Background: Treatment of sudden sensorineural hearing loss (SSNHL) consists of administration of blood flow–promoting drugs with or without the addition of glucocorticoids. General guidelines based on scientific data do not currently exist.

Objective: To investigate the effect of glucocorticoids on the treatment of SSNHL.

Setting: Academic medical center.

Patients and Methods: We retrospectively analyzed the audiograms of 603 patients with SSNHL: 301 patients (cared for between January 1, 1986, and December 31, 1991) received intravenous blood flow–promoting drugs without glucocorticoids and 302 patients (cared for between January 1, 1992, and December 31, 1998) received intravenous blood flow–promoting drugs with glucocorticoids (intravenous±oral application). The age distribution of patients with SSNHL in lower, middle, and higher frequencies was similar in both groups.

Results: Patients with SSNHL in lower and middle frequencies (250-2000 Hz) who received glucocorticoids (prednisolone-21-hydrogen-succinate) showed significantly better recovery of hearing levels compared with those who did not receive glucocorticoids ($P < .05$). There was no significant difference at higher frequencies between the 2 groups. Patients with SSNHL throughout all frequencies (pancochlear hearing loss) who received glucocorticoids also had significantly better recovery of hearing levels compared with those who received blood flow–promoting drugs alone ($P < .05$). Also, patients with elevated blood sedimentation rates had better improvement of their hearing levels after receiving glucocorticoids.

Conclusions: Administration of glucocorticoids should be recommended for treatment of patients with SSNHL. In particular, patients with SSNHL in the lower and middle frequency range and pancochlear hearing loss have significantly better recovery of hearing levels.


Sudden Sensorineural Hearing Loss

Does Application of Glucocorticoids Make Sense?

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UDDEN SENSORINEURAL hearing loss (SSNHL) is a frequent disease and occurs in 1 per 3000 inhabitants in the industrial world. It is sudden in onset, isolated, or associated with vertiginous episodes or tinnitus. The physiopathologic mechanism of this cochlear disorder is unclear, and a series of causative factors—including viral infection, microcirculatory disorders, and immunopathologic and autoimmune factors—are considered to be possible explanations. In general, the treatment of SSNHL is nihilistic (no therapy) or is based on the use of blood flow–promoting drugs with or without glucocorticoids. However, general guidelines, founded on “evidence-based medicine,” are not available, although there are many individual studies in the literature of the successful treatment of SSNHL. Furthermore, most of these studies lack suitable control groups to prove the therapeutic effect of the respective agent and include only small patients cohorts. The objective of this study was to evaluate, in a retrospective analysis of 603 patients, the therapeutic effect of glucocorticoids for the treatment of SSNHL.

RESULTS

Onset of SSNHL was unilateral in 96% of patients and bilateral in 4% of patients. The median ± SD time from the onset of SSNHL to the start of therapy was 3 ± 2 days for both groups. The mean ± SD age of Rh patients was 49 ± 16 years; 141 were women (47%) and 160 were men (53%). The mean ± SD age of RhG patients was 47 ± 15 years; 132 were women (44%) and 170 were men (56%). In the RhG group, 157 patients received an oral glucocorticoid scheme.

ADVERSE EFFECTS

The adverse effects listed in the Table were observed during therapy in both study groups.
MATERIALS AND METHODS

DEFINITION OF SSNHL

Sudden sensorineural hearing loss is usually unilateral and consists of impaired hearing or deafness, which appears suddenly without a recognizable cause. Tinnitus, pressure sensation, or vestibular disorders can also be present. Inclusion criteria for this study were (1) hearing loss that appeared acutely and without a recognizable cause, (2) hearing loss of more than 30 dB hearing level (dB HL) affecting 2 or more consecutive frequency levels, (3) therapy starting within the first 7 days after onset of hearing loss, and (4) no hearing deficiency in the affected ear in the past. Exclusion criteria were (1) recurrent SSNHL, (2) therapy starting later than 7 days after onset of hearing loss, (3) previous surgery in the respective ear, and (4) previously known hearing impairment.

