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Intratympanic dexamethasone with hyaluronic acid in the treatment of idiopathic sudden sensorineural hearing loss after failure of intravenous steroid and vasoactive therapy

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Abstract The purpose of this prospective study was to test whether intratympanic application of dexamethasone/hyaluronic acid improves hearing outcome in patients with pantonal idiopathic sudden sensorineural hearing loss (ISSHL), in patients with sudden deafness or sudden profound SHL and in patients with predominant high-frequency ISSHL who are refractory to intravenous steroid and vasoactive therapy. The study took place in an academic tertiary referral hospital involving 21 patients with pantonal ISSHL, 10 patients with sudden deafness or sudden profound SHL and 9 patients with a high-frequency ISSHL. Intratympanic dexamethasone/hyaluronic acid was administered in the affected ear. Hearing was evaluated by means of standard pure-tone audiometry. The differences between pure-tone hearing thresholds by air conduction before intravenous therapy and before the beginning of the intratympanic therapy, as well as before and after intratympanic therapy, were calculated. Statistical analysis was performed by means of the Wilcoxon's test for paired samples. Intratympanic injection of dexamethasone/hyaluronic acid results in a significant global (pantonal) improvement in hearing in patients with pantonal ISSHL. It also effects improvement in hearing at selected frequencies (namely at 1.5 and 3 kHz) in patients with a predominant high-frequency ISSHL and at selected frequencies (namely at 0.5, 0.75 and 1 kHz) in patients with sudden deafness or sudden profound SHL. Neither systemic nor local side effects were observed. Intratympanic administration of dexamethasone/hyaluronic acid provides a safe and efficacious therapeutic option for the treatment of patients with pantonal and high-frequency ISSHL who don't respond to intravenous steroid and vasoactive therapy.

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Abbreviations *dB HL* decibel hearing level · *(IS)SHL* (idiopathic sudden) sensorineural hearing loss · *kHz* kiloHertz

Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) has been defined as a 30-dB or more sensorineural hearing loss over at least three contiguous audiometric frequencies occurring within 3 days or less [19, 20]. The term "idiopathic" means that after performing clinical and laboratory (including radiological) investigations, no known cause of sensorineural hearing loss could be identified. Treatment modalities for idiopathic sudden sensorineural hearing loss (ISSHL) currently include various oral or intravenous corticosteroid regimens alone or in combination with pentoxifyllin and hydroxyethylstarch (HES) or low molecular weight dextran, hyperbaric oxygen therapy or plasmapheresis [6, 7, 8, 11, 16, 20, 21].

Intravenous therapy with prednisolone, pentoxifylline and hydroxyethylstarch (HES) has been shown to achieve complete recovery of hearing (defined as hearing thresholds equal to hearing thresholds of the non-affected ear ±10 dB HL at each tested frequency) in 75% of patients with ISSHL and partial recovery (defined as any improvement of the hearing threshold of more than 10 dB HL at any of the tested frequencies on the affected ear) in 12% of patients with ISSHL [21]. For patients who don't respond to intravenous therapy (13% of patients with ISSHL, according to Ziegler et al. [21]), other therapeutic alternatives are hyperbaric oxygen therapy, plasmapheresis or no intervention [8, 11].

Recently, it has been advocated that intratympanic dexamethasone application results in significantly higher perilymph steroid concentrations than those achieved by means of a systemic route [4, 5]. Topically applied intratympanic steroids have been used for the treatment of

Meniere's disease, idiopathic sudden sensorineural low-frequency hearing loss and tinnitus with varying and sometimes controversial results [1, 5, 12]. Hyaluronic acid has been shown in animal studies to increase the permeability of the round window membrane without cochlear ototoxic effects [2, 10, 13].

Patients with pantonal ISSHL and high-frequency ISSHL have a worse prognosis when compared to patients with low-frequency ISSHL. Under therapy with the treatment regimen described in the study done by Ziegler et al. in our institution [21], the recovery rate, including cases with both complete as well as partial recovery, was 95% in patients with high-frequency ISSHL, 68% in patients with pantonal ISSHL and 100% in patients with low-frequency ISSHL [21].

The aim of this study was to test whether the simultaneous intratympanic application of dexamethasone and hyaluronic acid improves hearing outcome in patients with pantonal ISSHL (including patients with sudden deafness or sudden profound SHL) and high-frequency ISSHL who are refractory to intravenous steroid and vasoactive therapy.

