Corticosteroid Treatment of Idiopathic Sudden Sensorineural Hearing Loss: Randomized Triple-Blind Placebo-Controlled Trial

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Objective: To compare the effect of Prednisolone and placebo on recovery of unilateral Idiopathic Sudden Sensorineural Hearing Loss.

Study design: Prospective, randomized, triple-blind placebo-controlled multicentre trial.

Setting: Four tertiary and ten secondary referral centers

Patients: Of 103 patients randomly assigned, 93 were included in the modified Intention-To-Treat analysis. The patients, aged 18–80 years were seeking care within one week after onset of acute unilateral sensorineural hearing loss with a mean decrease of ≥ 30 dB in the three most affected contiguous frequencies.

Intervention: Patients were randomly assigned in permuted blocks of ten to receive Prednisolone or placebo in tapering doses from 60 mg for 3 days, and thereafter 10 mg less each day until day 8. If complete recovery, no more medication given, otherwise medication continued at 10 mg per day until day 30. Final follow-up was after 3 months with audiogram. 47 patients received Prednisolone and 46 placebo.

Main outcome measure: Primary endpoint was efficacy of treatment on recovery at day 90. Secondary endpoints were prognostic factors for hearing recovery. Analyses by modified Intention-To Treat and Per Protocol.

Results: Hearing improvement for 47 Prednisolone treated patients was 25.5 ± 27.1 dB compared to 26.4 ± 26.2 dB for 46 placebo treated patients at day eight and 39 ± 20.1 dB vs. 35.1 ± 38.3 dB after three months. Vertigo had significant negative effect on hearing improvement and inflammatory signs in laboratory work-up a positive prognostic effect, irrespective of treatment.

Conclusion: Prednisolone in customary dosage does not seem to influence recovery of idiopathic sudden sensorineural hearing loss.

Keywords: Idiopathic Sudden Sensorineural Hearing Loss, Sudden Deafness, Prednisolone, Randomized, Triple-blind trial.

INTRODUCTION

Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) is by definition a disease with unknown etiology and pathogenesis. Treatments used have been built on different hypotheses of the etiology such as vascular compromise (1-3), viral/inflammatory causes (4) or perilymphatic fistula (5,6).

Corticosteroid treatment was developed in the USA during the 70's based on the hypothesis that most ISSNHL cases had a viral/inflammatory cause. In the 80's, two studies where corticosteroids were used demonstrated a positive effect (7,8). One of these trials by Wilson et al. 1980 was placebo controlled and randomized. This Wilson study has been the foundation for a therapy tradition that over many years has become internationally the most common treatment for ISSNHL. Corticosteroid dosage has been successively increased without any evidence of better effect (9). Several later investigations with corticosteroids have not been able to demonstrate any specific effect even if administered through the round window (10). Moreover, the Wilson study has later been criticized by Cochrane reports 2006 and 2009 as not fulfilling modern standards for RCT (11,12). When studying a disease that, without treatment, has about a 30% chance of total, and additional 30% chance of partial recovery (13,14), a strict RCT with a sufficient number of patients is needed to show evidence of effect.

The purpose of the present investigation is to evaluate whether, in comparison to placebo, corticosteroids (Prednisolone) used in high tapering dosage in any way influence the outcome of ISSNHL. The chosen dosage and therapy scheme is based on the highest level accepted and used among Swedish otorhinolaryngologists and audiologists today (15,16).

MATERIALS AND METHODS

Study design

A randomized triple-blind¹ placebo-controlled multicenter trial on the effect of corticosteroids on ISSNHL was performed between January 2006 and September 2010. 14 public otorhinolaryngological centers in Sweden were successively enrolled and each center contributed for 1 to 4.8 years.

Patients asked to participate were those aged 18–80 years, referred by general practitioners or seeking care directly, presenting with sudden onset of hearing loss developing within 24 hours, and without any known etiology (no earlier or present ear diseases). The average change in hearing threshold should be ≥ 30 dB for the three most affected contiguous frequencies in the affected ear. Enrollment and treatment was to be started within 7 days from onset.

Each study center had one physician responsible for implementing the study. Exclusion criteria were the common medical reasons for not using corticosteroids: pregnancy, diabetes, chronic infections, peptic ulcer, uncompensated heart disease, recent surgery, or psychiatric disease. The patients' ordinary medication for concomitant disease was permitted except vascular, antiviral or corticosteroid treatment.

The study, EudraCT 2005-001487-32 was approved by the regional ethics review board and Swedish Medical Products Agency.

Randomization

The active (*Prednisolonum* mixed with *Lactosum monohydricum DCL 11*) and placebo (*Lactosum monohydricum DCL 11*) capsules were identical in color, size, weight and packaging. Randomization was carried out by Apoteket Production & Laboratories (APL Stockholm) independent of participating researchers in permuted-blocks of 10 and allocation ratio of 1:1. The randomization code was double-blinded and kept by APL. Packaged randomized/numbered bottles containing 60 capsules were delivered to the university hospital's pharmacy in Linköping for further distribution and the investigators were supplied with sealed, individual code-break envelopes to be opened in case of a serious adverse event. All study personnel, participants, and data analysts were blinded to treatment allocation.