STUDY DESIGN

Pure-tone audiograms (before and after therapy) from 603 patients in our hospital (Department of Otorhinolaryngology–Head and Neck Surgery, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany) care between January 1, 1986, and December 31, 1998, with the diagnosis of SSNHL were evaluated retrospectively. The patient collective was divided into 2 study groups: rheo-therapy without glucocorticoids (Rh) and rheo-therapy with glucocorticoids (RhG).

Rh Study Group

A total of 301 patients (cared for between January 1, 1986, and December 31, 1991) received Rh. These patients were given 500 mL of isotonic sodium chloride solution intravenously daily for 14 to 16 days, which included pentoxifylline, 100 mg (Trental [1 ampoule with 5 mL=100 mg of pentoxifylline]; Marion-Roussel, Bad Soden, Germany), in an increasing dosage (day 1, 100 mg; day 2, 200 mg; and day 3 and on, 300 mg), or 500 mL of hetastarch (6% HAES-steril; Fresenius-AG, Bad Homburg, Germany) combined with vitamin B complexes (Polybion forte N Dragees; Merck, Darmstadt, Germany), 25 mg 3 times daily.

RhG Study Group

A total of 302 patients (cared for between January 1, 1992, and December 31, 1998) received RhG. During the first 3 days, these patients received a daily intravenous dose of 500 to 1000 mg of prednisolone-21-hydrogen-succinate (Solu-Decortin H; Merck). In some cases, e.g., patients with diabetes, 250 mg daily was given. These patients also received ranitidine, 150 mg orally (Sostril [150-mg tablets twice daily]; Cascan/Cascapharm, Hamburg, Germany) for 4 to 5 days to protect the gastric mucosa. In selected patients, if there was no improvement, the glucocorticoid treatment was continued orally after intravenous therapy (the oral glucocorticoid scheme began with 100 mg of prednisolone [Decortin H; Merck] for 16 days, with a decreasing dosage supplemented by ranitidine, 150 mg twice daily; 52% of patients (n=157) were given this additional oral therapy.

OPERATIVE INTERVENTION

Seven patients (1.2%) had complete unilateral deafness. A tympanoscopy was performed on the affected ear in these patients to determine whether the round window membrane of the inner ear had ruptured.

SUBJECTIVE VARIABLES

On hospital admission and discharge, patients were questioned regarding the quality and quantity of tinnitus, pressure in the ear region, and subjective feelings of dizziness. All these data were documented.

LABORATORY VARIABLES

On hospital admission, a blood analysis was performed that included serum levels of sodium, potassium, glumatic oxalatic transaminase, glumatic pyruvic transaminase, cholinesterase, protein, C-reactive protein, and blood coagulation variables (Quick test and partial thromboplastin time); a complete blood cell count (hemoglobin, hematocrit, erythrocytes, and leukocytes); and the blood sedimentation rate.

The following variables were ascertained to evaluate cochlear-vestibular function: complete pure-tone audiogram (frequency levels, 250-8000 Hz), tympanogram, stapedius reflex, auditory brainstem responses 10 to 14 days after the onset of hearing loss, and electronystagmogram.

For evaluation of response to therapy, audiometric examinations (pure-tone audiograms) were performed every 2 to 3 days during hospitalization, always by the same examination team.

COLLECTION OF DATA AND STATISTICAL ANALYSIS

A form was developed in cooperation with the Institute for Medical Statistics and Epidemiology, Technical University of Munich, Munich, Germany, to systematically collect data. On this form, a short medical history and results of pure-tone audiography, blood analyses, and the ear, nose, and throat examinations of 603 patients were recorded. Data were analyzed using the SPSS software program.16 The U test for unpaired samples was used to compare the mean values of absolute hearing improvement in dB HL in both study groups. The sound threshold audiograms before and after treatment were calculated. Differences were considered statistically significant at P<.05.

