Effectiveness of systemic high-dose dexamethasone therapy for idiopathic sudden sensorineural hearing loss.

Egli Gallo, D; Khojasteh, E; Gloor, M; Hegemann, S C A

Abstract: Objective: To evaluate the effectiveness of systemic high-dose dexamethasone therapy for sudden sensorineural hearing loss in comparison to the previous treatment regimen at our clinic with systemic prednisone 100 mg daily for 7 days analyzed in a previous study. Methods: We conducted a retrospective review of an electronic patient database of 79 patients with idiopathic sudden sensorineural hearing loss. The standard treatment was orally applied dexamethasone (1st to 3rd day: 40 mg daily, 4th to 6th day: 10 mg daily) in an ambulant setting. The primary endpoint was change in hearing threshold from the initial audiogram to an audiogram at least 4 weeks later. Factors that were analyzed included patient’s age, interval between onset of symptoms and start of treatment, presence or absence of dizziness and tinnitus, the audiogram pattern, severity of hearing loss and hearing in the opposite ear. Hearing gain was expressed either as absolute or relative hearing gain. Functionally relevant recovery of hearing was defined as the final pure-tone average (PTA) of 30 dB or less (or the same as the PTA of the opposite ear ± 10 dB). Furthermore, we calculated the percentage of patients with complete, partial and no recovery as defined in the recently published Clinical Practice Guideline of the American Academy of Otolaryngology - Head and Neck Surgery Foundation. We then compared our results with the previous treatment regimen carried out at our clinic. Results: The average initial PTA hearing loss in the affected ear compared to baseline PTA of the unaffected ear was 51.5 ± 20.9 dB (mean ± SD). The mean absolute hearing gain was 44.4 ± 18.1 dB. The mean relative hearing gain was 86 ± 19%. Of the total, 87% had functionally relevant recovery of hearing. All of our patients showed partial (24%) or complete recovery (76%). No difference in recovery rate could be detected between patients with start of therapy within 24 h and patients with beginning of therapy within 7 days. We found a correlation between the severity of hearing loss and functionally relevant recovery. A mild hearing loss was noted in 34% of patients, with an average relative hearing gain of 89% and a functionally relevant recovery in 96% of them; the 9% of patients with initial deafness showed a mean relative hearing gain of 69% and a functionally relevant recovery in 43%. The audiogram pattern with low- or high-frequency hearing loss showed the best recovery rate; the poorest recovery rate was found in patients with initial deafness. Conclusion: Application of high-dose orally applied dexamethasone seems to improve the recovery outcomes in comparison to prednisone 100 mg p.o. for 7 days.

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Effectiveness of systemic high-dose dexamethasone therapy for idiopathic sudden sensorineural hearing loss

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Key Words
Idiopathic sudden sensorineural hearing loss · High-dose dexamethasone therapy · Glucocorticoids · Steroids

Abstract
Objective: To evaluate the effectiveness of systemic high-dose dexamethasone therapy for sudden sensorineural hearing loss in comparison to the previous treatment regimen at our clinic with systemic prednisone 100 mg daily for 7 days analysed in a previous study.

Methods: We conducted a retrospective review of an electronic patient data base of 79 patients with idiopathic sudden sensorineural hearing loss (ISSHL). The standard treatment was orally (= p.o.) applied dexamethasone (1. – 3. day 40 mg daily, 4. – 6. day 10 mg daily) in an ambulant setting. The primary endpoint was change in hearing threshold (dB PTA) from the initial audiogram to an audiogram at least 4 weeks later. Factors that were analysed included patient’s age, interval between onset of symptoms and start of treatment, presence or absence of vertigo and tinnitus, the audiogram pattern, severity of hearing loss and hearing in the opposite ear. Hearing gain was expressed either as absolute hearing gain or as relative hearing gain. Functionally relevant recovery of hearing was defined as the final pure-tone average (PTA) of 30 dB or less (or the same as the PTA of the opposite ear ± 10 dB). Furthermore we calculated the percentage of patients with complete, partial and no recovery as defined in the recently published Clinical Practice Guideline of the American Academy of Otolaryngology – Head and Neck Surgery Foundation [Stachler et al., 2012]. We then compared our results with the previous treatment regimen carried out at our clinic [Cvorovic et al., 2008].

