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Hearing changes after intratympanically applied steroids for primary therapy of sudden hearing loss: a meta-analysis using mathematical simulations of drug delivery protocols

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Abstract

Objective—Controlled and uncontrolled studies with primary intratympanic (IT) or combined intratympanic and systemic application of glucocorticosteroids for idiopathic sudden hearing loss (ISSHL) were analyzed by means of a meta-analysis in an attempt to establish optimal local drug delivery protocols.

Study Design—A total of 25 studies with 28 treatment groups between January 2000 and June 2014 were selected that adequately described drug delivery protocols. Cochlear drug levels were calculated by a validated computer model of drug dispersion in the inner ear fluids based on the concentration and volume of glucocorticoids applied, the time the drug remained in the middle ear, and on the specific timing of injections. Various factors were compared with hearing outcome, including baseline data, individual parameters of the application protocols, calculated peak concentration (C_{max}), and total dose (Area under the curve, AUC).

Results—There was no dependence of hearing outcome on individual parameters of the application protocol, C_{max} or AUC. Final hearing threshold was notably independent of delay of treatment.

Conclusion—During primary IT or combined steroid therapy of ISSHL, the tendency towards early treatment having a positive effect on hearing improvement is thought to be a “sham effect”, likely related to spontaneous recovery. Change in pure tone average (PTA) may not be an adequate outcome parameter to assess effectiveness of the intervention, as it depends on the degree of initial hearing loss. Final PTA provides a better alternative.

Keywords

computer model; intratympanic; meta-analysis; pharmacokinetics; steroids; sudden hearing loss

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Introduction

There is an increasing interest in the use of local drug therapy to treat inner ear diseases. Following the wide acceptance of intratympanic applications of gentamicin for the treatment of Menière's disease, intratympanically applied glucocorticosteroids ("steroids") have become commonly-applied drugs for the therapy of patients with either Menière's disease or idiopathic sudden sensorineural hearing loss (ISSHL) (1–4). Drug application protocols and the choice of steroid vary considerably between studies. Variations in parameters such as the applied drug concentration, the applied volume and timing of injections with different treatment protocols makes it difficult to directly compare the outcome in studies, especially with respect to the actual dose of steroid delivered (2).

The aim of this meta-analysis was to quantitatively compare different dosing regimens, application protocols and steroids used. Therefore, baseline data (e.g. initial hearing loss, start of therapy and age), and specific parameters of the treatment protocols, including the applied concentration, volume, number and frequency of injections etc., were correlated with the reported hearing outcome of the studies. A similar approach was successfully used to interpret human studies of intratympanic gentamicin treatment for Menière's disease using a wide variety of dosing protocols (5). In that study, larger hearing losses were associated with protocols producing the highest estimated perilymph gentamicin concentrations.

To assess the impact of differences in application protocols on inner ear drug concentration, the maximum intracochlear drug concentration (C_{max}) and total dose over the duration of treatment (AUC) were calculated with a validated computer simulation program for intracochlear drug distribution. The simulations were based on the specific application protocols in published controlled and uncontrolled clinical studies, with model parameters based on pharmacokinetic data derived from experiments in animals and from clinical studies. The calculated doses were compared to the mean change in hearing thresholds reported in the respective studies.

Here we discuss results of studies on primary intratympanic or combined therapy of ISSHL. A separate analysis will focus on clinical studies with intratympanic steroids used as secondary therapy for ISSHL.

Methods

Data Sources and Study Selection

The databases PubMed and GoogleScholar were searched for clinical studies on intratympanic or combined (intratympanic and systemic) steroid treatment for ISSHL as a primary therapy. Prospective and retrospective, randomized and non-randomized, controlled and non-controlled studies were included. Only treatment groups including single injection or continuous application, e.g. via a round-window-catheter were considered. Studies using the MicroWick for drug delivery were not included, as currently available pharmacokinetic details of this drug delivery system e.g. contact time of drug with the round window membrane, are insufficient for reliable simulation of the procedure.

Further inclusion criteria were: 1) IT dexamethasone or methylprednisolone used (since pharmacokinetic data were only available for these two drugs), 2) mean hearing loss (pure tone average, PTA) before start of local treatment ≥ 90 dB HL in order to exclude patient populations with only profound hearing loss, and 3) delay between onset of ISSHL and start of treatment ≥ 5 weeks (35 days).

Published studies between January 2000 and June 2014 were selected based on detailed description of treatment protocols with respect to drug concentration, application time, dosing regimen (i.e. start, number and time intervals of treatment), and outcome parameters (change of hearing thresholds between before and after treatment, PTA hearing gain) permitting analysis with the computer model. If relevant information was not provided in the publications, the authors were contacted.

Calculation of inner ear drug distribution

A validated computer model of drug distribution in the inner ear fluids (Washington University Cochlear Fluids Simulator, Version 3.082, http://oto2.wustl.edu/cochlea/) was used to calculate the distribution of steroids with time in the perilymph of scala tympani for different application protocols.

Parameter settings

The computer model takes into account the length and variation of cross-sectional areas of the fluid and tissue spaces of the cochlear and vestibular spaces of the human inner ear. The compartments included in the model (with total volume given in μL) are scala tympani (40.5), scala media (7.7), scala vestibuli (including the vestibule) (84.9), spiral ligament (16.5), spiral ganglion (10.3) and the organ of Corti (2.3). Each was derived from 3D reconstruction of a segmented human inner specimen obtained by non-destructive OPFOS imaging (6).

Cochlear drug levels were calculated based on the applied drug (methylprednisolone; diffusion coefficient $0.784 * 10^{-9}$ m^2/s (7) or dexamethasone phosphate; diffusion coefficient $0.77 * 10^{-9}$ m^2/s (8)), the concentration and volume of steroids applied, the time the drug remained in the middle ear, and on the specific timing of injections, i.e. intervals and total number. For intratympanic injections, it was assumed that middle ear concentration was constant and did not vary with time, as application times were brief. Similarly, the co-administration of the drug in hyaluronic acid gel was ignored as the quantitative influence on round window permeability and middle ear residence time is currently unknown, so no modifications in the simulations were made relative to normal injections. No entry location other than the round window was used even though significant entry at the stapes occurs for other substances (9,10). Direct entry of steroids at the stapes has not yet been demonstrated or quantified. Since there is only very limited data on steroid concentrations in the inner ear fluids after systemic application, calculations are based only on the local drug application protocols and do not include estimates of perilymph concentrations resulting for systemic drug application.