SUBJECTIVE VARIABLES

Tinnitus was perceived in 78% of the Rh group (234 patients) and in 82% of the RhG group (248 patients). Tinnitus improved in or was no longer perceived by 71% of Rh patients (n=165), with the remaining 29% (n=69) noting no improvement at discharge from the hospital. In the RhG group, improvement or cessation of tinnitus was noticed in 75% of patients (n=186), showing no significant difference to Rh (P<.68).
AUDIOMETRIC VARIABLES

**Figure 1** shows mean±SEM values for the Rh group of audiograms performed on hospital admission and the threshold elevation in the pure-tone audiogram at discharge, which were used for assessment of response to therapy. After therapy, an average improvement in hearing was achieved in the Rh group at frequency ranges of 250, 500, and 1000 Hz of 17.6±1.4 dB HL (low frequencies), at 2000 to 4000 Hz of 16.0±1.2 dB HL (middle frequencies), and at 6000 to 8000 Hz of 14.2±1.2 dB HL (high frequencies) (*Figure 2*).

**Figure 3** shows the corresponding data for the RhG group. Mean±SEM improvement was 23.7±1.8 dB HL at frequency levels of 250, 500, and 1000 Hz, 20.3±1.6 dB HL at 2000 to 4000 Hz, and 11.7±1.0 dB HL at 6000 to 8000 Hz (Figure 3).

**Figure 1.** Average values for threshold elevation in the pure-tone audiogram in the rheotherapy without glucocorticoids group (n=301) before and after treatment. Error bars indicate SEM.

**Figure 2.** Average values for threshold elevation in the pure-tone audiogram in the rheotherapy with glucocorticoids group (n=302) before and after treatment. Error bars indicate SEM.

**Figure 3.** Absolute hearing gain in the pure-tone audiogram after therapy in patients with and without use of glucocorticoids. Asterisk indicates P<.05. Error bars indicate SEM.

At 6000 Hz (P<.65), although a greater hearing gain was noticeable in the Rh group at 8000 Hz, which, however, was not statistically significant (P<.13).

Pancochlear hearing loss is a severe situation inflicting all frequencies, and patients have at least a 30-dB hearing loss. This was noted in 23% of Rh patients (n=68) and in 17% of RhG patients (n=52). The absolute hearing gain at all frequencies, defined as hearing improvement of more than 10 dB HL over all frequency ranges (pancochlear), was 43% in the Rh group and 62% in the RhG group (P<.05) (*Figure 4*).

**Adverse Effects in Both Treatment Groups**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Patients, No.</th>
<th>Rh</th>
<th>RhG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>8</td>
<td>10</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Blood pressure elevation</td>
<td>16</td>
<td>13</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Erythema (especially facial)</td>
<td>5</td>
<td>14</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Serum blood glucose elevation</td>
<td>3</td>
<td>19</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Prednisolone allergy</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Rh indicates rheotherapy without glucocorticoids; RhG, rheotherapy with glucocorticoids.*
lymph fistula) was discovered; it was sealed with connective tissue and resulted in improved hearing.

Twenty-nine percent of patients (n=174) also reported dizziness coincident with the onset of SSNHL. A dysfunction in the ipsilateral vestibular organ was noted in 65% of these patients (n=113) in an electronystagmogram. Most of them subjectively improved; a detailed analysis of the results was not performed.

An electrocochleogram was performed in 22 patients (12 in the Rh group and 10 in the RhG group), during which a hydrops was found in 7 patients (1.2%). These patients were not included in any further evaluation.

