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ORIGINAL ARTICLE

High-Dose Glucocorticoids for the Treatment of Sudden Hearing Loss

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Abstract

BACKGROUND Systemic glucocorticoids are commonly used for primary therapy of idiopathic sudden sensorineural hearing loss (ISSNHL). However, the comparative effectiveness and risk profiles of high-dose over lower-dose regimens remain unknown.

METHODS We randomly assigned patients with sudden hearing loss of greater than or equal to 50 dB within 7 days from onset to receive either 5 days of high-dose intravenous prednisolone at 250 mg/d (HD-Pred), 5 days of high-dose oral dexamethasone at 40 mg/d (HD-Dex), or, as a control, 5 days of oral prednisolone (Pred-Control) at 60 mg/d followed by 5 days of tapering doses. The primary outcome was the change in hearing threshold (pure tone average) in the three most affected contiguous frequencies from baseline to day 30. Secondary outcomes included speech understanding, tinnitus, communication competence, quality of life, hypertension, and insulin resistance.

RESULTS A total of 325 patients were randomly assigned. Mean change in $3PTA_{most\ affected}$ hearing threshold from baseline to 30 days was 34.2 dB (95% CI, 28.4 to 40.0) in the HD-Pred group, 41.4 dB (95% CI, 35.6 to 47.2) in the HD-Dex group, and 41.0 dB (95% CI, 35.2 to 46.8) in the Pred-Control group (P=0.09 for analysis of variance). There were more adverse events related to trial medication in the HD-Pred (n=73) and HD-Dex (n=76) groups than in the Pred-Control group (n=46).

CONCLUSIONS Systemic high-dose glucocorticoid therapy was not superior to a lower-dose regimen in patients with ISSNHL, and it was associated with a higher risk of side

A complete list of the investigators in the HODOKORT trial (Studie zur Wirksamkeit und Sicherheit der HOchDOsis-GlukoKORTikoid-Therapie beim akuten, idiopathischen, sensorineuralen Hörverlust [Efficacy and safety of high dose glucocorticoid therapy for idopathic sudden sensorineural hearing loss]) is provided in the Supplementary Appendix, available at evidence.nejm.org.

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Introduction

Hearing impairment is the most prevalent sensory deficit in humans, affecting 360 million people worldwide. It is responsible for more than 40 million years lived with disability and was ranked as the third most common cause of years lived with disability in the Global Burden of Disease study.[1-5] Sensorineural hearing loss is the most common cause of permanent hearing impairment and may occur because of aging, ototoxic drugs, exposure to injurious noise, or a range of genetic causes. In a high proportion of cases, no etiologic cause can be identified, and the term idiopathic sudden sensorineural hearing loss (ISSNHL) is applied. Most commonly, it is defined as an unexplained, rapid loss of hearing of 30 dB or greater affecting at least three consecutive frequencies within 72 hours, and it often affects only one ear.[6,7]

There is no approved medical treatment for ISSNHL. Systemic glucocorticoids are widely used for primary therapy worldwide.[6,8-11] For salvage treatment, intratympanic application is recommended on the basis of guidelines and meta-analyses of randomized controlled trials (RCTs).[6,8,12,13]

Access to the inner ear fluids with systemic therapy is limited by tight blood–labyrinth barriers.[14] In some countries, it is therefore standard clinical practice to use high doses of systemic glucocorticoids for the initial treatment of ISSNHL.[12,15,16] However, evidence for this practice is limited.[12,15-19]

Common side effects of glucocorticoid treatment are reduced glucose tolerance, enhanced blood glucose levels, exacerbation of preexisting hypertension, or de novo arterial hypertension.[20-22] Nevertheless, the adverse effects of a short course of high-dose systemic glucocorticoids for ISSNHL have not been systematically documented. We therefore conducted an RCT to test the hypothesis that administration of high-dose glucocorticoids for the primary treatment of ISSNHL improves the gain in hearing threshold at 30 days after the start of therapy compared with a more commonly used lower glucocorticoid dose.

Methods

TRIAL OVERVIEW

This three-arm, parallel-group, randomized, triple-blind (participants, investigators, and outcome assessments) clinical trial was conducted at 46 sites in Germany. Sites included otorhinolaryngology doctors' practices and otorhinolaryngology departments at academic and community hospitals that patients reached through the emergency department or through direct referral from private otolaryngologists (clinical sites and investigators are presented in the HODOKORT Trial Investigators Group Section in the Supplementary Appendix). All members of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC) and the German Professional Association of ENT Surgeons were informed about the trial.

The trial included eight visits (in-person, on-site, and either outpatient or inpatient depending on local preference), with the primary end point on day 30 and a follow-up period of 6 months (Table S1).[23] The trial was sponsored by Martin Luther University Halle-Wittenberg, funded by the German Federal Ministry of Education and Research, and approved by the German Competent Authority and the responsible ethics committees at each of the participating centers. Written informed consent was obtained from each patient. The trial was registered before recruitment commenced (German Clinical Trials Register number, DRKS00010738). The commercially available trial drugs and the matching placebos were manufactured, labeled, packed, and shipped to sites by mibe GmbH Arzneimittel (Sandersdorf-Brehna, Germany).