Pharmacokinetic parameters used for the simulations were: Round window membrane permeability: Methylprednisolone: $7.8 * 10^{-9}$ m/s (7), dexamethasone: $50 * 10^{-9}$ m/s (11),

perilymph elimination half time: Methylprednisolone: 27 min (7), dexamethasone: 22.5 min (12), and flow rate of cerebrospinal fluid entering at the cochlear aqueduct: 3 nl/min (12).

Drug time courses were quantified in terms of the maximum concentration (C_{max}) and the area under the curve (AUC) of the drug in the 4 kHz – 500 Hz cochlear segment, calculated as 8.6 mm − 20.3 mm along scala tympani measured from base (13). This refers to the frequency range pure tone average measures are typically based on ($PTA_{0.5\text{-}4kHz}$).

In each case, a 24h time period after the start of injection was simulated. Distances furthest from the application site follow the slowest time courses and are most susceptible to drug accumulation with repeated applications. If C_{max} at the apical turn was less than 1/1000 of scala tympani maximum concentration in a 24h period it was assumed that the drug was completely eliminated during this period. Since time intervals between two injections in the treatment protocols evaluated were at least one day, a relevant drug accumulation effect could thus be ruled out. While C_{max} remained the same for multiple injections, total dose (AUC) in perilymph was calculated by multiplying the AUC for a single injection by the number of injections.

Statistical evaluation

Perilymph concentration and dose in the cochlea (C_{max} and AUC), parameters of the delivery protocol, and demographic data were compared with changes of hearing thresholds (PTA hearing gain) and final outcome (Final PTA). For statistical evaluation (linear regression analysis), the software GraphPad Prism 5.02 (GraphPad Software, La Jolla, USA) was used.

Results

Twenty-five studies with 28 treatment groups for a total of 1275 patients were included in the meta-analysis (figure 1). Characteristics, extracted parameters of the application protocols, and calculated drug concentrations are listed in tables 1 and 2.

The upper part of figure 2 shows calculated time courses of drug concentration in the scala tympani over 24 hours after injection for five different protocols. Higher drug concentrations used for injection resulted in higher perilymph concentrations. Due to the fast clearance half time of dexamethasone in the inner ear of 22.5 minutes, concentrations declined rapidly within few hours. There was relatively little influence of application time on the concentrations reached, as the differences between protocols were small. In contrast, continuous intratympanic drug application using pumps was calculated to result in much higher inner ear drug concentrations.

The lower part of figure 2 shows the time course over the total duration of the therapy protocol for two different injection schemes. Since the drug is almost completely eliminated within 24 hours after a single injection (figure 2) the time courses suggest that there is no accumulation of drug after multiple injections.

For primary intratympanic or combined therapy of ISSHL there was no dependence of change in hearing threshold on the drug concentration used (figure 3a, 3b), the number of

injections (figure 3c), the frequency of injections (figure 3d), the estimated time of drug in the middle ear (time provided in the publications where the patient had to lay down on the contralateral side before standing up) (figure 3e), the total duration of treatment (figure 3f), the age of patients (figure 3g), or on the time of the endpoint measurement (figure 3h). Neither the hearing change (PTA hearing gain) nor the average final hearing threshold (final PTA, data not shown) individually depended on parameters of the application protocol or demographic factors.

There was no dependency of simulated maximum drug concentration (C_{max}) and total drug dose (AUC) in the cochlea on hearing outcome for either dexamethasone (figure 4a, 4b) or methylprednisolone (figure 4c, 4d).

There was a tendency (statistically not significant) for larger hearing gain with earlier start of treatment after onset of ISSHL (figure 5a). However, this tendency was not present when “final PTA” was chosen as outcome parameter (figure 5c).

A strong correlation was found between hearing loss before treatment and change of hearing threshold (R^2=0.46, p=0.0001, figure 5b) but not between hearing loss before treatment and final PTA (figure 5d).

There was a correlation between the delay of starting treatment after onset of ISSHL and hearing loss at the beginning of treatment (R^2=0.19, p=0.029, figure 6).

Discussion

Individual parameters of the different treatment protocols failed to show an influence on recovery of hearing (figure 3). Calculations of drug concentrations in the inner ear (C_{max} or total dose AUC), with a validated computer model using the specific individual parameters of the respective treatment protocols, showed no effect on hearing outcome across studies (figure 4).

There are a number of possible explanations of these findings, as follows: (i) the drug concentrations and total doses reached in the inner ear after intratympanic application in the human may be insufficient (too low) for the treatment of ISSHL; (ii) the dosing regime may have no influence on treatment success so that all treatment protocols are equally effective/ineffective; (iii) the effects of different treatment protocols may be masked by differing patient backrounds across the studies and/or statistical effects due to averaged baseline parameters and averaged outcome results rather than individual patient data, (iv) effects may be masked by a dominance of spontaneous recovery in the patient populations, (v) the patient numbers may not be high enough to detect small changes with statistical significance and thus small effects with respect to treatment parameters and/or (vi) steroid therapy may be ineffective for treating ISSHL.

The concentration of the steroids dexamethasone and methylprednisolone that could potentially influence cochlear function can be estimated from a variety of studies in the literature. One study based on the activation kinetics of the signal cascades in the glucocorticoid receptor and mineralocorticoid receptor (table 3) suggest that the calculated

intracochlear drug concentrations achieved by the evaluated treatment protocols could induce drug mediated changes in inner ear tissue (14). An in vivo study on a cochlear implant electrode insertion trauma (EIT) model using an electrode dummy as delivery device for dexamethasone demonstrated that alterations in gene expression induced by the insertion trauma were reduced in comparison to a control group with electrode dummies implanted without incorporated dexamethasone (15). In this study an inner ear dexamethasone steady state concentration of 0.1 μg/ml was achieved in the scala tympani (15,16). In another study using a similar dummy and EIT animal model a down regulation of TNF-a in cochlear tissue was shown in comparison to control group (17).