Results: The average initial PTA hearing loss in the affected ear compared to baseline PTA of the unaffected ear was 51.5 dB ± 20.9 (mean ± SD). The mean absolute hearing gain was 44.4 dB ± 18.1 dB. The mean relative hearing gain was 86% ± 19 %. 87% of patients had functionally relevant recovery of hearing. All of our patients showed partial (24%) or complete recovery (76%). No difference in recovery rate could be detected in patients with start of therapy within 24 hours in comparison to patients with beginning of therapy in up to 7 days. We found a correlation between the severity of hearing loss and functionally relevant recovery. 34% of patients had a mild hearing loss with an average relative hearing gain of 89% and a functionally
relevant recovery in 96% of them; the 9% of patients with initial deafness showed a mean relative hearing gain of 69% and a functionally relevant recovery in 43%. The audiogram pattern with low or high frequency hearing loss showed the best recovery rate, the poorest recovery rate was found in patients with initial deafness.

**Conclusion:** Application of high-dose dexamethasone p.o. seems to improve the recovery outcomes in comparison to 100 mg prednisone p.o. for 7 days.

**Introduction**

Sudden hearing loss is an acute and often dramatic experience for the patient that often prompts an urgent visit to a physician. Prompt recognition and management of idiopathic sudden sensory hearing loss (ISSHL) may improve hearing recovery and patient quality of life.

According to recent studies from Germany, the incidence of ISSHL is between 160 and 400/100,000 per year [AWMF-Leitlinien: Hörsturz, 2010; Klemm et al., 2009; Elies, 2002; Suckfüll, 2009] which is much higher than generally assumed. ISSHL has been defined as a loss of hearing sensitivity of 30 dB HL or greater over 3 continuous frequencies occurring in less than 3 days, with no marked vestibular symptoms and no identifiable cause [National Institute on Deafness and Communications Disorders, 2000]. Various theories have been proposed for the cause of this condition. Numerous studies have shown mechanisms by which infectious, ischemic, mechanical or immunologic insults may induce cochlear dysfunction. Because of the uncertainties regarding cause and pathogenesis, the treatment of ISSHL is highly empirical and no standard protocol is universally accepted. The most commonly used treatment has been corticosteroids, either systemically and/or intratympanically applied. Although the mechanism of the action of steroids in the inner ear remains unclarified and the optimal dose of administration has not been determined, higher concentrations of the steroids in the cochlea are associated with greater hearing recovery [Seggas et al., 2010]. There is laboratory evidence of an apoptotic inflammatory cell death cascade in ISSHL which is modified by steroid therapy. Corticosteroids are known to have sites of action in the inner ear with efficacy in viral, vascular, syphilitic, autoimmune, endolymphatic hydrops and other etiologies of hearing loss.

Despite their widespread use, there is little consensus on the effectiveness of oral steroids in this setting and the needed dosage. Many trials have been published investigating the use of corticosteroids in patients with ISSHL; however, these trials adopted a variety of methodologies and drew varying conclusions. Most studies, however, do not meet present-day criteria in terms of highest quality evidence, as identified by RCTs, systematic reviews, meta-analyses, or evidence reports.

A Cochrane review [Wei and Mubiru, 2006, updated 2009] found only 2 trials [Wilson et al., 1980; Cinamon et al., 2001] that met their inclusion criteria, and both were of low methodological quality and with small numbers of subjects.

In another systematic review [Conlin and Parnes, 2007] no valid RCTs were found to determine the effectiveness of corticosteroids in ISSHL and the study pointed out limitations in landmark studies on which such treatment has been traditionally based on.