RANDOMIZATION AND ASSIGNMENT

To assure equal assignment of salient variables (age, sex, and baseline hearing threshold) across treatment groups, a computer-generated randomization scheme with a fixed block size of six was used to assign participants in a 1:1:1 ratio to a trial group. Groups were stratified according to baseline hearing threshold (four-frequency pure tone average [$4PTA_{0.5\text{-}4\,kHz}$; 0.5, 1, 2, and 4 kHz] <81 dB hearing level (HL) corresponding to more moderate to severe or severe hearing loss or ≥81 dB HL corresponding to profound hearing loss; the range for all pure tone average [PTA] hearing level was from –10 to 120 dB [higher values

indicate worse hearing]) based on the observation that prognosis is much poorer in profound hearing loss.[4,6,10,24] To ensure concealment of randomization for participants, investigators, and raters for outcome assessments, the following procedure was applied: six identical-looking, participant-specific medication packs — two packs for each trial group — were coded according to the block-wise randomization scheme and delivered to each participating center as one shipment. The codes were assigned to the respective trial site in the electronic randomization system. Upon enrollment, the participant was electronically assigned to one of these six codes and treated with the appropriately numbered package.[23] Therefore, no permuted block randomization was necessary to assure concealment of the assignment of participants to treatment.

PARTICIPANTS

Adults 18 to 80 years of age with unilateral sudden sensorineural hearing loss of unknown etiology were eligible for enrollment. The main inclusion criteria were a difference in hearing threshold of 30 dB or higher for the three most affected contiguous frequencies ($3PTA_{most\ affected}$) in the affected ear in the range of 0.25 to 8 kHz compared with the audiogram of the unaffected ear, a pre-event audiogram of the affected ear if present from outside the trial, or, if no valid audiograms for comparison were available, the median age- and sex-related normative hearing threshold of otologically normal persons as described by the International Organization for Standardization (document number 7029) and an absolute average threshold of 50 dB HL or greater in these frequencies. In all trial sites, clinical routine audiology assessments with the same testing protocols were performed.[23]

The main exclusion criteria were a recurrent ISSNHL in the last 12 months at the affected side, medical pretreatment for the ISSNHL, known systemic or other otologic causes of hearing loss (on the basis of history and physical examination), and conductive or mixed hearing loss (a complete list is provided in the Inclusion and Exclusion Criteria Section in the Supplementary Appendix). Bilateral sudden hearing loss was excluded because it is rare and should prompt consideration of other causes.[6,7,24]

INTERVENTIONS

Participants were randomly assigned to one of three treatment groups (Fig. S1). Each treatment group received a total of 5 days of intravenous therapy concurrent with 10 days of oral therapy (either treatment or placebo). The first treatment group received 5 days of 250 mg daily intravenous prednisolone-21-hydrogensuccinate plus 10 days of oral placebo (high-dose prednisolone group [HD-Pred]). The second treatment group received 5 days of intravenous placebo plus 5 days of 40 mg daily oral dexamethasone followed by 5 days of oral placebo (high-dose dexamethasone group [HD-Dex]). The control group received 5 days of intravenous placebo plus 5 days of 60 mg daily oral prednisolone followed by 5 days of oral tapering doses (standard-dose prednisolone control group [Pred-Control]). Investigators could not detect the difference between placebo and appearance of the medication.

OUTCOMES

The primary outcome was the change in PTA of the three most affected contiguous frequencies between 0.25 and 8 kHz ($3PTA_{most\ affected}$, minimal clinically important difference [MCID] of 10 dB)[6] from baseline to 30 days from the start of intervention using calibrated audiometers according to international standards.

Prespecified secondary outcomes were absolute hearing threshold at 10, 30, and 180 days for $3PTA_{most\ affected}$; change from baseline to 10 days and baseline to 180 days for $3PTA_{most\ affected}$; changes of the average hearing threshold for the three-frequency PTAs (0.5, 1, and 2 kHz [$3PTA_{0.5\text{-}2\,kHz}$]) and four-frequency PTAs (0.5, 1, 2, and 4 kHz [$4PTA_{0.5\text{-}4\,kHz}$]); change in speech understanding (percentage of correctly understood monosyllables ["Freiburger Einsilber"], range from 0 to 100 [higher scores indicate better speech understanding]; MCID 10 percentage points[6]) at 65 and 80 dB sound pressure levels; rates of partial or complete improvement in hearing according to a current clinical practice guideline[6] (details provided in the Partial and Complete Improvement as Outcome Measures section in the Supplementary Appendix); change in communication competence (Hearing Handicap Inventory of the Elderly [HHIE]; range from 0 to 100 [higher scores indicate greater hearing problems]; no MCID known[25,26]); quality of life (12-item Short Form Survey [SF-12][27]; range from 0 to 100 [higher scores indicate better physical and mental health functioning]; no MCID related to hearing known); proportion of participants with recommendation for hearing aid or cochlear implant; proportion of participants receiving salvage (rescue) therapy; change in scores on the tinnitus visual analog rating scales (Fig. S2; range from 0 to 100 [higher scores indicate worse loudness or distress]; MCID 15[28]); proportion of participants with hypertension according to

24-hour ambulatory blood pressure measurement, absent systolic blood pressure nighttime lowering on day 5, or impaired insulin sensitivity at day 5 (Homeostatic Model Assessment for Insulin Resistance [HOMA-IR] $\geq$2.6 with insulin and glucose measured by a central laboratory from venous plasma stored at −20°C)[29]; and delta HOMA-IR. Special safety interest events were worsening of hearing, hyperglycemia (glucose value >100 mg/l or >5.5 mmol/l, at least one visit during the trial), and steroid-induced psychosis.