In vitro studies show that dexamethasone concentrations of 0.04 ug/ml were required to modulate ion transport in epithelium of cochlea scalae (18,19) and dexamethasone concentrations of 0.01 μg/ml are needed to impede fibroblast growth (20,21). It was demonstrated in vivo that a dexamethasone concentration of both 0.1 μg/ml and 0.05 μg/ml stable over several weeks reduces fibrosis after EIT and protects hair cells and neural elements in the cochlea in comparison to a control group (22) (Liebau, unpublished data). The same study also could show that a drug concentration of 0.0006 μg/ml leads to an incomplete protection of hair cells and neural elements under equal EIT conditions (22) (Liebau et al., unpublished data). However a reduced protective effect against apoptosis was still present in comparison to control group (22).

For effective immune suppression dexamethasone concentrations above 0.018 μg/ml is thought to be necessary and for methylprednisolone it is 0.051 μg/ml (23). It was demonstrated that an electrode dummy loaded with dexamethasone achieving an inner ear steady state drug concentration of 0.1 μg/ml in the scala tympani was effective to significantly reduce lymphocyte, macrophage, and giant cell infiltration into the cochlea after EIT (16,24).

It is therefore possible that drug concentrations achieved in the PTA range (0.5 – 4 kHz; 8.6 to 20.3 mm from the base of scala tympani) by intratympanic injection may be too low to ensure the biological changes needed for therapeutic success. It is believed that there are much higher drug levels present after intratympanic injections in the basal region of the cochlea, corresponding to the high frequency range (25,26). However, hearing recovery is reported to be the lowest in the high frequency range after ISSHL (27–31).

In our meta-analysis on secondary treatment of ISSHL simulations of application protocols using the round window catheter showed constant drug concentrations above 0.36 μg/ml in the $PTA_{(0.5–4kHz)}$ range for dexamethasone as well as methylprednisolone for the whole duration of treatment. Nevertheless we did not find a higher hearing recovery in patients of studies using the round window catheter in comparison to studies using intratympanic injections for application.

Bird and colleges measured the intra cochlear dexamethasone concentration after 70 minutes after systemic application (iv, 0.17 mg/kg) by sampling the first 20 μl perilymph through the round window and found on average a concentration of 0.12 μg/ml in 9 patients (26). If it is assumed there is a homogenous drug concentration in the scala tympani after systemic

application therefore the determined concentration is also representative for the $PTA_{(0.5–4kHz)}$ range (25). Combined application protocols may have produced higher drug levels in the inner ear, however the treatment success in study groups with combined therapy is not superior to study groups with intratympanic injection only (figure 4).

We found that there was no influence of the age of patients on hearing outcome (figure 3g). In prior studies, however, multivariable statistical analysis suggested that increasing age slightly worsened the prognosis for hearing recovery (32–34). Some authors have stated that the highest incidence for ISSHL is around an age of 50 years (35,36). This appears to be merely a statistical effect based on todays life expectancy in industrial countries of about 80 years and the fact that young people (<20 years) are rarely affected by ISSHL. The mean of the remaining range is about 50 years, but cases of ISSHL are distributed throughout this age spectrum (37,38).

The importance of baseline data for the evaluation of treatment success is demonstrated by the strong correlation between hearing improvement and hearing loss before treatment (figure 5b). While hearing improvement (PTA change) significantly correlated with hearing loss before treatment, final PTA was nearly independent on hearing loss before treatment (figure 5b, 5d). Therefore the correlation of higher hearing improvement with higher hearing loss before treatment may only reflects the greater potential of improving in patients with more pronounced hearing loss. There was also a tendency (not significant) for larger hearing gain, i.e. larger change in PTA with earlier onset of treatment (figure 5a). This is in correspondence with arguments often used in communication of doctors with patients when they suggest to start a therapy as soon as possible to get the greatest benefit from the treatment (39–42). However, such an argument appears not to be supported by the present data. The tendency for an apparently better outcome disappeared if instead of „hearing gain“, „final PTA“ was used as an outcome criterion (figure 5c). In addition, a significant correlation across studies was found for an earlier start of therapy in studies with higher initial hearing loss (R^2=0.12, p=0.029, figure 6), and hearing gain also significantly correlated with initial hearing loss (figure 5b). We therefore consider the tendency towards a positive effect of early treatment on hearing gain during therapy as a “sham effect”, which is most likely due to spontaneous recovery and not due to the time point of the start of the intervention.

The shorter the delay between onset of ISSHL and measuring PTA before treatment (reference PTA), the higher is the proportion of hearing gain due to spontaneous recovery that is contributing to the treatment success. This influence is greatest when therapy is initiated within the first two weeks after onset since in most patients showing some degree of spontaneous recovery the largest proportion of hearing gain occurs during this time period (35,36,43,44). Additionally, within this time period the influence of spontaneous recovery is increasing in a nearly exponential way (figure 5a). In most patients hearing gain due to spontaneous recovery follows a time course of exponential decrease (45,46).

Figure 7 demonstrates that larger hearing loss at start of therapy is compensated with higher hearing gain. This effect is most likely due to spontaneous recovery. Similar final hearing levels are reached in all groups independent of treatment protocol, although there is a

tendency for a poorer prognosis with larger hearing loss before treatment. In figure 2 of their 1977 publication, Mattox and Simmons already have shown on a frequency specific manner that a similar final PTA was reached regardless of hearing loss before treatment and type of treatment. Patients attained higher gain in low frequencies and lesser gain in high frequencies resulting in similar final audiograms independent on initial audiograms but only when considering averaged audiograms in a considerably large patient group (98 patients), compared to many of the currently published uncontrolled or retrospective controlled reports (43).