A recent meta-analysis of various medical treatments, including corticosteroids, showed a slight but not statistically significant improvement with medical therapy compared to placebo [Labus et al., 2010].

On the basis of the studies cited above, the clinician might choose not to prescribe corticosteroids for ISSHL. However, faced with a patient with the serious consequences of a severe to profound ISSHL, corticosteroid treatment is one of the
few treatment options showing at least some evidence for efficacy, although even those data are somehow arbitrary. Coexistent morbidities such as dizziness and tinnitus pose considerable economic and psychological burden for the patient. It is appropriate, therefore, to approach these idiopathic cases in a common way, understanding that the underlying etiologies may be very dissimilar. Considering the devastation of ISSHL and the profound impact on quality of life that a hearing improvement may offer, we conclude that even a small possibility of hearing improvement makes this a reasonable treatment to offer to patients.

There are only a few studies using high-dose steroid treatment orally for the treatment of ISSHL. Aoki et al showed 2006 a significant and rapid improvement in recovery in patients with ISSHL [Aoki et al., 2006]. According to the German Guidelines [AWMF-Leitlinien: Hörsturz, 2004] which recommend at least 250 mg prednisone daily for the first three days we increased the steroid dose in August 2006 from 100 mg prednisone for 7 days to 40 mg dexamethasone daily for the first 3 days followed by 10 mg dexamethasone daily for the following 3 days. This is equivalent to 250 mg [Högger, 2003] or 300 mg [Henzen, 2003; Forth et al., 2005] prednisone. Dexamethasone has no mineralocorticoid effect like prednisone and prednisolone, a longer biological half-life-time (36 - 54 hours) [www.endotext.org, 2011; www.uptodate.com, 2012] and a 10 times better receptor affinity than prednisolone [Högger, 2003]. The aim of this study was to assess the efficacy of our high-dose treatment regimen and to compare the recovery rate with standard prednisone treatment, previously used at our clinic.

Materials and methods
A retrospective evaluation of an electronic patient database of the University Hospital Zurich from December 2006 until December 2011 was performed. We could include 79 patients with ISSHL in this study. Others had to be excluded because the data were incomplete (no follow-up audiogram after at least 4 weeks in 203 patients) or the criteria for an idiopathic sudden sensorineural hearing loss were not fulfilled (152 patients). Patients with anamnestic recorded signs of cochleo-vestibular dysfunction as detectable nystagmus, pathologic head impulse testing (HIT) and/or a pathologic caloric testing were excluded. Other exclusion criteria were bilateral or recurrent hearing loss as well as fluctuating hearing loss and specific diseases as stated in Table 1. Records were evaluated only if at least 2 audiograms were available: the first at presentation before treatment, and the second at least 4 weeks after the initial audiogram (or complete recovery in the second audiogram when conducted within the first 4 weeks). If more than 2 audiograms were available, then the last one (maximal 5 months later) was taken as the final audiogram. Ear-specific, masked air and bone conduction thresholds were obtained of both ears at each visit. Air conduction thresholds were measured at 250 to 8000 Hz. Bone conduction thresholds were measured at 250 to 4000 Hz. Pure-tone average (PTA), the arithmetic mean of the hearing thresholds at 500, 1000, 2000 and 4000 Hz, was calculated for the affected and unaffected ear separately (initial PTA and final PTA of affected ear, baseline PTA of unaffected ear). The PTA in the unaffected ear was used as the presumed premorbid hearing (baseline) in the affected ear. Patients with pre-existing hearing loss in the contralateral ear were only included, if a recent audiogram of the affected ear was available and then this audiogram was used as baseline. A threshold value of 100 dB HL was assumed if the average hearing loss exceeded the limits of the audiometric equipment [Probst et al., 1992].
The standard therapy was dexamethasone p.o. (1. – 3. day 40 mg daily, 4. – 6. day 10 mg daily) in an ambulant setting. This treatment changes with increase of the steroid dose – before 2006 all patients were treated with 100 mg prednisone p.o. for 7 days – was according to the recommendation of the German Guidelines for sudden idiopathic sensorineural hearing loss [AWMF-Leitlinien: Hörsturz, 2004]. We chose dexamethasone because of its missing mineralocorticoid effect and its tenfold better glucocorticoid-receptor affinity [Högger, 2003].