Glucocorticoids have cellular actions that target the genome (DNA within the nucleus) that become evident within 1 to 2 hours and cytoplasmic effects, mostly at very high doses, that occur after only a few minutes. Each cell contains 2 classes of corticoid receptors, type I (glucocorticoid) and type II (mineralocorticoid) receptors, both of which are present in the cochlear and vestibular tissues of mammals. When cytoplasmatic glucocorticoid receptors are activated, transcription and expression of specific genes are activated, which then inhibit the synthesis of inflammatory mediators and cytokines, which are responsible for the anti-inflammatory effects of glucocorticoids. Glucocorticoids also affect carbohydrate and protein metabolism and change the physicochemical characteristics of cell membranes by promoting their stabilization and reducing the permeability of cations (cytoplasmic effect). Finally, glucocorticoids also regulate cellular osmolarity by binding to type II mineralocorticoid receptors, which activate the enzyme Na,K-ATPase. This enzyme is found at the base of the external and internal hair cells, the tympanic nerve fibers, and the spiral ganglion cells of mammals. The activation of Na,K-ATPase by prednisolone could have positive effects on disturbed intracellular and extracellular osmolarity, electrochemical gradients, and neuronal activities, which are disturbed by noise-related cellular, functional cochlear damage and autoimmune inner ear disease.

Sudden sensorineural hearing loss usually occurs in healthy persons and is a dramatic experience for the affected patient because it impairs an important sensory perception, thus severely limiting the quality of life. Although dysfunction of the inner ear is not life threatening, the resulting communication problems can have drastic consequences for the individual’s professional or social life. It has been reported that use of glucocorticoids might positively affect the expected improvement of hearing in the therapy of SSNHL. Concerning the effect of glucocorticoids compared with placebo or no treatment, only 4 clinical trials have been performed.

Mattox and Simmons came to the conclusion that 20 (71%) of 28 nontreated patients recovered their hearing “completely or at a good percentage,” and 63 (72%) of 88 patients showed similar results after glucocorticoid therapy. Wilson et al reported that of 52 nontreated patients, 29 regained normal hearing ability (ie, 56%). Excluding patients with a middle-frequency hearing loss, because spontaneous recovery was always demonstrated, 17 (49%) of 35 nontreated patients with a low- or high-frequency hearing loss regained their hearing ability by 3 months after onset of the affliction. In contrast, 11 (32%) of 34 placebo-treated patients recovered their hearing, and 20 (61%) of 33 glucocorticoid-treated patients, particularly those with moderate hearing loss, showed similar results.

Moskowitz et al deduced that 24 (89%) of 27 glucocorticoid-treated patients “recovered at least 50% of their hearing,” whereas 4 (44%) of 9 patients recovered their hearing without any treatment. Veldmann et al found an effective response to glucocorticoid treatment in 6 (50%) of 12 patients, whereas only 6 (32%) of 19 nontreated patients showed similar results.

Visscher and Arnold observed a similar effect, and during that time the term “cortisone-sensitive inner ear disease” was created. Recently, a significant hearing improvement using anti-inflammatory substances (ie, prednisolone) in noise-induced guinea pigs was observed com-
pared with an untreated animal group. A limiting factor for the evaluation of the effect of glucocorticoids in all of these human studies has been the limited number of cases and, therefore, did not include large enough control groups. Furthermore, the number of patients in each group is too low to express recovery rates as percentages. Especially for dividing the group into patients with hearing loss in the low, middle, and high frequencies, the respective collectives were too small. The present study demonstrates in a large number of patients (N=603) a statistically significant benefit with use of glucocorticoids (prednisolone) for the improvement of frequency-specific hearing, ie, in the lower and mediocochlear levels, compared with a control group receiving no glucocorticoids (Figure 3). The 2 study groups were comparable with respect to age and sex and showed that sudden hearing loss more frequently affects the left ear (53%). Furthermore, administration of glucocorticoids for sudden panocochlear hearing deficiency revealed a significant improvement in hearing (>10 dB HL at all frequency levels in 43% of the Rh group and 62% of the RhG group) (Figure 4).