STATISTICAL ANALYSIS

Assuming a mean improvement in $3PTA_{most\ affected}$ from baseline to day 30 of 30.7 dB (SD 21.3) in the Pred-Control group, we calculated that 88 participants per therapy group would provide the trial with 80% power (two-sided Student's t-test at a level of 0.025, global alpha level of 0.05) to detect a 10 dB improvement in one of the high-dose groups compared with control. With anticipated loss to follow-up, we aimed to recruit 104 participants according to all inclusion and exclusion criteria per therapy group.

The statistical analysis was prespecified in the statistical analysis plan (available in the Supplementary Protocol provided with the full text of this article at evidence.nejm.org). All participants underwent magnetic resonance imaging (MRI) to exclude a vestibular schwannoma as the cause for the sudden hearing loss. However, on the basis of a recommendation by the German Workgroup of Audiologists, Neurotologists, and Otologists of the DGHNO-KHC to avoid excessive noise exposure in the first days after an acute inner ear insult, MRI was only performed later (i.e., after randomization). Participants then given a diagnosis of vestibular schwannoma by MRI were excluded from the analysis. Therefore, this analysis was conducted based on a modified intention-to-treat (mITT) population. Sensitivity analyses were conducted on the basis of a prespecified per-protocol population.

The primary outcome was assessed with the use of analysis of variance to test the null hypothesis of equal mean values in the three groups at a two-sided alpha rate of 0.05. Pairwise comparisons of each high-dose therapy group versus the Pred-Control group and comparison between the high-dose therapy groups were planned by using post hoc Scheffé tests only if the null hypotheses was rejected. Assuming a missing-at-random mechanism, pooling analysis of variance results from 100 multiply imputed data sets using the R packages "mice" and "mitml" was conducted to handle missing values for the primary outcome and was used to be the primary efficacy analysis.[30] A complete case analysis supplemented this primary analysis.[31] All analyses of secondary outcome parameters were based on complete cases. Comparison of secondary outcomes on the basis of audiometric measures was performed with the use of analysis of variance and Scheffé tests analogous to the analysis of the primary outcome. Comparisons of secondary outcomes on the basis of proportions were performed by using chi-square tests or Cochran–Mantel–Haenszel tests for dichotomous outcomes. Continuous outcomes on the basis of speech understanding, scores of communication competence, subjective quality of life, blood pressure, and insulin resistance were checked for normal distribution and analyzed with the use of analysis of variance and Scheffé tests if they were normally distributed or Kruskal–Wallis and U tests if they were nonnormally distributed.

Effect estimators, including 95% confidence intervals (CIs), for comparison between groups were computed by using mean differences for continuous outcomes and relative risks for proportions. For the primary and secondary outcomes, we also conducted prespecified analyses in subgroups defined according to baseline hearing threshold at the affected ear ($4PTA_{0.5\text{-}4\,kHz}$ <81 dB HL or $4PTA_{0.5\text{-}4\,kHz}$ $\geq$81 dB HL). Further subgroup analyses were defined post hoc according to a plan for additional statistical analyses. The analyses of the secondary outcomes did not include a provision for correction for multiplicity and were based on selection of complete cases without using any imputation concerning missing values. The results are therefore reported as point estimates and unadjusted 95% CIs and should not be used to infer treatment effects.

SAS version 9.4 (SAS Institute, Inc.) and R version 4.3.2 (R Foundation for Statistical Computing) were used for analyses.

Results

CHARACTERISTICS OF THE PARTICIPANTS

From November 2016 to March 2020, a total of 325 patients were randomly assigned to treatment at 39 centers (Fig. 1). According to the protocol, 17 patients (5%)