A number of clinical studies have noticed that patients with profound hearing loss (80 – 120 dB HL) have a very poor prognosis (35,47–50). It seems, that there exists a “boundary” between approximately 80 and 90 dB HL were hearing loss is less likely compensated by recovery and prognosis gets significantly worse. Most patients belonging to this group have “flat” with pancochlear hearing loss or show a profound high frequency loss. It has been described on many occasions that “flat” audiograms have the poorest prognosis and patients with profound high frequency loss often reach only small amounts of recovery (37,43,50). Another negative prognostic factor especially in the latter ones seems to be associated vertigo (43,51–53).

The lack of any correlation between specific parameters of the treatment protocol or calculations of C_{max} and dose (AUC) and hearing outcome, i.e. the absence of a clear dose-effect relationship, may call into question the efficacy of intratympanic steroid therapy for the primary therapy of ISSHL.

We did not include systemically applied steroids in combined therapy strategies in our calculation of inner ear drug concentration and doses (C_{max} an AUC). We also did not consider other additionally used substances or treatments (e.g. vitamins, hyperbaric oxygen therapy). Nonetheless, since we found a similar final PTA across the groups, there seems to be no clear impact of treatment protocol on the treatment success.

Limitations of the present meta-analysis arise from the limitations of the published data in studies on ISSHL treatment.

Firstly, no uniform scheme for audiological evaluation was used across the studies (i.e. PTA frequencies, time points of measurements). This could distort objective evaluation of hearing outcome in patients and make it difficult to compare them especially when having different types of hearing loss. Standardization of outcome parameters are needed for a better comparability between studies (38).

Secondly, as the hearing gain seems to strongly depend on hearing levels at the beginning of the therapy, final hearing might be considered as a better, more robust outcome measure when comparing studies in meta-analysis.

Thirdly, to avoid “smoothing out” of treatment effects by averaging outcome data, we encourage authors to publish outcome data for individual patients. Such data were only available in very few publications. For more detailed analyses of treatment effects it is of utmost importance to have individual patient data available with different degrees or

different types of hearing loss. Impact of patient background on treatment success, such as patient's age, treatment delay or associated symptoms like vertigo can only be analyzed in an advanced way if the individual attribution to specific patients is not lost by averaging data. Some studies performed multivariable statistical analysis to filter out important factors influencing the prognosis. However, we think it would help advance the field to also have individual patient data available for meta-analyses (34,54–58). Even in times of continuing efforts of cost reductions for print publication, publishers need to understand the importance of providing individual patient data, at least in the form of supplementary digital materia

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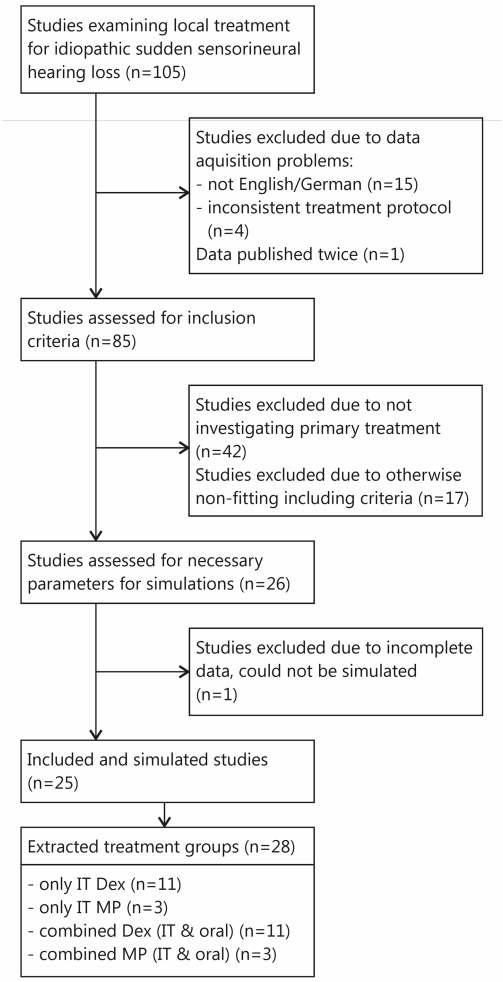

Figure 1.

Flowchart summarizing the selection of studies included in the current analysis. IT=intratympanic, Dex = dexamethasone, MP = methylprednisolone.

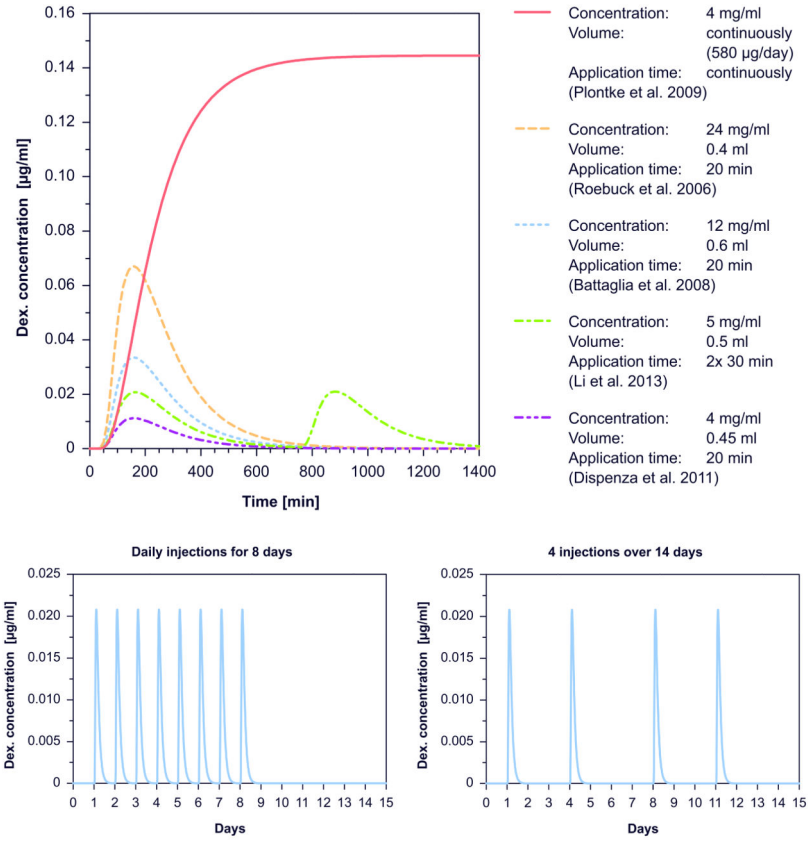

Figure 2.