No routine laboratory testing was conducted. In certain cases specific laboratory tests were based on specific individual patient conditions, such as drawing Lyme titers in patients with tick bite. Magnetic resonance imaging or acoustic evoked potentials were performed in patients with incomplete recovery of hearing to exclude retrocochlear pathology.

Factors that were analysed included patient’s age, interval between the onset of symptoms and start of treatment, presence or absence of vertigo (diffuse dizziness without signs of cochleo-vestibular dysfunction) and tinnitus, the audiometric pattern and severity of hearing loss.

The pattern of the audiogram was categorized into 1 of 5 types using the classification scheme of Mazzoli [Mazzoli et al., 2003]. Low frequencies were defined ≤ 0.5 kHz, midfrequencies > 0.5 kHz and ≤ 2 kHz, and high frequencies >2 kHz and < 8 kHz. The following types of audiograms were defined: 1) low frequency, ascending, greater than 15 dB HL from the poorer low-frequency thresholds to the higher frequencies; 2) midfrequency, U-shaped, greater than 15 dB HL difference between the poorest thresholds in the midfrequencies and those at higher and lower frequencies; 3) high frequency, descending, greater than 15 dB HL difference between the mean of 0.5 and 1 kHz and the mean of 4 and 8 kHz; 4) flat, less than 15 dB HL difference between the mean of 0.25 and 0.5 kHz thresholds, the mean of 1 and 2 kHz, and the mean of 4 and 8 kHz; 5) total deafness, hearing loss of 100 dB or more at 0.5, 1, 2 and 4 kHz.

The severity of the hearing loss was calculated as difference between initial PTA of the affected ear and baseline PTA: 1) mild, PTA of 15 to 39 dB; 2) moderate, PTA of 40 to 59 dB; 3) severe, PTA of 60 to 79 dB; 4) profound, PTA of 80 to 100 dB; 5) deaf, PTA of greater than 100 dB.

The primary endpoint was the change in hearing threshold (dB PTA) from the initial PTA to the final PTA of the affected ear.

Hearing gain was expressed either as absolute hearing gain (decibel values from initial PTA minus decibel values from final PTA) or as relative hearing gain (absolute hearing gain divided by initial PTA minus baseline PTA). Functionally relevant recovery of hearing was defined as the final PTA of 30 dB or less (or the same as the PTA of the opposite ear ± 10 dB). Furthermore we calculated the percentage of patients with complete, partial and no recovery as recently defined [Stachler et al., 2012]. We then compared our results with a previously assessed study at our clinic, where the standard treatment was prednisone orally (100 mg daily for 7 days) and carbogen inhalation [Cvorovic et al., 2008].

Statistical analyses were performed using MATLAB built-in functions (The MathWorks Inc., MA, USA). To examine correlations between different parameters (such as age or the timing of treatment) and the outcomes of the treatment, nonparametric rank tests were used. We report Spearman’s rank correlation coefficient, Rho- and the P-values indicating statistical significance of the correlation. To verify statistically significant differences in the treatment outcome based on initial severity assessments or the shape of the audiogram, non-parametric methods for the
analyses of variance were used. We report P-values resulting from Kruskal-Wallis test. P-values greater than 0.05 were considered statistically insignificant.

Results
A total of 79 patients with ISSHL were available for analysis. There were 48 men and 31 women with an average age of 50 years, ranging from 11 to 82 years. The average follow-up period was 56 days. The average initial PTA hearing loss in the affected ear compared to baseline PTA of the unaffected ear was 51.5 dB ± 20.9 (mean ± SD).