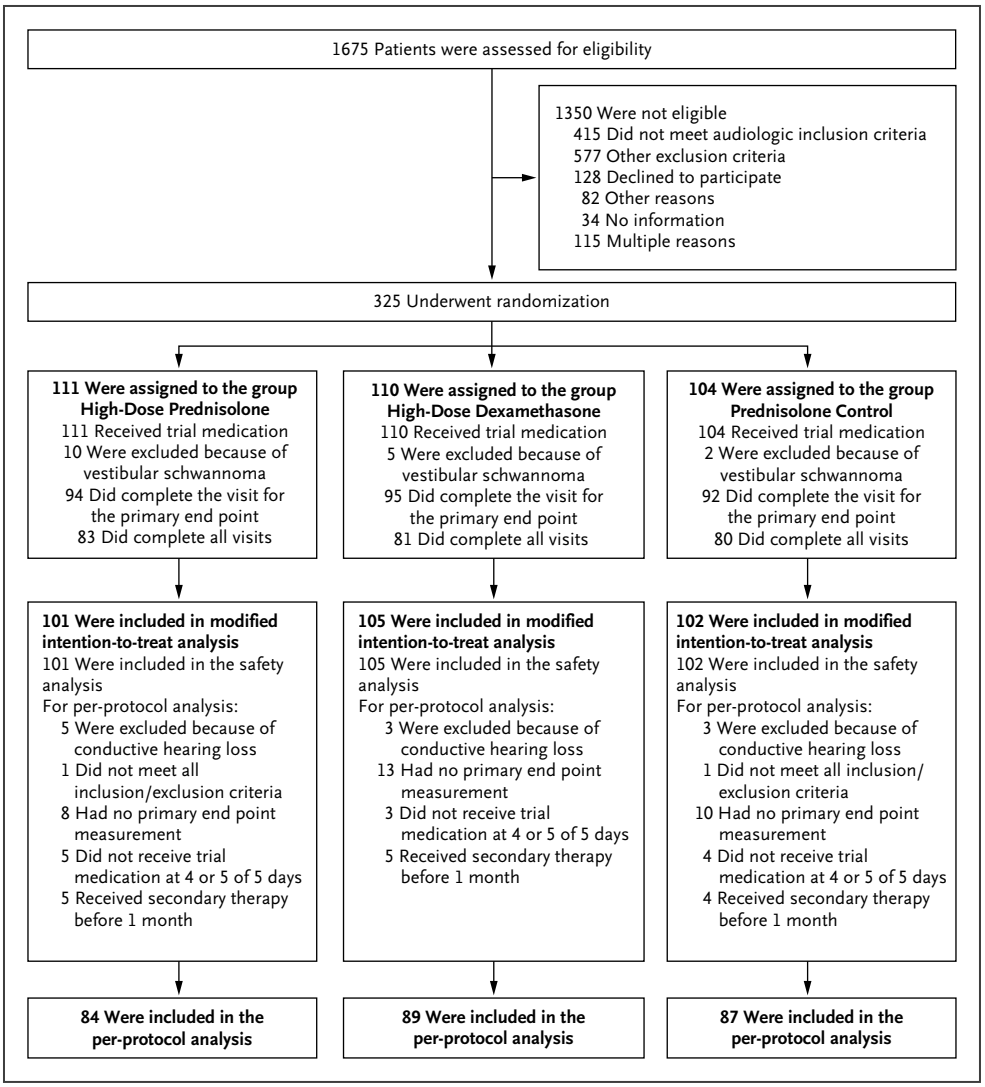

Figure 1. Consolidated Standards of Reporting Trials Flowchart.

The flowchart shows the screening and random assignment of participants and groups for analysis.

were excluded from the analysis because of the presence of a vestibular schwannoma diagnosed after randomization. All participants in the mITT population (n=308) received trial medication; thus, the safety population is identical to the mITT population. For a per-protocol analysis, an additional 48 participants were excluded, mostly because they were missing the primary end point measurement. Baseline characteristics were balanced in the three groups except for differences in preexisting hypertension (Table 1). The population included in this trial was broadly representative of and generalizable to adult patients with ISSNHL (Table S10).

PRIMARY OUTCOME

Mean change in $3PTA_{\text{most affected}}$ hearing threshold from baseline to 30 days was 34.2 dB (95% CI, 28.4 to 40.0) in the HD-Pred group, 41.4 dB (95% CI, 35.6 to 47.2) in the HD-Dex group, and 41.0 dB (95% CI, 35.2 to 46.8) in the Pred-Control group (P=0.09 for analysis of variance) (Table 2). The difference in change in $3PTA_{\text{most affected}}$ hearing thresholds was –6.8 dB (95% CI, –15.1 to 1.4) between HD-Pred and Pred-Control, 0.5 dB (95% CI, –7.8 to 8.7) between HD-Dex and Pred-Control, and –7.2 dB (95% CI, –15.5 to 1.0) between HD-Pred and HD-Dex. Results according to subgroup of complete cases are presented in Table S2.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Treatment Groups		Control Group	
	HD-Pred (n=101)	HD-Dex (n=105)	Pred-Control (n=102)	All (N=308)
Age† — yr	57.3±13.4	54.1±15.1	55.1±13.7	55.5±14.1
Men/women† — N	60/41	65/40	60/42	185/123
Right/left† (affected ear) — N	44/57	47/58	43/59	134/174
Hearing† — dB $PTA_{most\ affected}$				
Affected ear	80.1±20.4	81.1±21.3	77.7±19.4	79.7±20.4
Median [25th, 75th percentiles]	75.0 [63, 92]	78.3 [65, 95]	72.8 [65, 90]	75.2 [64, 92]
Unaffected ear	15.8±9.2	13.4±8.0	14.9±8.6	14.7±8.6
Median [25th, 75th percentiles]	13.3 [8, 20]	11.7 [8, 17]	13.8 [9, 20]	12.7 [8, 18]
Word recognition — % correct at 65 dB SPL				
Affected ear	18.6±28.4	15.5±27.9	17.8±28.1	17.3±28
Median [25th, 75th percentiles]	0.0 [0, 25]	0.0 [0, 18]	0.0 [0, 30]	0.0 [0, 30]
Missing values	18 (17.8)	22 (21.0)	28 (27.5)	68 (22.1)
Unaffected ear	92.4±15.1	91.0±22.5	91.8±17.3	91.7±18.6
Median [25th, 75th percentiles]	97.5 [90, 100]	100 [95, 100]	100 [93, 100]	100 [93, 100]
Missing values	27 (26.7)	26 (24.8)	35 (34.3)	88 (28.6)
Other symptoms				
Tinnitus†	78 (77.2)	89 (84.8)	80 (78.4)	247 (80.2)
Spontaneous nystagmus‡	10 (9.9)	12 (11.4)	9 (8.8)	31 (10.1)
Pathologic caloric test‡	9 (8.9)	11 (10.5)	10 (9.8)	30 (9.7)
Pathologic vHIT‡§	2 (2.0)	2 (1.9)	4 (3.9)	8 (2.6)
Preexisting risk factors				
Myocardial infarction†	7 (6.9)	6 (5.7)	7 (6.9)	20 (6.5)
Coronary heart disease†	4 (4.0)	10 (9.5)	9 (8.8)	23 (7.5)
Atrial fibrillation†	7 (6.9)	2 (1.9)	2 (2.0)	11 (3.6)
Hypertension†	53 (52.5)	48 (45.7)	39 (38.2)	140 (45.5)
Diabetes†	11 (10.9)	14 (13.3)	13 (12.7)	38 (12.3)
Stroke†	1 (1.0)	3 (2.9)	1 (1.0)	5 (1.6)

* Values are presented as the mean (±SD) or no. (%) unless otherwise indicated. dB $PTA_{most\ affected}$ denotes decibel pure tone average hearing level over the three most affected frequencies; HD-Dex, high-dose dexamethasone group; HD-Pred, high-dose prednisolone group; Pred-Control, standard-dose prednisolone control group; SPL, sound pressure level; and vHIT, video head impulse test.