Upper part Examples for time courses of calculated drug concentrations in scala tympani in the 500 – 4000 Hz region after injection for different application protocols according to Dispenza et al. 2011 (55), Li et al. 2013 (78), Battaglia et al. 2008 (62), Roebuck et al. 2006 (79), and Plontke et al. 2009 (80) respectively. **Lower part:** Example time courses of calculated drug concentrations in scala tympani in the 500 – 4000 Hz region over the total duration of treatment for different treatment protocols: **Left:** daily injections for 8 days, 5 mg/ml, 0.35 ml, for 30 min application time according to Hong et al. 2009 (68). **Right:** 4 injections over 14 days, 5 mg/ml, 0.55 ml, for 30 min application time according to Bae et al. 2013 (54).

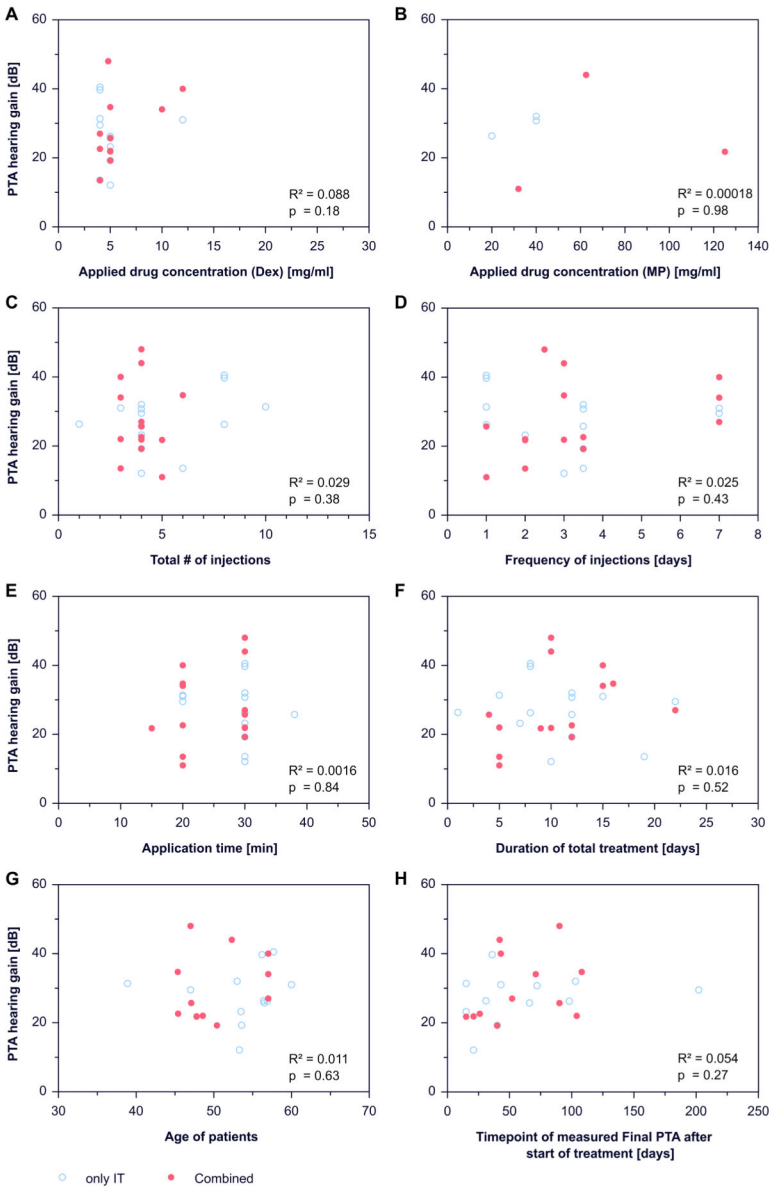

Figure 3.

Dependence of change in pure tone average (PTA hearing gain) on: (a) use of dexamethasone formulation for injection, (b) use of methylprednisolone formulation for injection, (c) total number of injections, (d) frequency of injections, (e) application time of the injection, (f) duration of treatment, (g) age of patients and (h) time of endpoint measurement.

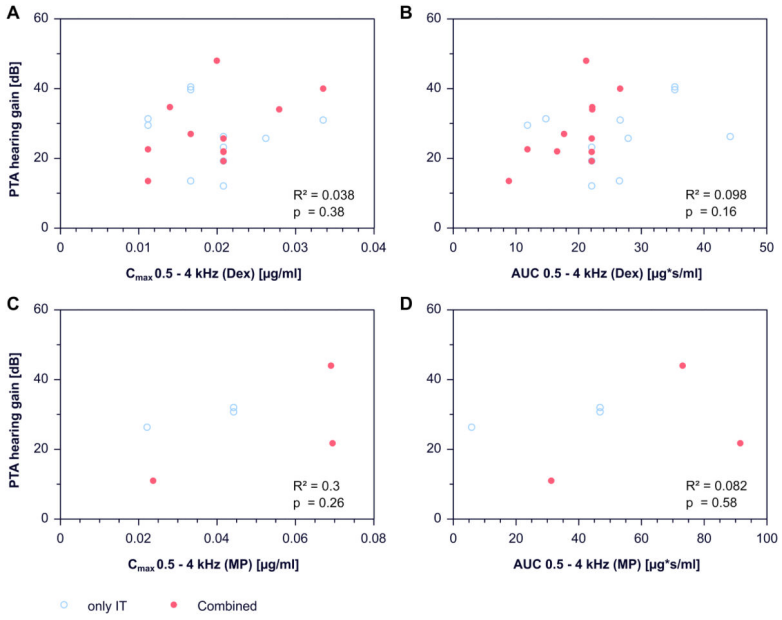

Figure 4.