Of special interest is the fact that all studies report spontaneous remission in SSNHL. For example, Wein- auger described 63 patients in whom hearing recovered completely in 68% and improved in 89%. Because both study groups in the present investigation are comparable regarding the number of patients, age and sex, etc, a comparable spontaneous remission rate would be expected in both groups, meaning that the significantly higher rate of hearing improvement in RhG can be attributed to the glucocorticoid therapy.

It has been suggested that disorders of the microcirculation in the cochlear region and changes in plasma viscosity impaired cochlear microcirculation due to sludging of red blood cells, vasospasm, and endothelial swelling. A complete blood profile was determined in all patients and did not show any significant abnormalities in hematocrits, hemoglobin levels, leukocyte and erythrocyte counts, or serum electrolyte levels. Blood sedimentation rates were determined in 451 patients; 18% showed elevated blood sedimentation rates (>15 mm/h), and 96% of RhG patients had recovery of HLs compared with 74% in the Rh group (Figure 5). This underscores the thesis that inflammatory processes may cause SSNHL and could be successfully treated with anti-inflammatory agents such as glucocorticoids.

Mattucci and Bachoua described disorders of coagulation in patients with SSNHL. In the present SSNHL study groups we saw only a marginal change in blood coagulation status. The cumulative partial thromboplastin time of our patients was 25.5 seconds (reference range, 26-37 seconds). The cumulative Quick value (thromboplastin time) was 99% (reference range, 70%-120%).

Only a few patients experienced adverse effects during therapy with glucocorticoids, such as increased blood glucose levels, elevated blood pressure, and transient erythema (mainly in the facial area). By completion of therapy, however, all symptoms had resolved. For increased blood glucose levels, patients were temporarily given insulin subcutaneously (Actrapid; Novo Nordisk Pharma, Mainz, Germany). Patients with diabetes mellitus (n=21) received only 250 mg of prednisolone-21-hydrogen-succinate for the first 3 days and were closely monitored for blood glucose levels. Only a few patients showed blood pressure changes, which were probably caused by application of the rheologic agents (500 mL of Ringer/pentoxifylline or 500 mL of 6% HAES-steril). None of our patients had dysrhythmia. Allergic reactions, a rare adverse effect of prednisolone therapy, occurred in only 1 RhG patient and could be controlled.

Contraindications for glucocorticoid administration are a recent history of a stomach ulcer, known left-sided heart insufficiency, renal insufficiency, or an active bacterial infection. In principle, pregnancy is not a contraindication; however, a gynecologist should always be consulted for individual cases.

Sudden sensorineural hearing loss is an acute and often dramatic experience for the patient that might strongly limit the quality of life. Therefore, at the beginning of our treatment of SSNHL and according to the principles of high-dose (pulse-dose) corticoid therapy used by other specialties (neurology, transplantation medicine, etc), we applied similar high doses. Bührer et al demonstrated in humans that after intravenous administration of prednisolone, the concentration in cerebrospinal fluid was only approximately one third of the corresponding plasma concentration. One hour after intravenous application of methylprednisolone in the perilymph of guinea pigs, Parnes et al measured only one sixth of the concentration of the corresponding plasma level. Therefore, high doses are justified to reach effective glucocorticoid levels in the perilymph and endolymph fluid. More recent experimental studies, however, have shown that all corticoid receptors are occupied when using approximately 300 mg of prednisolone. However, there are no currently available data, to our knowledge, concerning the concentration of glucocorticoids in the perilymph after intravenous application in humans. An ongoing study is presently being conducted at our institution. Based on the available knowledge, we give our patients with SSNHL 500 mg of prednisolone-21-hydrogen-succinate intravenously, combined with histamine2-receptor blockers to protect the stomach, during the first 3 days of hospitalization.

According to our results, administration of glucocorticoids to patients with SSNHL is highly recommended, especially for those with acute hearing deficiencies at the lower, middle, and panocochlear sound levels. However, the results of this retrospective analysis should be confirmed with a prospective, randomized, multicenter study.

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