† There were no missing values.

‡ Reporting of missing values was not applicable.

§ This test is a further development of the head impulse test according to Halmagyi and Curthoys for examination of the vestibulo-ocular reflex, a reflex acting to stabilize gaze during head movement, with eye movement because of activation of the vestibular system. This test can provide site-specific information on the vestibular system and its function. A pathologic test is characterized by a reduced gain and/or corrective saccades. Another way of testing the vestibulo-ocular reflex response is a caloric reflex test, which is an attempt to induce nystagmus by applying cold or warm water into the outer ear canal. A pathologic test is characterized by a missing or reduced response.

SECONDARY OUTCOMES

Participants in the HD-Pred group exhibited poorer absolute final thresholds and smaller improvements than those in the HD-Dex and Pred-Control groups ($3PTA_{most\ affected}$, $3PTA_{0.5\text{-}2\,kHz}$, and $4PTA_{0.5\text{-}4\,kHz}$) at any of the time points. In the HD-Pred group, fewer participants experienced complete hearing improvement at day 30 compared with those in the HD-Dex or Pred-Control group. The HD-Pred and HD-Dex groups showed worse speech understanding as demonstrated by lower final word recognition scores compared with the control group (Table 2 and Table S3).

In the patient-reported outcome measures HHIE and SF-12, a slight mean improvement in each therapy group was observed. In both groups treated with high-dose therapy, there were more recommendations for hearing aids or cochlear implants compared with the control group, especially for the HD-Pred group. Approximately 20% of

Table 2. Outcome Measures of Hearing Thresholds and Word Recognition.*

Outcome (Modified Intention-to-Treat Analysis)	Treatment Groups		Control Group	P Value
	HD-Pred	HD-Dex	Pred-Control	
Primary outcome				
Change in $PTA_{most\ affected}$ — dB at 30 days	34.2±25.8	41.4±26.2	41.0±26.0	0.09†
No. of participants	101	105	102	
Secondary outcomes				
10–13 days (end of treatment)				
$PTA_{most\ affected}$ — dB HL	54.1±29.6	47.4±32.4	45.2±30.4	
No. of participants	94	98	96	
Change in $PTA_{most\ affected}$ — dB	24.1±22.2	32.0±26.7	32.5±23.7	
No. of participants	89	94	94	
Change in $3PTA_{0.5\text{-}2\ kHz}$ — dB	20.9±21.4	28.8±24.8	26.8±25.5	
No. of participants	89	94	95	
Change in $4PTA_{0.5\text{-}4\ kHz}$ — dB	19.3±20.0	26.3±22.7	26.3±21.6	
No. of participants	89	94	94	
30 days (time of primary end point)				
$PTA_{most\ affected}$ — dB HL	45.8±28.4	39.3±30.7	36.6±27.6	
No. of participants	98	98	96	
Change in $3PTA_{0.5\text{-}2\ kHz}$ — dB	29.8±26.4	38.2±25.7	35.1±23.8	
No. of participants	94	96	93	
Change in $4PTA_{0.5\text{-}4\ kHz}$ — dB	27.4±24.6	34.5±23.4	33.1±21.6	
No. of participants	94	96	93	
Word recognition score — %	57.4±41.4	61.1±41.3	70.4±39.6	
No. of participants	97	95	93	
Change in word recognitions score from baseline — %	37.5±35.9	47.8±40.4	51.9±39.5	
No. of participants	89	93	87	
Hearing improvement on the basis of PTA‡ — no. (%)				
Partial improvement	44 (43.6)	36 (34.3)	40 (39.2)	
Complete improvement	33 (32.7)	48 (45.7)	46 (45.1)	
Hearing improvement on the basis of PTA and word recognition‡ — no. (%)				
Partial improvement	26 (25.7)	19 (18.1)	23 (22.5)	
Complete improvement	24 (23.8)	40 (38.1)	40 (39.2)	
6-month follow-up				
$PTA_{most\ affected}$ — dB HL	40.7±26.4	34.2±26.1	31.3±26.1	
No. of participants	83	76	77	
Change in $PTA_{most\ affected}$ — dB	38.1±25.2	45.4±24.7	44.6±23.2	
No. of participants	83	76	77	
Change in $3PTA_{0.5\text{-}2\ kHz}$ — dB	33.8±25.0	41.1±24.4	38.8±24.6	
No. of participants	84	76	77	
Change in $4PTA_{0.5\text{-}4\ kHz}$ — dB	30.6±23.3	36.5±22.5	36.0±22.6	
No. of participants	84	76	77	
Word recognition score — %	61.0±41.0	68.7±39.7	74.4±36.4	
No. of participants	87	82	84	

(continued)

Table 2. (cont.)