Dependence of change in pure tone average (PTA hearing gain) on the calculated maximum intra-cochlear drug concentrations (C_{max}) or total doses (AUC) in the scala tympani within the 500 – 4000 Hz region for dexamethasone and methylprednisolone: (a) dexamethasone C_{max}, (b) dexamethasone AUC, (c) methylprednisolone C_{max}, (d) methylprednisolone AUC .

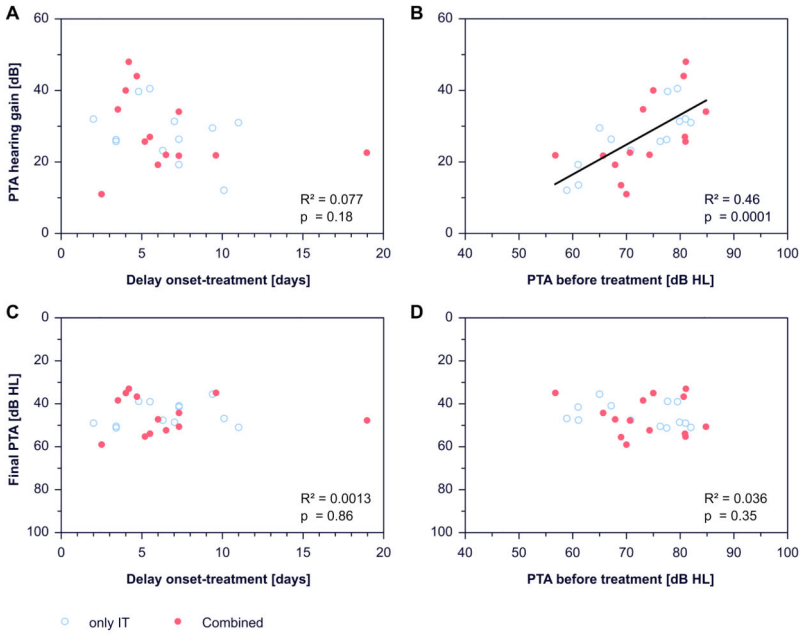

Figure 5.

Dependence of change in pure tone average (PTA hearing gain) on: (a) the start of treatment (treatment delay) after onset of ISSHL, (b) hearing threshold (PTA) at the beginning of treatment. Dependence of the final hearing threshold (final PTA) on: (c) the start of treatment (treatment delay) after onset of ISSHL, (d) hearing threshold (PTA) at the beginning of treatment.

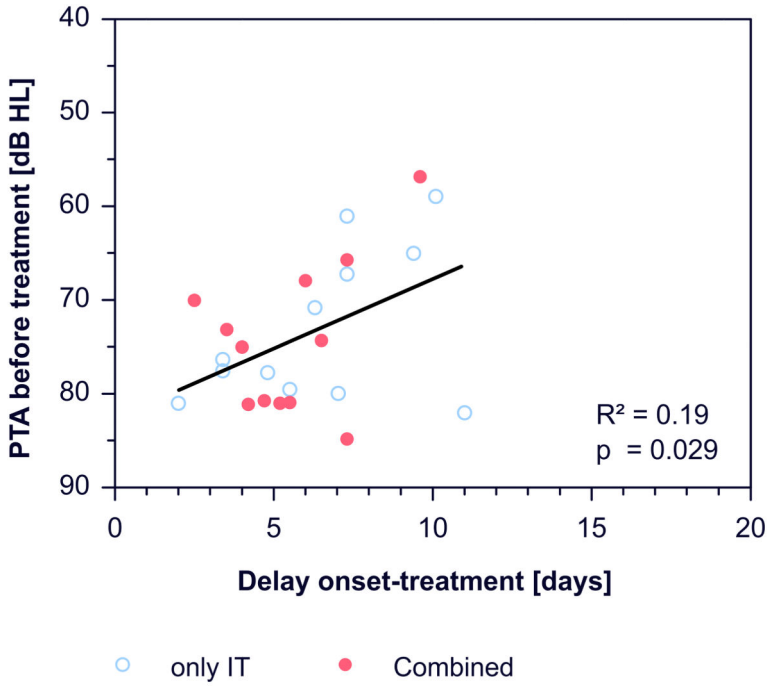

Figure 6.
Dependence of the PTA at the beginning of treatment on the delay of treatment after onset.

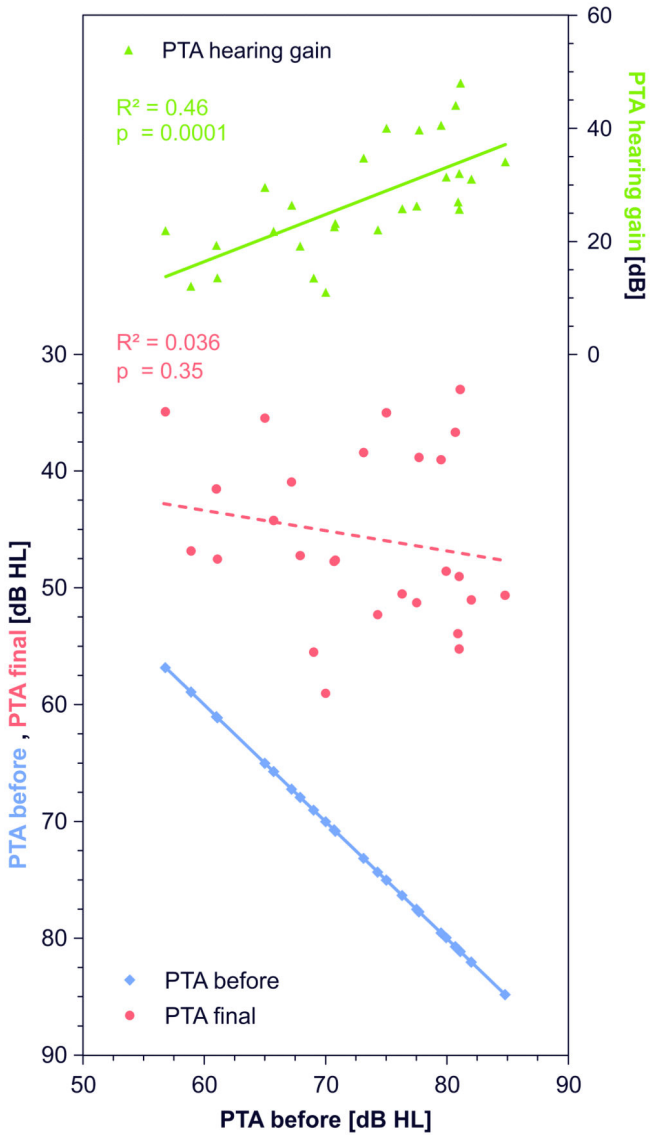

Figure 7.

