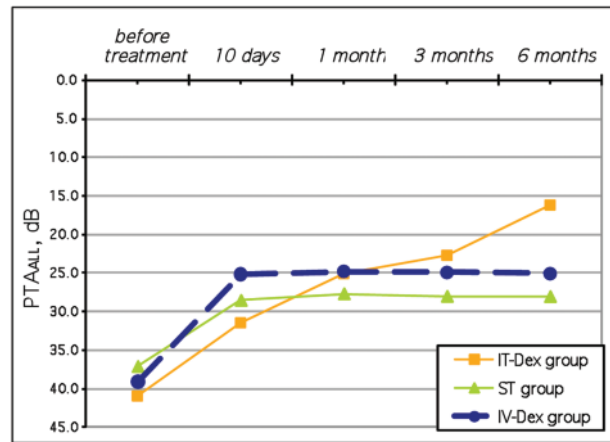


Figure 2. Hearing changes in 3 groups during 6 months.

Table 5. PTA_{ALL} dynamics at different stages of the treatment

Time after the treatment beginning	Δ PTAALL IT-Dex, dB	p	Δ PTAALL ST, dB	p	Δ PTAALL IV -Dex, dB	p
0 - 10 days	9.5 ± 2.94	< 0.05	8.5 ± 2.74	< 0.05	14.0 ± 3.58	< 0.05
10 days - 1 month	6.4 ± 1.85	< 0.05	0.5 ± 0.52	> 0.05	0.1 ± 0.21	> 0.05
1 month - 3 months	2.4 ± 1.25	> 0.05				
3 – 6 months	6.5 ± 2.40	< 0.05				
All the period of treatment (0 – 6 months)	24.8 ± 5.83	< 0.05	9.0 ± 3.02	< 0.05	14.0 ± 3.58	< 0.05

PTA_{ALL} – pure tone average on all the frequencies

Treatment results for the three groups consisting of the decreasing of PTA on low, medium and high frequen-

cies, as well as on all the frequencies in whole, are presented in the Table 6.

Table 6. The difference of average hearing levels (Δ PTA) within different frequency ranges.

Frequency ranges, Hz	Groups	Δ PTA (before the treatment – 1 month after), dB	Δ PTA (before the treatment – 6 months after), dB	Initial hearing level (PTA), dB
125 – 250	IT-Dex group	10.5 ± 4.37	23.6 ± 6.63	35.1 ± 19.6
	ST group	9.5 ± 3.59	8.8 ± 3.47	32.9 ± 22.0
	IV-Dex group	13.5 ± 4.21	12.9 ± 4.11	33.1 ± 21.3
	p	> 0.05	< 0.05	> 0.05
500 - 2,000	IT-Dex group	17.2 ± 4.79	23.7 ± 5.88	38.5 ± 16.1
	ST group	9.5 ± 3.35	9.8 ± 3.42	35.2 ± 17.0
	IV-Dex group	15.1 ± 3.97	15.1 ± 4.02	38.4 ± 22.0
	p	> 0.05	< 0.05	> 0.05
4,000 - 8,000	IT-Dex group	19.0 ± 5.53	27.1 ± 6.66	50.1 ± 15.0
	ST group	8.8 ± 2.88	8.0 ± 2.68	44.3 ± 18.4
	IV-Dex group	13.1 ± 3.34	13.1 ± 3.40	45.8 ± 18.5
	p	< 0.05	< 0.05	> 0.05
125 - 8,000	IT-Dex group	15.9 ± 4.38	24.8 ± 5.83	41.0 ± 12.9
	ST group	9.4 ± 3.08	9.0 ± 3.02	37.1 ± 16.7
	IV-Dex group	14.3 ± 3.62	14.0 ± 3.58	39.1 ± 17.0
	p	> 0.05	< 0.05	> 0.05

The analysis of variance was used to evaluate the significance of the differences of therapy efficacy within different frequency ranges in three groups 1 and 6 months after the treatment's beginning. It was found that 1 month later there were significant differences between groups over the high-frequency range only, whereas 6 months after – on all frequencies ($p < 0.05$). Further analysis demonstrated that this difference over the high-frequency range 1 month after the treatment's beginning was due to a more expressed effect ($p < 0.05$) in the IT-Dex group compared to the ST group. Differences between the ST and IV-Dex groups were not significant (Fig. 3).

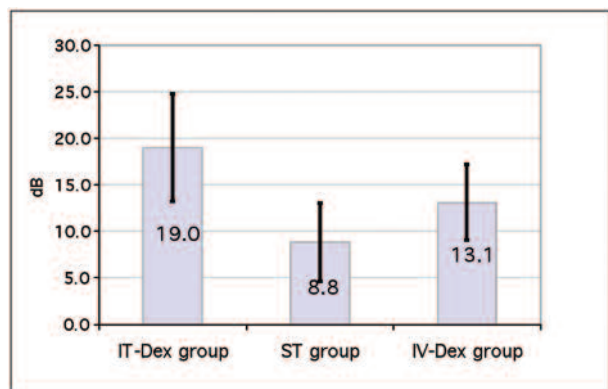


Figure 3. Changes of PTAHF ($\Delta\text{PTA}_{\text{HF}}$) 1 month after the treatment beginning in 3 groups..

At the same time, 6 months after the treatment's beginning the PTA changes in the IT-Dex group were more noticeable than in the ST and IV-Dex groups within the high-frequency range and on all frequencies overall ($p < 0.05$). No significant differences in PTA changes on all frequencies separately and in total between ST and IV-Dex groups were found ($p > 0.05$).