Outcome (Modified Intention-to-Treat Analysis)	Treatment Groups		Control Group	P Value
	HD-Pred	HD-Dex	Pred-Control	
Change in word recognition score from baseline — %	41.0±36.6	55.6±39.3	54.9±39.1	
No. of participants	78	73	71	

* Values are presented as the mean (±SD) unless otherwise indicated. Analyses of secondary outcomes are on the basis of complete cases. The PTA hearing level ranges from −10 to 120 dB, with higher values indicating worse hearing (minimally clinical important difference of 10 dB). The word recognition score using monosyllables ranges from 0 to 100%; higher scores indicate better speech understanding (minimally clinical important difference of 10%). HD-Dex denotes high-dose dexamethasone group; HD-Pred, high-dose prednisolone group; HL, hearing level; Pred-Control, standard-dose prednisolone control group; PTA, pure tone average; $PTA_{most\ affected}$, pure tone average over the three most affected frequencies; $3PTA_{0.5\text{-}2\,kHz}$, three-frequency pure tone average; and $4PTA_{0.5\text{-}4\,kHz}$, four-frequency pure tone average.

† The P value is shown for the multiple imputation analysis of variance test of the null hypotheses of equal mean change in $PTA_{most\ affected}$ in decibels at 30 days in all three groups.

‡ Partial hearing improvement was calculated based on hearing threshold ($PTA_{most\ affected}$ >10 dB improvement) and based on the recommendations in a Clinical Practice Guideline[6] (return to serviceable hearing or >10 dB improvement for ears with serviceable hearing at baseline). Complete hearing improvement was calculated in comparison to the reference audiograms at baseline (a difference of ≤10 dB [hearing improvement based on PTA] or ≤10 dB and ≤10% WRS [hearing improvement based on PTA and WRS], respectively). For details, see "Partial and Complete Improvement Outcome Measures" in the Supplementary Appendix.

participants were treated with "salvage" therapy. In all three groups, tinnitus improved over time, although less so in the HD-Pred group (Table 3 and Table S4).

Hypertension according to 24-hour ambulatory blood pressure measurement on day 5 was observed in 112 (36.4%) participants. The number of participants experiencing hypertensive blood pressure was similar in all intervention groups. Mean 24-hour blood pressure was lower in participants treated with dexamethasone than those in the control group. Absent nighttime lowering of blood pressure was observed in 88 participants (28.6%), with no difference between the three groups. A HOMA-IR of greater than or equal to 2.6 at day 5 was observed in 69 (22.4%) participants. In the HD-Dex group, more participants experienced a hyperglycemic episode, and HOMA-IR increased more, although fewer participants had an HOMA-IR of greater than or equal to 2.6 at day 5 (Table 3 and Table S4).

SUBGROUPS

The prespecified subgroup analyses showed poorer outcomes for participants with worse initial hearing loss ($4PTA_{0.5\text{-}4\,kHz}$ ≥81 dB HL) but, in general, similar results for the differences between treatment groups (Table S5). Results of other prespecified post hoc analyses are shown in Tables S6 to S8 and in forest plots (Figs. S3 to S5).

SAFETY

In the HD-Pred group, 139 adverse events (AEs) were reported, with a maximum of eight events per participant. In the HD-Dex group, there were 135 events (up to 10 per participant), and in the control group, there were 90 events (up to 5 per participant). The mean number of AEs per participant was smaller in the control group than in the two high-dose groups. Seventy-three (52.5%) of the events in the HD-Pred group, 76 (56.3%) of the events in the HD-Dex group, and 46 (51.1%) of the events in the control group were classified as causally treatment related. The mean number of treatment-related events was 0.7 per patient in both high-dose groups and 0.5 per patient in the control group.

Ten events among nine participants were rated as serious adverse events (SAEs), of which four were rated as causally related to trial medication. Of those, one participant (in the HD-Dex group) was temporarily hospitalized for singultus, and two participants (in the HD-Dex group) were temporarily hospitalized because of hyperglycemia, which was treated with insulin. All resolved at the end of trial. One participant in the HD-Pred group experienced an infected carotid artery stent, possibly because of glucocorticoid-related immunosuppression. The participant died of cerebral ischemia and multiple cerebral hemorrhage after surgical replacement of the infected stent. The other five SAEs judged as not related to trial medication were categorized as SAEs owing to hospitalization and were resolved (Table 4 and Table S9).

Discussion

In this randomized, triple-blind, parallel-group trial, the administration of high-dose prednisolone or dexamethasone for primary therapy of ISSNHL was not superior to a more

Table 3. Outcome Measures of Impaired Insulin Resistance, Hyperglycemia, Tinnitus, Communication Competence, and Quality of Life.*