Overall Recovery:
The mean absolute hearing gain between the initial PTA and the final PTA was 44.4 dB ± 18.1 dB. To assess the treatment success the relative hearing gain should be used because it adequately reflects both severity of the initial hearing loss and the absolute hearing gain. The mean relative hearing gain in our study was 86% ± 19% (mean ± SD). 69 patients (87%) showed a functionally relevant recovery of hearing. All of our patients showed partial (24%) or complete recovery (76%) according to the recently published guideline [Stachler et al., 2012].

Recovery related to age:
There was no significant correlation between age and relative hearing gain (Rho = 0.15, P = 0.2).

Recovery related to the interval between the onset of symptoms and start of treatment:
77 of 79 patients started treatment within 7 days after onset of symptoms. No significant difference in recovery existed between patients who received therapy within 24 hours and patients receiving therapy between 1 and 7 days after onset of symptoms (Rho = 0.016, P = 0.88). Figure 6 shows the uniform distribution of the recovery rates distributed over the first 7 days. In only 2 patients the treatment started later than 7 days after onset of hearing loss. Therefore no meaningful statement can be made for delayed start of treatment. The average time between onset of hearing loss and begin of treatment was 2.1 days. All patients received their first audiogram just before treatment was started.

Recovery related to the presence or absence of vertigo and tinnitus:
Tinnitus was recorded in association with hearing loss in 64 of the patients (81%) and vertigo (diffuse dizziness without signs of cochleo-vestibular dysfunction) in 5 (6%). Patients with vertigo had a significantly lower relative hearing gain than those without vertigo (Kruskal-Walis test P = 0.02). No significant correlation was found between tinnitus and relative hearing gain (Rho = 0.01, P = 0.93).

Recovery related to the audiogram pattern by Mazzoli:
The audiogram pattern with low or high frequency hearing loss showed the best recovery rate, the poorest recovery rate was found in patients with initial deafness (Fig. 1). There is a statistically significant correlation between the audiogram pattern and the absolute hearing gain (Rho = 0.28, P = 0.01) and the functionally relevant recovery (Rho = -0.3, P = 0.01). Because of the large standard deviation no significant correlation could be found between the audiogram pattern and the relative hearing gain (Rho = -0.03, P = 0.8) (Fig. 4).
Recovery related to the severity of hearing loss:
The severity of hearing loss was evaluated using the difference between the initial PTA of the affected ear and the baseline PTA of the unaffected ear. 34% of patients had a mild hearing loss with an average relative hearing gain of 89% and a functionally relevant recovery in 96% of them; the 9% of patients with initial deafness showed an average relative hearing gain of 69% and a functionally relevant recovery in 43% (Fig. 2). There is a statistically significant correlation between the severity of hearing loss and the absolute hearing gain (Rho = 0.76, P < 0.01) and the functionally relevant recovery (Rho = -0.33, P = 0.002). Because of the large standard deviation no significant correlation could be found between the severity of hearing loss and the relative hearing gain (Rho = -0.21, P = 0.07) (Fig. 5).

Comparison of recovery rate between high-dose dexamethasone therapy with 100mg prednisone therapy:
Table 2 shows detailed information about the two study groups. We found a notable improvement of the mean absolute and relative hearing gain in the dexamethasone study. Also the percentage of patients with functionally relevant recovery was higher in the dexamethasone group (Table 2).
In the study of Cvorovic et al. 451 patients (85%) received treatment within 7 days. 60% of them had functionally relevant recovery of hearing. This percentage dropped to 40% if the patient received treatment later than 7 days after onset. The average time between onset of hearing loss and begin of treatment was 4.9 days averaged over all patients in the study.
We compared the relative recovery rate of the dexamethasone group with the prednisone group in 10 percent steps (Fig. 3).
Furthermore we specified the distribution of the audiogram pattern of the two studies, categorized into 1 of 5 types and added the respective percentage of functionally relevant recovery (Table 3).