Thus, after 1 month of therapy, differences between groups were valid only for high frequencies because of a significantly greater efficacy in the IT-Dex group compared to the ST group. Six months after the IT-Dex group demonstrated a better effectiveness over the high-frequency range and on all frequencies in total compared to the two other groups. These last-mentioned didn't differ from each other for all criteria.

Evaluation of factors associated with therapy efficacy.

The association of the treatment efficacy with patient's age, degree of hearing loss, time on commencement of therapy and vertigo was evaluated.

Vertigo and hearing loss degree were not associated with the therapy efficacy. Patient's age and the time between the onset of SSHNL and the beginning of the therapy seemed to influence the effectiveness of the treatment. The rate of complete recovery was less in patients older than 35 years old and with time between the onset and the beginning of the treatment more than 7 days.

Discussion

Our study demonstrated an identical treatment efficacy of the IT and IV administration of steroids and the standard therapy 1 month after the treatment's beginning. Despite the absence of differences in one-month therapy efficacy between groups, the analysis of the method impact on different frequencies revealed a better effectiveness of IT administered steroid on high frequencies compared with standard therapy. Salt and Plontke postulated that agents, delivered to the RWM locally, were not regularly distributed in the inner ear, but demonstrated a base-to-apex gradient of concentration, so that basal parts of the cochlea received far bigger medicine concentrations than apical parts [15]. This fact seems to explain the greater efficacy of IT steroids over the high-frequency range.

Patients who were treated with IT steroids demonstrated an improvement (PTA decrease on all frequencies) during the whole treatment period, contrary to those from the 2 other groups, treated systemically, who were improving only during the first 10 days of the therapy. These data let us suppose a potential possibility of hearing improvement resulting from a longer course of treatment. The length of treatment with systemic steroids is limited because of their side effects. Probably, there are 2 possible reasons of the highest efficacy of administration of IT Dex 10 days after the beginning of the therapy. First, there is a chance of spontaneous hearing recovery, which is more likely to happen within 2 weeks from the onset. Second, hearing level might be restored better during the early period of the disease.

Many studies indicate that spontaneous recovery occurs in 30-65% of cases [1, 16-20]. Generally, the recovery happens within the first two weeks after the disease onset [16]. Zhao et al. claim that the treatment which was started within 2 weeks after the onset is more effective than the one 2 weeks after the onset and later [21].

The absence of positive response after 10 days of therapy (1, 3, 6 days after) in the groups of patients treated with systemic steroids over 10 days argues for the absence of spontaneous recovery in the later time. This fact confirms once more the exceptional influence of the local therapy on the period of treatment. Due to the significant differences of PTAALL, obtained in our study (on the 10th day of therapy comparing with 1 month after its beginning, as well as 1 month after comparing with 6 months after), long-term IT administration of steroids is better justified.

According to our data, in the IT-Dex group the efficacy of the treatment was more significant than in the ST and IV-Dex groups 6 months after the beginning of the therapy. This is illustrated by the number of complete and partial recoveries and hearing improvements. Furthermore, the rate of complete recoveries 6 months after the treatment's beginning was higher for local therapy than for standard and systemic steroid therapy. This is also a proof of the capacity of hearing restoration after a longer course of treatment.

The chance of hearing improvement at the later times of therapy has been demonstrated by many authors, pointing the effectiveness of IT administration of steroids after an earlier inefficient systemic therapy [13, 22-28].

Keeping in mind all these data we consider further investigations of the IT steroid administration as a supplementary method in case of inefficiency or partial effect of standard or systemic steroid treatment to be reasonable.

Our results demonstrate equal efficiency of therapy for all the 3 protocols 1 month after the treatment beginning allows us to confirm the IT administration of steroids as an independent treatment mode. Generally, it concerns patients having contraindications against the systemic steroid therapy. Similar data were received by Peng et al. They found that patients with hearing loss less than 70 dB showed no difference between the effectiveness of local and systemic steroid application, whereas those patients who had hearing loss more than 70 dB showed a better response to the local therapy [29]. In our study only one patient from IT-Dex group had a hearing loss more than 70 dB. Kakehata et al. obtained results differing from our data: they described a higher efficacy of local

steroid treatment over 8 days compared to systemic steroid therapy in patients with diabetes [30].

We couldn't set an optimal duration of local treatment in our study, because the obtained data (improvement during all the period of treatment – 6 months, and different number of patients with complete hearing recovery at different moments of treatment) show that this duration is individual for each patient.

Therefore, it might be reasonable to continue the treatment as long as an improvement is observed, for example, until obtaining 2 same audiograms spaced a month apart, hearing survey being done monthly.

Also, optimal dosage of steroids for IT administration has never been precisely estimated, as well as treatment protocols for local steroid application have not yet been designed. It is possible that increasing the dosage and more frequent injections of the medicament could reduce the treatment duration.

No serious side effects related to systemic administration of steroids were observed in our study. 9 patients in ST group and 12 patients in IV-Dex group complained of sleep loss, which was completely corrected after withdrawal. No systemic adverse effects related to IT application of steroids were noticed. In one case an acute suppurative otitis media was developed that was eliminated by local antibacterial therapy. This patient was excluded from the study. There were no residual perforations of MT, all patients demonstrated a complete healing of MT after the tympanostomy tube removal.

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