Patients and methods

Forty consecutive patients with ISSHL and failure of intravenous therapy (mean age: 53.4 years, 20 females and 20 males) participated in this prospective study. All suffered from ISSHL, and intravenous prednisone and vasoactive (HES and pentoxifylline) therapy was initiated according to the regimen described by Ziegler et al. [21]. Intravenous therapy with the aforementioned regimen was initiated on the day of initial presentation of the patient to our department. The day of initial presentation ranged between the 1st and the 20th days (average: 5. 45 days) after the acute onset of ISSHL.

The hearing loss in all these patients was sudden, meaning that is had occurred within 3 days or less. Auditory brainstem response was recorded in every patient and was either normal or pathological. In case of a pathological auditory brainstem response, a brain magnetic resonance imaging scan with gadolinium contrast enhancement was performed in order to exclude any intracranial anatomical abnormalities, especially on the anatomical structures of the temporal bone, cerebellopontine angle and brainstem. All performed scans were normal.

Twenty-one patients suffered a pantonal ISSHL (group 1, Table 1). A patient was considered to have a pantonal ISSHL when the following pure-tone audiometrical criteria were fulfilled: (1) a greater than 30-dB HL average sensorineural hearing loss (SHL) at low (0.125, 0.25, 0.5 and 0.75 kHz), middle (1, 1.5 and 2 kHz) as well as high (3, 4, 6 and 8 kHz) frequencies; (2) averages of pure-tone hearing thresholds by air conduction at low, middle and high frequencies (as defined above) should not differ by more than 20 dB HL among them; (3) a better than 80-dB HL average pure-tone hearing threshold by air conduction at 0.5, 1, 2 and 3 kHz. Patients with an average of the pure-tone hearing thresholds by air conduction at low frequencies (0.125, 0.25, 0.5 and 0.75 kHz) greater (i.e., worse) than 20 dB HL than the average of the pure-tone hearing thresholds by air conduction at either middle or high frequencies were excluded from the study, as these patients may have suffered from Meniere's disease.

Another ten patients with a pantonal ISSHL presented with sudden deafness or sudden profound sensorineural hearing loss (SHL) and were evaluated separately (group 2, Table 1). Deafness was defined as a greater than 100-dB HL average of the pure-tone hearing thresholds by air conduction at 0.5, 1, 2 and 3 kHz. Profound SHL was defined as an average pure-tone hearing threshold by air conduction at the four aforementioned frequencies worse than 80 dB HL (but better than 100 dB HL).

Nine patients presented with a restricted predominant high-frequency ISSHL (group 3, Table 1). A predominant high-frequency ISSHL was any ISSHL with an average of the pure-tone hearing thresholds by air conduction at 3, 4, 6 and 8 kHz greater than 30 dB HL than the average of the pure-tone hearing thresholds by air conduction at 0.125, 0.25, 0.5 and 0.75 kHz and greater (although not necessarily greater than 30 dB HL) than the average of the pure-tone hearing thresholds by air conduction at the middle audiometric frequencies (namely at 1, 1.5 and 2 kHz).

Ten (out of the 40) patients had vertigo at the onset of the ISSHL. Eight out of these ten patients had a peripheral vestibular lesion on the involved ear on electronystagmography. None of the remaining 32 (out of the 40) patients had any signs of a peripheral vestibular lesion on the affected ear on electronystagmography.

Hearing was evaluated by means of pure-tone audiometry at 11 frequencies (namely at 0.125, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 kHz). Averages of the pure-tone air-conduction hearing thresholds (in dB HL) at presentation (and hence beginning of intravenous therapy) for each of the three ISSHL patient groups are shown in Table 1. None of these patients showed any improvement in hearing threshold of more than 10 dB HL at any of the tested standard audiometric frequencies within the first 10 days of the intravenous treatment. Therefore, intratympanic dexamethasone/hyaluronic acid injections were initiated. Improvement in hearing was defined as any lowering (improvement) of the hearing threshold of more than 10 dB HL in one or more of the 11 audiometric frequencies in the affected ear.