Discussion
We retrospectively analysed 79 patients with unilateral ISSHL and found excellent recovery rates when treated with high-dose dexamethasone p.o. in comparison to the previously conducted retrospective study at our hospital, where the patients were treated with 100mg prednisone p.o..
The initial symptoms of ISSHL may be predictors of the prognosis. The presence of vertigo was a negative predictor of the prognosis as many previous studies have reported [Nosrati-Zarenoe and Hultcrantz, 2012]. In our study only 6% of patients complained about vertigo whereas in most other studies this number was higher. The reason for this might be the strict exclusion of all patients with cochleo-vestibular dysfunction as mentioned in the text above. In our study, 81% of affected ears had tinnitus but no correlation was found with recovery rate.
Several studies have concluded that the earlier the patient receives treatment, the better the outcome [Byl, 1984; Shaia and Sheehy, 1976]. But no exact period of time within which therapy should be started has been defined. Considering the spontaneous course of the recovery occurring in approximately two thirds of the cases without treatment [Mattox and Simmons, 1977], usually within the first 2 weeks, no single study has evidenced clearly the beneficial effect of any early treatment. In our study the treatment started in 77 of 79 patients within the first week. No significant difference was detected in final outcome if the treatment was started within the first 24 hours or within the first week. This result suggests that it is not
critical to begin the treatment of ISSHL immediately as an emergency but best as soon as possible and within one week as also stated in other studies [Tran Ba Huy and Sauvaget, 2005; Cvorovic et al., 2008].

A statistically significant relationship was found between severity of hearing loss and functionally relevant recovery. 96% of the patients with mild hearing loss had a functionally relevant recovery, whereas a functionally relevant recovery was found in only 50% of the patients with profound hearing loss (80 – 100 dB) and in 43% of completely deaf ears.

A main limitation of the study was the retrospective approach. Such an approach includes the lack of objectivity of whether symptoms such as tinnitus or vertigo were present or not. In addition, the patients were not part of a protocol; they were treated based on clinical judgment at the time. The standard treatment in the period analysed was dexamethasone p.o. (1. – 3. day 40mg daily, 4. – 6. day 10mg daily) in an ambulant setting. Given the lack of a control group in the present study we could only assess the influence of treatment on recovery by comparing our data with the previously conducted prednisone study at our clinic. Although we used the same inclusion criteria and analysed the same parameters of the same electronic patient database we have to recognise a possible bias in patients collective in these two studies as the data analysis was done by two different persons. Nevertheless, the recovery rate of our dexamethasone group seems noticeably higher than of the prednisone group in the study of Cvorovic. Since there is no evidence for any significant effect of carbogen inhalation, we interpret that as a useless additional old treatment. A reason for the good recovery rate reported in our study might be the higher dosage used in our study as well as the higher potency of dexamethasone with better receptor affinity than prednisone. The study of Hargunani (Hargunani et al., 2006) describes the inner ear distribution of dexamethasone and its receptor affinity there. Nevertheless, there is still a lack of understanding in the mechanism of action of dexamethasone in the inner ear and further investigations in the fields of pharmacology needs to be done.

We also compared our results with other studies in the literature although the inclusion criteria and parameters of analysis are different in many other studies. We found never so good recovery rates neither spontaneously nor with lower steroid treatments. A maximum of 32% to 68% of cases of ISSHL may recover spontaneously [Wilson et al., 1980; Weinaug, 1984] although the study showing 68% spontaneous recovery did include ISSHL cases that did not fulfill the current guidelines. Other authors have documented the efficacy of steroid treatment with reported recovery rates ranging between 35% [Slattery et al., 2005] and 73% [Wilson et al., 1980]. In our study we had a functionally relevant recovery in 87% of patients, which is higher than in all standard prednisone treatment trials reported. We so could demonstrate a beneficial effect when steroid treatment is applied in a high-dose treatment protocol that surpasses clearly the spontaneous recovery rate reported in literature.