Secondary Outcomes (Modified Intention-to-Treat Analysis)	Treatment Groups		Control Group
	HD-Pred	HD-Dex	Pred-Control
Day 5 of medication			
Impaired insulin resistance, HOMA-IR ≥2.6 — no. (%)	26 (28.6)	14 (14.7)	29 (31.5)
No. of participants	91	95	92
Hyperglycemia — no. (%)	6 (6.2)	12 (11.8)	3 (3.0)
No. of participants	97	102	99
Blood pressure			
Hypertension (24-h measurement) — no. (%)	44 (46.8)	32 (34.0)	36 (37.9)
No. of participants	94	94	95
Systolic pressure — mm Hg	133.3±13.5	130.1±15.8	132.6±16.7
No. of participants	94	96	96
Diastolic pressure — mm Hg	78.7±10.2	75.9±9.8	78.9±10.1
No. of participants	94	96	96
Absent nocturnal fall — no. (%)	28 (30.4)	27 (29.7)	33 (36.3)
No. of participants	92	91	91
30 days (time of primary end point)			
Tinnitus, VAS score as improvement from baseline (distress) — median [25th, 75th percentiles]	–8.0 [–29.0, 5.0]	–25.0 [–50.0, 0.0]	–22.0 [–40.0, –5.0]
No. of participants	68	76	67
Tinnitus, VAS score as improvement from baseline (loudness) — median [25th, 75th percentiles]	–5.0 [–20.0, 5.0]	–16.5 [–37.5, 0.0]	–20.0 [–31.0, –5.0]
No. of participants	67	76	68
Communication competence (HHIE)			
Change difference from baseline — median [25th, 75th percentiles]	4.0 [–2.0, 18.0]	5.0 [–4.0, 20.0]	9.0 [–2.0, 21.0]
No. of participants	77	78	72
Quality of life, SF-12, physical score as improvement from baseline — median [25th, 75th percentiles]	–0.5 [–3.8, 6.9]	0.7 [–2.6, 6.3]	2.9 [–4.3, 8.9]
No. of participants	85	85	88
Quality of life, SF-12 mental score as improvement from baseline — median [25th, 75th percentiles]	0.0 [–6.9, 7.6]	2.1 [–2.0, 4.6]	2.1 [–4.3, 6.1]
No. of participants	85	85	88
6-month follow-up			
Tinnitus, VAS score as improvement from baseline (distress) — median [25th, 75th percentiles]	–10.0 [–32.0, –1.0]	–30.0 [–57.0, –7.0]	–30.0 [–46.0, –5.0]
No. of participants	61	57	57
Tinnitus, VAS score as improvement from baseline (loudness) — median [25th, 75th percentiles]	–10.0 [–25.5, 1.0]	–23.0 [–44.0, 0.0]	–25.0 [–40.0, –10.0]
No. of participants	61	57	58
Communication competence (HHIE)			
Change difference from baseline — median [25th, 75th percentiles]	8.0 [0.0, 16.0]	8.0 [0.0, 24.0]	12.0 [0.0, 22.0]
No. of participants	62	62	67

(continued)

Table 3. (cont.)

Secondary Outcomes (Modified Intention-to-Treat Analysis)	Treatment Groups		Control Group
	HD-Pred	HD-Dex	Pred-Control
Recommendations for hearing aid or cochlear implant — no. (%)	46 (52.3)	36 (42.9)	26 (30.2)
No. of participants	88	84	86
Rescue therapy received — no. (%)	28 (27.7)	20 (19.0)	20 (19.6)
No. of participants	101	105	102
Quality of life, SF-12, physical score as improvement from baseline — median [25th, 75th percentiles]	3.3 [–1.8, 9.3]	2.2 [–2.7, 9.0]	3.2 [0.0, 10.8]
No. of participants	72	71	78
Quality of life, SF-12 mental score as improvement from baseline — median [25th, 75th percentiles]	1.3 [–3.3, 14.1]	1.5 [–2.3, 5.7]	3.7 [–1.6, 9.0]
No. of participants	72	71	78

* Values are presented as the mean (±SD) unless otherwise indicated. Analyses of secondary outcomes are on the basis of complete cases. The HHIE ranges from 0 to 100; higher scores indicate greater hearing problems, and there is no minimally clinical important difference known. The SF-12 ranges from 0 to 100; higher scores indicate better physical and mental health functioning, and there is no minimally clinical important difference related to hearing known. The tinnitus VAS scale ranges from 0 to 100; higher scores indicate worse loudness or distress, and there is a minimally clinical important difference of 15. HD-Dex denotes high-dose dexamethasone group; HD-Pred, high-dose prednisolone group; HHIE, Hearing Handicap Inventory for the Elderly; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; Pred-Control, standard-dose prednisolone control group; SF-12, 12-item Short Form Survey; and VAS, visual analog scale.

commonly used lower dose of prednisone with respect to hearing recovery at 30 days. Moreover, treatment with high-dose glucocorticoids was associated with more AEs and SAEs than the control group.

Glucocorticoid treatment may lead to hypertension or disturbance of glucose metabolism, particularly in predisposed individuals. Our trial suggests only minor differences in such risk between the different therapies. Because ISSNHL also occurs in participants with hypertension or impaired glucose sensitivity, these participants need to be closely monitored. In the group of participants treated with dexamethasone, fewer exhibited impaired insulin resistance, and mean diastolic blood pressure was lower than when treated with prednisolone. Given the fact that glucocorticoids activate two types of steroid receptors, glucocorticoid receptors and mineralocorticoid receptors, this finding may be because of the low mineralocorticoid activity of dexamethasone.[32,33] However, a higher rate of hyperglycemic events was found in this group.

Why did we not find a dose effect with the systemic treatment of ISSNHL with glucocorticoids? Despite widespread acceptance of glucocorticoids as the standard for primary treatment of ISSNHL, there is no proof of efficacy.[6,8,10,13,24,34] The current trial, therefore, raises several important possibilities. First, glucocorticoids may not be effective in treating ISSNHL (or other acute inner ear disorders). Second, they may actually be harmful based on their association with increased numbers of AEs. Third, although the underlying pathophysiology of some ISSNHL may be treatable by glucocorticoids, dose, timing, and selection of the type of glucocorticoids (e.g., with respect to the activation of mineralocorticoid receptors and glucocorticoid receptors) might be crucial.