Intratympanic administrations were performed every 2nd day. Local anesthesia of the eardrum was achieved by a Gelita-sponge impregnated with a 4% lidocaine solution. After 20 min, the sponge was removed and the external ear canal was cleared of any remaining fluids. With the patient in a supine position and the patient's head turned to the non-affected side, intratympanic injection of 0.3–0.4 ml solution of 8 mg/ml dexamethasone with 0.2 mg/ml hyaluronic acid was performed. Filling of the middle ear space with the injected solution could be observed medial to the tympanic membrane. The patient was then asked to remain in the supine position with the head turned to the non-affected side for 20 min following the injection in order to create the optimal conditions for the solution to continuously fill the round window niche. Intratympanic administrations were given every 2nd day as long as needed to improve hearing thresholds. On average, 2.7 injections per patient were used. Six patients received one injection, 13 patients were given 2 injections, 11 patients were given 3 injections, 8 patients were given 4 injections, one patient received 5 injections and one patient was given 7 injections.

Pure-tone audiograms were performed at presentation (before the beginning of intravenous therapy), before starting intratympanic steroid therapy (after failure of intravenous therapy) and at the end of intratympanic steroid therapy. The differences between

Table 1 Pure-tone hearing threshold averages (by air conduction, in dB HL) before the beginning of intravenous therapy for each of the three patient groups (see text) at each of the 11 pure-tone audiometric frequencies

Frequency (kHz)	0.125	0.25	0.5	0.75	1	1.5	2	3	4	6	8
Group 1 (dB HL)	55	64	68	66	64	63	62	61	64	69	66
Group 2 (dB HL)	88	102	109	107	106	106	105	103	105	107	99
Group 3 (dB HL)	24	25	31	35	40	43	47	56	65	76	77

pure-tone hearing thresholds by air conduction before intravenous therapy and just before the beginning of the intratympanic therapy, as well as just before beginning and after ending intratympanic steroid therapy, were calculated.

Results

The pure-tone hearing thresholds averages by air conduction (1) before the beginning of the intravenous therapy, (2) just before the beginning of intratympanic injection(s) as well as (3) after intratympanic injection(s) for each of the three groups of patients are shown in Tables 1, 2 and 3, respectively. The differences between the pure-tone hearing thresholds before the beginning of the intravenous therapy and just before the beginning of intratympanic injection(s) as well as just before the beginning and after ending intratympanic injection(s) were calculated for each of the three groups of patients. Statistical analysis was performed by means of the non-parametric Wilcoxon's test for paired samples.

In the group of patients with pantonal ISSHL without sudden deafness or sudden profound SHL (group 1), improvement of the hearing threshold after intratympanic dexamethasone/hyaluronic acid treatment reached statistical significance at all of the 11 audiometric frequencies tested ($P<0.05$). The benefit for hearing was particularly prominent (i.e., $P<0.01$) for the frequencies 8, 4, 3, 0.25, 0.5, 6, 1.5, 2 and 0.75 kHz, with a decreasing order of statistical significance. In the group of patients with sudden deafness or sudden profound SHL, the improvement in hearing after intratympanic dexamethasone/hyaluronic acid solution reached statistical significance ($P<0.05$) at the audiometric frequencies 0.5, 0.75 and 1 kHz (with a decreasing order of statistical significance). There was no P value less than 0.01 in this group of patients.

In the group of patients with predominant high-frequency ISSHL (group 3), statistically significant improvement in hearing ($P<0.05$, but $P>0.01$) was achieved after intratympanic dexamethasone/hyaluronic acid administration only at the 3- and 1.5-kHz audiometric frequencies (with a decreasing order of statistical significance). No statistically significant improvement in hearing thresholds was noted at higher frequencies (4 to 8 kHz).

Complete recovery (i.e., hearing threshold at each frequency within a range of ±10 dB HL of the hearing threshold of the non-affected ear) was noted in 7 out of the 21 patients (33.3%) of group 1. No case of complete recovery (as defined above) was noted in groups 2 or 3. No recovery (i.e., no improvement in hearing threshold of more than 10 dB HL at any of the tested frequencies) was observed in 6 out of 21 patients (28.6%) in group 1, in 4 out of 10 patients (40%) in group 2 and in 5 out of 9 patients (55.5%) in group 3. Any other case of improvement of the hearing threshold was considered to be a partial recovery (7). A partial recovery was noted in eight patients (39.1%) in group 1, six patients (60%) in group 2 and four patients (44.5%) in group 3.

In summary, intratympanic injection of dexamethasone/hyaluronic acid resulted in a significant global (pantonal) improvement in hearing in patients with pantonal ISSHL without sudden deafness or sudden profound SHL who were refractory to treatment with intravenous steroid and vasoactive therapy. It also effected improvement in selected frequencies in patients with a predominant high-frequency ISSHL (namely at 1.5 and 3 kHz) and in patients with sudden deafness or sudden profound SHL (namely at 0.5, 0.75 and 1 kHz).