Kim reported that patients given an initial dose of 200 mg prednisolone exhibited a significantly better prognosis than did patients initially given 60 mg prednisolone [Kim et al., 1991]. Alexiou could demonstrate that patients with ISSHL receiving a daily intravenous super-high-dose of 500 - 1000 mg of prednisone during the first 3 days showed significantly better recovery of hearing levels compared to those who did not receive glucocorticoids [Alexiou et al., 2001]. This is the highest dose reported in literature. He justified high doses to reach effective glucocorticoid levels in the perilymph and endolymph fluid. On the other hand he mentioned that experimental studies have
shown that all corticoid receptors are occupied when using approximately 300 mg of prednisolone [Kaiser and Kley, 1997]

Our findings also match with another high-dose steroid therapy study [Aoki et al., 2006], where 43 patients with ISSHL were treated with hydrocortisone starting with 1200 mg hydrocortisone (≈ 48 mg dexamethasone) intravenous in a tapering dosage and a second group of 69 patients with lower steroid therapy starting with 600 mg hydrocortisone (≈ 24 mg dexamethasone) in a tapering dosage. The study shows a recovery rate of 90.7% and a complete recovery rate of 55.8% of patients treated with initial dose of 1200 mg hydrocortisone. They suggest that it might result in higher perilymph steroid levels, which so far is not proven by clinical tests.

On contrary, another study [Westerlaken et al., 2007] could not show a significant improvement in recovery rate comparing super-high-dose pulse therapy (300 mg dexamethasone for 3 days) with control treatment (initial 70 mg prednisone in tapering dosage). As the authors explained, the study group might have been too small to achieve statistical significance. Second, we still do not know the precise mechanism of action of dexamethasone in the inner ear. One can guess that at least a 6 day course of treatment is needed for better recovery. Hardly any study is found in literature where treatment lasted only 3 days as in the above mentioned study.

So far there is no proven or universal empiric treatment for ISSHL. Because of the uncertainties regarding cause and pathogenesis, the treatment of ISSHL remains highly empirical. Steroid treatment of ISSHL may act in several ways, producing an anti-viral effect, a local or systemic immunosuppressive effect, a direct anti-inflammatory effect, or possibly by an effect on inner ear homeostasis. Much work remains to elucidate these mechanisms and optimize treatment of this common otologic emergency.

Common side effects of orally applied corticosteroids include insomnia, dizziness, weight gain, increased sweating, gastritis, mood changes, photosensitivity, hyperglycaemia, and hypertension. Severe side effects as pancreatitis, bleeding, cataracts, myopathy, osteoporosis, osteonecrosis manifesting as fractures and aseptic necrosis of the femoral and humeral heads were not registered in our study nor in other studies with short-term high-dose steroid treatment [Alexiou et al., 2001; Aoki et al., 2006]. To minimize the risk of treatment, patients with systemic medical conditions such as insulin-dependent or poorly controlled diabetes, labile hypertension, tuberculosis, peptic ulcer disease, prior psychiatric reactions to corticosteroids, among others, have been excluded. The lack of clear evidence supporting this treatment, as well as the existence of potential adverse treatment effects, supports a large role for shared decision making with patients. Most serious side effects, however, occur with chronic use, and adverse events are usually acceptable and manageable for the short 6-day course of steroids we recommend for ISSHL.

**Conclusion**

Interesting information emerged about the treatment timing, as supported by results; the delay of treatment does not influence the outcome, allowing treating patients within 7 days of onset. As a retrospective analysis, this study lacks formal controls and should be interpreted as a description of a large clinical series. Based on these results, our regime of high-dose dexamethasone treatment used in the analysed period revealed excellent recovery rates in ISSHL without long lasting or significant side effects. However, a prospective randomized controlled trial is planned to verify our results.
It is important for further studies that the definition of ISSHL match precisely the NICDC definition [National Institute on Deafness and Communications Disorders, 2000] and it is imperative that universally accepted definitions to define improvement and recovery in ISSHL are applied, so that between-study comparisons are possible [Stachler et al., 2012].
References