The etiology of ISSNHL is, by definition, unknown. Several hypotheses have been offered, such as infectious (viral and bacterial), inflammatory, vascular, autoimmune, and genetic predisposition; however, these hypotheses have yet to be confirmed.[6,35-37] Glucocorticoids likely neither adequately address all hypothetical causes of ISSNHL nor influence many of the common pathophysiological pathways of insults to the cochlea such as oxidative stress, apoptosis, synaptopathy, and neural degeneration. The protective effects of different stressors against trauma-induced inner ear function are discussed as a direct effect of glucocorticoids on the cochlea in addition to their anti-inflammatory action.[38] Our observations are of interest in view of the known balanced and complementary corticosteroid action in the brain[39] and suggestions from preclinical studies that different actions (and doses) of glucocorticoids have different effects also in the auditory system.[38,40,41] For example, a recent study using knockout mice with limbic deletion of glucocorticoid receptors or mineralocorticoid receptors showed that top-down

Table 4. AEs and SAEs.*

Characteristic	Treatment Groups				Control Group		All (N=308)	
	HD-Pred (n=101)		HD-Dex (n=105)		Pred-Control (n=102)			
	No. of AEs Reported	Unique Participants	No. of AEs Reported	Unique Participants	No. of AEs Reported	Unique Participants	No. of AEs Reported	Unique Participants
AEs								
No AE reported — no. (%)		36 (35.6)		42 (40.0)		47 (46.1)		125 (40.6)
AEs total	139		135		90		364	
No. of AEs per participant	1.4±1.6		1.3±1.8		0.9±1.1		1.2±1.6	
AEs with causality attributed to trial drug	73		76		46		195	
Total AEs — %	52.5		56.3		51.1		53.6	
No. of AEs related to trial drug per participant	0.7±1.2		0.7±1.2		0.5±0.8		0.6±1.0	
AEs of special interest								
Increase in hearing loss >10 dB from baseline	2	2	0	0	3	3	5	5
Hyperglycemia >100 mg/l	18	12	21	20	15	12	52	42
Steroid psychosis	0	0	0	0	0	0	0	0
SAEs								
SAEs total — no. (%)	4	3 (3.0)	4	4 (3.8)	2	2 (2.0)	10	9 (2.9)
Treatment-related SAEs	1	1	3	3	0	0	4	4
Singultus			1				1	
Hyperglycemia			2				2	
Carotid stent infection†	1						1	
Nontreatment-related SAEs	3	3	1	1	2	2	6	6
Intracranial bleedings†	1						1	
Increase in hearing loss	2				1		3	
Increase in dizziness			1		1		2	

* Values are presented as the mean (±SD) unless otherwise indicated. AE denotes adverse event; HD-Dex, high-dose dexamethasone group; HD-Pred, high-dose prednisolone group; Pred-Control, standard-dose prednisolone control group; and SAE, serious adverse event.

† Because this is the same participant, the numbers of unique patients with SAEs in the groups HD-Pred and All do not appear to add up.

mineralocorticoid receptor/glucocorticoid receptor signaling contributes to cochlear sound processing, with differential influences of these receptors on the discharge rate and synchrony of auditory nerve responses.[41] Although there is a known complex association between neurotrophins (e.g., brain-derived neurotrophic factor) and glucocorticoids, and because neurotrophins are important for survival of cochlear spiral ganglion neurons and synaptogenesis,[42,43] it needs to be better investigated how glucocorticoids influence repair processes in the auditory system. At this point, however, it remains hypothetical how the findings on physiological levels of glucocorticoids relate to the glucocorticoid doses used for therapy and if they are helpful or detrimental to auditory repair processes after ISSNHL.

Limitations of the current trial include the lack of a placebo control. Because systemic glucocorticoids have been considered standard treatment of ISSNHL for nearly 50 years,[6,8-11] at the time of this trial, a placebo group seemed neither ethically justified nor practically possible with respect to patient expectations and recruitment. With the results from this trial, however, a placebo-controlled trial or — if this is not feasible — a randomized controlled dose de-escalation trial is now warranted. In addition, the reports for the secondary outcomes, including safety, were based on complete cases, which may have introduced bias. There are other challenges associated with RCTs of ISSNHL, including the choice of outcome parameters, determining a minimal important difference between treatment groups (absolute differences or relative risks for the numbers of patients improving), and missing internationally accepted standards. We considered here currently available suggestions for reporting of outcomes as discussed elsewhere in detail.[6,13,24,44-47]

Despite prompt therapy with glucocorticoids, audiologic deficits persisted in 61 to 76% of participants. Given the impact of hearing loss on humans,[1-5] including increased risk for cognitive decline and dementia,[48-50] the search for the causes of this condition and the development of medical, biologic, or genetic therapies for sensorineural hearing loss remain of paramount importance.[5,45,47,50-53]

Conclusions

Therapy with systemic high-dose glucocorticoids did not show benefits for patients with sudden sensorineural hearing loss compared with standard lower doses of glucocorticoids but increased the risk of side effects. Further trials are needed to compare glucocorticoid therapy with placebo or — if this is not feasible — with further dose de-escalation.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

A data-sharing statement provided by the authors is available with the full text of this article at NEJM.org.

The HODOKORT trial (Studie zur Wirksamkeit und Sicherheit der HOchDOsis-GlukoKORTikoid-Therapie beim akuten, idiopathischen, sensorineuralen Hörverlust [Efficacy and safety of high dose glucocorticoid therapy for idopathic sudden sensorineural hearing loss]) was funded by the German Federal Ministry of Education and Research (BMBF) in the grant program "Clinical trials of high relevance for patient care" within the German Federal Government's "Health Research Framework Program" (grant number 01KG1427; to Dr. Plontke). The trial was endorsed by by the German Study Center for Otolaryngology, Head and Neck Surgery, a joint institution of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery and the German Professional Association of ENT Surgeons, which advertised the trial through their publication organs and conferences.

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