Dependence of change in pure tone average (PTA hearing gain) and final hearing threshold (final PTA) on hearing threshold at the beginning of ("PTA before") treatment (see figure 5b, 5d). PTA hearing gain, final PTA, and PTA before treatment of each group are arranged at the y-axis and study results are sorted by increasing PTA before treatment on the x-axis. Larger hearing loss at start of therapy is compensated by higher hearing gain resulting in similar final hearing thresholds (final PTA) with a tendency for a poorer prognosis with larger hearing loss before treatment.

Table 1

Individual study groups characteristics and pure tone audiometry outcome measures for primary therapy of ISSHL.

Study	Type of study	Treatment	Number of patients	Age		Delay onset-treatment [days]		PTA type	PTA frequencies	Timepoint of measured final PTA after start of treatment [days]	
				Mean	SD	Mean	SD			Mean	SD
Ahn et al. 2008 (31)	prospective	Combined	60	48.6	15.4	6.5	3.9	4 PTA	500, 1000, 2000, 3000	104	n.a.
Alimoglu et al. 2011 (59)	retrospective	only IT	43	n.a.	n.a.	< 30	n.a.	4 PTA	500, 1000, 2000, 4000	n.a.	n.a.
Arastou et al. 2013 (60)	prospective	Combined	36	45.4	14.8	18.97	23.6	5 PTA	250, 500, 1000, 2000, 4000	26	n.a.
Arslan et al. 2011 (61)	prospective	Combined	85	47.8	13.1	7.3	5.5	4 PTA	500, 1000, 2000, 4000	15	n.a.
Bae et al. 2013 (54)	retrospective	only IT	94	53.6	9.9	7.3	8.3	4 PTA	500, 1000, 2000, 3000	40	n.a.
Bae et al. 2013 (54)	retrospective	Combined	197	50.4	15.2	6	6.7	4 PTA	500, 1000, 2000, 3000	40	n.a.
Battaglia et al. 2008 (62)	prospective	only IT	17	60	n.a.	11	14	3 PTA	500, 1000, 2000	43	n.a.
Battaglia et al. 2008 (62)	prospective	Combined	16	57	n.a.	4	3	3 PTA	500, 1000, 2000	43	n.a.
Battaglia et al. 2014 (63)	prospective	Combined	80	57	15	7.3	8	4 PTA	500, 1000, 2000, 4000	71	n.a.
Burkart et al. 2013 (64)	retrospective	Combined	23	47	13.7	4.2	1.9	4 PTA	500, 1000, 2000, 4000	90	n.a.
Dallan et al. 2011 (65)	prospective	only IT	10	56.4	14.7	7.3	2.1	4 PTA	500, 1000, 2000, 3000	31	n.a.
Dispenza et al. 2011 (55)	prospective	only IT	25	47	n.a.	9.4	n.a.	4 PTA	500, 1000, 2000, 4000	202	n.a.
Gouveris et al. 2011 (66)	retrospective	Combined	76	n.a.	n.a.	n.a.	n.a.	5 PTA	500, 1000, 2000, 4000, 8000	n.a.	n.a.
Gundogan et al. 2013 (56)	prospective	Combined	37	52.32	12.94	4.7	4	4 PTA	500, 1000, 2000, 3000	42	n.a.
Han et al. 2009 (67)	prospective	only IT	34	56.5	12.8	3.4	1.9	4 PTA	500, 1000, 2000, 3000	66	n.a.
Hong et al. 2009 (68)	prospective	only IT	32	56.9	n.a.	3.4	n.a.	4 PTA	500, 1000, 2000, 3000	98	n.a.
Jun et al. 2012 (69)	retrospective	Combined	30	47.1	14.8	5.2	11	4 PTA	500, 1000, 2000, 3000	90	n.a.

Study	Type of study	Treatment	Number of patients	Age		Delay onset-treatment [days]		PTA type	PTA frequencies	Timepoint of measured final PTA after start of treatment [days]	
				Mean	SD	Mean	SD			Mean	SD
Kakehata et al. 2006 (70)	prospective	only IT	10	57.7	n.a.	5.5	n.a.	5 PTA	250, 500, 1000, 2000, 4000	n.a.	n.a.
Kakehata et al. 2011 (71)	retrospective	only IT	19	56.2	9.7	4.8	n.a.	5 PTA	250, 500, 1000, 2000, 4000	36	n.a.
Kara et al. 2010 (72)	prospective	only IT	29	38.9	3.15	7.03	0.8	3 PTA	500, 1000, 2000	15	n.a.
Labatut et al. 2013 (73)	prospective	only IT	26	53	n.a.	2	n.a.	4 PTA	500, 1000, 2000, 4000	103	n.a.
Lautermann et al. 2005 (74)	prospective	Combined	13	n.a.	n.a.	2.5	n.a.	6 PTA	500, 750, 1000, 2000, 3000, 4000	n.a.	n.a.
Lim et al. 2013 (75)	prospective	only IT	20	53.3	15.3	10.1	8.1	4 PTA	500, 1000, 2000, 3000	21	n.a.
Lim et al. 2013 (75)	prospective	Combined	20	47.8	14.2	9.6	7.5	4 PTA	500, 1000, 2000, 3000	21	n.a.
Park et al. 2011 (76)	prospective	Combined	44	45.36	12.36	3.52	3.07	4 PTA	500, 1000, 2000, 3000	108	n.a.
Rauch et al. 2011 (77)	prospective	only IT	62	n.a.	n.a.	n.a.	n.a.	4 PTA	500, 1000, 2000, 4000	72	n.a.
Suzuki et al. 2012 (57)	retrospective	Combined	102	57	19.4	5.5	4.6	5 PTA	250, 500, 1000, 2000, 4000	52	n.a.
Zhang et al. 2012 (58)	prospective	only IT	35	53.5	16.7	6.3	7	5 PTA	250, 500, 1000, 2000, 4000	15	n.a.