- Byl FM Jr. Sudden hearing loss: eight years’ experience and suggested prognostic table. Laryngoscope 1984;94:647-61
- Hargunani CA, Kempton JB, DeGagne JM, Trune DR: Intratympanic injection of dexamethasone: time course of inner ear distribution and conversion to its active form. Otol Neurotol 2006;27:564-569

Weinaug P: Spontaneous remission in sudden deafness, HNO 1984:32:346-51


Fig. 1. The audiometric pattern by Mazzoli correlates with the relative hearing gain and functionally relevant recovery.
Fig. 2. The severity of hearing loss correlates with the relative hearing gain and functionally relevant recovery. Patients suffering initial a mild hearing loss recover more often than patients with profound hearing loss or initial deafness.
Fig. 3. We compared the relative hearing gain rate of the dexamethasone group with the prednisone group in 10 percent steps. With the high-dose dexamethasone treatment most patients show a relative hearing gain between 80 and 100%. The mean relative hearing gain in the dexamethasone group was 86%, in the prednisone group only 47%.
Fig. 4. The relative hearing gain is plotted against the Mazzoli classification (1 = low frequency, 2 = U-shaped, 3 = high frequency, 4 = flat audiogram, 5 = deafness). Data points are the mean values within each group and error bars indicate two standard deviations.
Fig. 5. The relative hearing gain is plotted against the severity of hearing loss (1 = mild, 2 = moderate, 3 = severe, 4 = profound, 5 = deaf). Data points are the mean values within each group and error bars show two standard deviations.
Fig. 6. It shows the uniform distribution of the recovery rates distributed over the first 7 days. No significant difference in recovery existed between patients who received therapy within 24 hours and patients receiving therapy between 1 and 7 days after onset of symptoms (Rho = 0.016, P = 0.88).
Table 1. Exclusion criteria and number of patients excluded. Other exclusion criteria are mentioned in the text.

<table>
<thead>
<tr>
<th>Exclusion criterion</th>
<th>Number of patients</th>
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<td>Recurrent hearing loss</td>
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<td>Dosage scheme</td>
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<tr>
<td>Average age</td>
<td>50 years (11 - 82 years)</td>
</tr>
<tr>
<td>Average initial hearing loss</td>
<td>51.5 dB</td>
</tr>
<tr>
<td>Average time for begin of treatment</td>
<td>2.1 days</td>
</tr>
<tr>
<td>Number (percentage) of patients with start of treatment within 7 days</td>
<td>77 (97%)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>81%</td>
</tr>
<tr>
<td>Vertigo</td>
<td>6%</td>
</tr>
<tr>
<td>Absolute hearing gain in dB</td>
<td>44.4 dB</td>
</tr>
<tr>
<td>Relative hearing gain in %</td>
<td>86%</td>
</tr>
<tr>
<td>Functionally relevant recovery in %</td>
<td>87%</td>
</tr>
<tr>
<td>Functionally relevant recovery in % when start of treatment within 24 hours</td>
<td>81%</td>
</tr>
<tr>
<td>Functionally relevant recovery in % when start of treatment within 7 days</td>
<td>87%</td>
</tr>
</tbody>
</table>
The pattern of the audiogram was categorized into 1 of 5 types using the classification scheme of Mazzoli. Below the distribution of the 5 types in the two studies (percentage of patients) with the respective percentage of functionally relevant recovery.

<table>
<thead>
<tr>
<th>Type</th>
<th>High-dose dexamethasone</th>
<th>Standard prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient (in %)</td>
<td>Functionally relevant recovery (in %)</td>
</tr>
<tr>
<td>low frequency</td>
<td>6%</td>
<td>100%</td>
</tr>
<tr>
<td>U-shaped</td>
<td>27%</td>
<td>90%</td>
</tr>
<tr>
<td>high frequency</td>
<td>15%</td>
<td>100%</td>
</tr>
<tr>
<td>flat</td>
<td>43%</td>
<td>88%</td>
</tr>
<tr>
<td>deaf</td>
<td>9%</td>
<td>43%</td>
</tr>
</tbody>
</table>