Discussion

Corticosteroids exert genomic as well as direct plasma membrane effects. They exert a stabilizing effect on the cellular surface membrane, influencing phospholipid metabolism, sodium and potassium plasma membrane transport and eicosanoid metabolism. They also exert a non-specific effect on GABA receptors. Pre- or postischemic intravenous administration of glucocorticoids (prednisolone or methylprednisolone) as well as preischemic administration of dehydroepiandrosterone sulfate (a neurosteroid) significantly ameliorate the post-ischemic compound action potential threshold shifts in guinea pigs subjected to transient cochlear ischemia of 30-min duration [17]. The intravenously administered glucocorticoids did not improve cochlear blood flow. On the other hand, transtympanic dexamethasone injection resulted in a significant

Table 2 Pure-tone hearing threshold averages (by air conduction, in dB HL) just before the beginning of intratympanic therapy for each of the three patient groups (see text) at each of the 11 pure-tone audiometric frequencies

Frequency (kHz)	0.125	0.25	0.5	0.75	1	1.5	2	3	4	6	8
Group 1 (dB HL)	49	55	62	63	62	60	61	60	63	72	71
Group 2 (dB HL)	88	106	112	110	109	111	110	108	109	112	104
Group 3 (dB HL)	19	18	25	26	31	36	40	54	65	75	72

Table 3 Pure-tone hearing threshold averages (by air conduction, in dB HL) at the end of intratympanic therapy for each of the three patient groups (see text) at each of the 11 pure-tone audiometric frequencies

Frequency (kHz)	0.125	0.25	0.5	0.75	1	1.5	2	3	4	6	8
Group 1 (dB HL)	38	38	44	46	47	46	47	48	52	58	57
Group 2 (dB HL)	78	90	95	95	96	98	98	98	101	103	95
Group 3 (dB HL)	17	14	16	17	21	27	31	36	50	63	58

increase in cochlear blood flow after ischemia-induced injury of the guinea pig cochlea, measured with laser doppler flowmetry, within 30 s without significant change in auditory sensitivity [15]. The increase in cochlear blood flow was sustained and did not return to the baseline for at least 1 h after drug application.

Substances applied to the perilymph readily reach all the cells of the hearing organ [18]. The simultaneous use of dexamethasone and hyaluronic acid would be expected to increase round window membrane permeability such that the concentration of dexamethasone in the perilymph (and possibly in the endolymph) would increase, thus increasing availability and activity of dexamethasone in the inner ear structures. Hyaluronic acid may not only increase the permeability of the round window membrane, but may also influence the distribution of dexamethasone within the inner ear.

A possible explanation for the reduced efficacy of intratympanic dexamethasone and hyaluronic acid on high-frequency ISSHL would be the differential vulnerability of basal and apical hair cells. The base of the cochlea is more vulnerable to trauma and free-radical damage than the apex [14]. Moreover, outer and inner hair cells in the base of the cochlea develop ultrastructural abnormalities more rapidly than those in the apical turns following severe, total cochlear ischemia [3]. Another alternative could be that the mechanism of damage is different among the three groups of patients described here, and therefore the response of tissue damage to steroid treatment differs as well. This may account for the reduced efficacy of the intratympanic therapy in significantly improving hearing thresholds at frequencies equal or higher than 4 kHz in patients with high-frequency ISSHL, while doing so in patients with pantonal ISSHL. The same could hold true for poor results in the high-frequency region of patients with sudden deafness or sudden profound SHL. In the group of patients with sudden deafness or sudden profound SHL, severe (ischemic or other) damage of the cellular structures of the organ of Corti probably causes a non-reversible lesion.

Previous experience with the use of various drug administration modalities has shown that no significant differences in clinical efficacy appear to exist between direct intratympanic steroid injection, intratympanic steroid injection through a middle ear ventilation tube or with drug delivery-release systems. Experience with intratympanic gentamycin application has shown that placement of a middle ear ventilation tube or the implantation of a drug-delivery system within the middle ear cavity can result in complications that haven't been observed with repeated direct intratympanic gentamycin or dexamethasone application in our practice [9]. Patient discomfort during injection is minimal, provided that adequate local anesthesia of the tympanic membrane as described above is achieved. No persisting tympanic membrane perforations were seen in this series of patients.

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