IT = intratympanic, SD = standard deviation, n.a. = not available, PTA = pure tone average.

Table 2

Extracted parameters of the application protocols for individual study groups, calculated inner ear drug concentrations, and hearing threshold (PTA) before and after treatment.

Study	Drug used	Drug concentraion	Application time	Total # of injections	Frequency of injections	Duration of treatment	C_{max}	AUC	PTA before		PTA hearing gain		Final PTA	
		[µg/ml]	[min]		[days]	[days]	[µg/ml]	[µg*s/ml]	[dB HL]		[dB]		[dB HL]	
									Mean	SD	Mean	SD	Mean	SD
Ahn et al. 2008 (31)	Dex	5000	30	3	2	5	0.021	16.56	74.3	27.8	22.04	n.a.	52.26	n.a.
Alimoglu et al. 2011 (59)	Dex	4000	30	6	3.5	19	0.017	26.5	61.08	22.97	13.57	n.a.	47.51	n.a.
Arastou et al. 2013 (60)	Dex	4000	20	4	3.5	12	0.011	11.83	70.7	26.8	22.6	3.7	47.7	n.a.
Arslan et al. 2011 (61)	MP	125000	15	5	2	9	0.069	91.55	65.7	22	21.8	18.4	44.2	25.5
Bae et al. 2013 (54)	Dex	5000	30	4	3.5	12	0.021	22.09	61	19.9	19.3	n.a.	41.5	n.a.
Bae et al. 2013 (54)	Dex	5000	30	4	3.5	12	0.021	22.09	67.9	25.8	19.2	n.a.	47.2	n.a.
Battaglia et al. 2008 (62)	Dex	12000	20	3	7	15	0.034	26.63	82	28	31	n.a.	51	25
Battaglia et al. 2008 (62)	Dex	12000	20	3	7	15	0.034	26.63	75	23	40	n.a.	35	21
Battaglia et al. 2014 (63)	Dex	10000	20	3	7	15	0.028	22.19	84.8	18	34.1	26.6	50.6	27.8
Burkart et al. 2013 (64)	Dex + Hyaluronic acid	4800	30	4	2.5	10	0.02	21.2	81.1	16.6	48	n.a.	33	n.a.
Dallan et al. 2011 (65)	MP	20000	30	1	n.a.	1	0.022	5.85	67.2	31	26.4	22	40.9	38.1
Dispenza et al. 2011 (55)	Dex	4000	20	4	7	22	0.011	11.83	65	n.a.	29.55	8.98	35.45	n.a.
Gouveris et al. 2011 (66)	Dex + Hyaluronic acid	4000	20	3	2	5	0.011	8.88	69	n.a.	13.53	n.a.	55.47	n.a.
Gundogan et al. 2013 (56)	MP	62500	30	4	3	10	0.069	73.14	80.7	22.81	44.05	21.53	36.65	n.a.
Han et al. 2009 (67)	Dex	5000	38	4	3.5	12	0.026	27.91	76.3	15	25.8	17.8	50.5	n.a.
Hong et al. 2009 (68)	Dex	5000	30	8	1	8	0.021	44.17	77.5	27.6	26.26	17.97	51.23	n.a.
Jun et al. 2012 (69)	Dex	5000	30	4	1	4	0.021	22.09	81	16.6	25.7	21.4	55.2	23.8

Study	Drug used	Drug concentraion [µg/ml]	Application time [min]	Total # of injections	Frequency of injections [days]	Duration of treatment [days]	C_{max} [µg/ml]	AUC [µg*s/ml]	PTA before [dB HL]		PTA hearing gain [dB]		Final PTA [dB HL]	
									Mean	SD	Mean	SD	Mean	SD
Kakehata et al. 2006 (70)	Dex	4000	30	8	1	8	0.017	35.34	79.5	n.a.	40.5	n.a.	39	n.a.
Kakehata et al. 2011 (71)	Dex	4000	30	8	1	8	0.017	35.34	77.7	18.2	39.7	18.4	38.8	n.a.
Kara et al. 2010 (72)	Dex	4000	20	5	1	5	0.011	14.79	79.93	4.05	31.38	5.02	48.55	n.a.
Labatut et al. 2013 (73)	MP	40000	30	4	3.5	12	0.044	46.81	81	21	32	21	49	30
Lautermann et al. 2005 (74)	MP	32000	20	5	1	5	0.024	31.24	70	7	11	15	59	n.a.
Lim et al. 2013 (75)	Dex	5000	30	4	3	10	0.021	22.06	58.9	31.2	12.1	14.6	46.8	28.2
Lim et al. 2013 (75)	Dex	5000	30	4	3	10	0.021	22.09	56.8	28.3	21.9	26.2	34.9	25.3
Park et al. 2011 (76)	Dex	5000	20	6	3	16	0.014	22.19	73.12	17.01	34.74	25.65	38.38	23.01
Rauch et al. 2011 (77)	MP	40000	30	4	3.5	12	0.044	46.81	n.a.	n.a.	30.8	n.a.	n.a.	n.a.
Suzuki et al. 2012 (57)	Dex	4000	30	4	7	22	0.017	17.67	80.9	20.1	27	22.1	53.9	27
Zhang et al. 2012 (58)	Dex	5000	30	4	2	7	0.021	22.09	70.8	25	23.2	18.8	47.6	n.a.

Dex = dexamethasone, MP = methylprednisolone, SD = standard deviation, n.a. = not available, PTA = pure tone average.

Table 3

Relative upregulation of genes depending on the activation of glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) (14).

	Calculated Cmax (500 – 4000 Hz) [μg/ml]	GR dependent genes	MR dependent genes
Dexamethasone	0.011 – 0.034	95 – 100%	85 – 95%
Methylprednisolone	0.022 – 0.069	85 – 100%	90 – 100%