¹ Triple-blind trial is a trial in which neither the subject, the person administering the treatment nor the person evaluating the response to treatment knows which treatment a particular subject is receiving.

Clinical examination

A case report form (CRF) was collected for each patient. The CRF consisted of a questionnaire, audiograms, information on radiological investigations (MRI or CT), laboratory work-ups, brainstem response audiometry (BRA) and vestibular work-up, according to the different clinics' praxis, and information on adverse events and/or serious adverse events. The questionnaire was a modified version of one used for the Swedish database for ISSNHL (15,16). It covered time course of the hearing loss's onset and associated symptoms such as tinnitus and vertigo, potential precipitating events preceding the SSNHL, patient's past medical history, medication for concomitant disease, hearing loss and associated symptoms before the SSNHL, and family history of different diseases especially hearing loss.

After an initial pure tone audiogram, new audiograms were taken at three follow-up visits: day eight of treatment, after one month, and three months. In cases where patients were known to have prior diagnosed hearing loss, a copy of any available previous audiogram was included in the CRF.

Intervention

All patients received written information about Sudden Sensorineural Hearing Loss, the aim of the study and instructions for taking the drugs. After informed consent to participate, the physician allocated the next available numbered study drug bottle containing Prednisolone or placebo. Prednisolone as 10mg capsules, or placebo was given as a single dose of 60mg daily for three days; the dose was then reduced by 10mg per day, with a total treatment period of eight days. If recovery was complete (complete recovery=the mean difference in hearing thresholds for the three most affected contiguous frequencies comparing the initial audiogram and audiogram at the follow-up <10 dB), treatment stopped, otherwise medication was continued at 10mg daily to a total of 30 days from beginning.

Patients were asked to return capsule containers at the first and the last follow-up visit. Compliance was checked by counting the capsules left in the returned containers.

Follow-up visits were scheduled for day eight $\pm$ one day, 1 month and 3 months after randomization. If recovery was complete at day eight, the next follow-up was at 3 months.

Adverse Events²

At each follow-up visit on day eight, thirty and ninety or where warranted, reports of side effects or other events were registered in patient's medical records and in the CRF and attended to.

Primary endpoint measures

To determine hearing recovery, the initial audiogram and audiograms taken at eight days of treatment and at three months after the onset of SSNHL were compared with respect to the average change in hearing thresholds at the three most affected contiguous frequencies.

Primary endpoint was a treatment effect of >10 dB at day ninety for the Prednisolone group compared to the placebo group calculated from the change in hearing thresholds at the onset (mean of the change of the hearing thresholds for the three most affected contiguous frequencies).

The mean of the change in hearing thresholds for the three most affected contiguous frequencies for each individual was characterized by comparison of the hearing thresholds from the affected ear to an audiogram obtained from the same ear not more than two years before the ISSNHL. If no previous audiogram was available, hearing was compared to the non-affected ear in its present state.

The evaluation of the audiograms was based on the differences of the mean of the hearing thresholds at three contiguous frequencies characterizing four different frequency regions (Table 1). If the average change in hearing thresholds in one frequency region exceeded the average change in the other two regions by at least 10 dB, the loss was characterized by that frequency region as low-, mid- or high-frequency loss. If both low frequencies and mid frequencies (but not high frequencies) were included and the average change of hearing thresholds in the low frequency region compared to mid frequency was larger but still less than 10 dB, the hearing loss was defined as a low frequency hearing loss.

Similarly, if the change in hearing thresholds for the high-frequency region differed from that for the mid-frequency region by less than 10 dB, the high-frequency region would characterize the loss. If the differences between the average thresholds for all three frequency regions were less than 10 dB, the loss was characterized as flat.

² Adverse Events is any adverse change in health or side effects that occur in a person who participates in a clinical trial.

Table 1. Frequency regions used for characterizing the hearing loss.

Frequency regions	
Low frequency region	125 Hz, 250 Hz and 500 Hz
Mid frequency region	1000 Hz, 1500 Hz and 2000 Hz
High frequency region	3000 Hz, 4000 Hz and 6000 Hz
“Flat loss”	The difference between the average thresholds in the three frequency regions is less than 10 dB

Secondary endpoint measures

Secondary endpoints were to evaluate prognostic variables efficacy including all questions in CRF on outcome regardless of treatment.

Abnormal findings of laboratory tests were categorized, before analysis as described in Table 2.

The results of Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) were categorized as abnormal when vascular or ischemic findings were observed.

Statistical analysis

To substantiate a treatment effect of >10 dB for the Prednisolone group compared to the placebo group calculated from the mean of the change in the hearing thresholds for the three most affected contiguous frequencies at the onset, we estimated that roughly 200 patients would be included. 200 patients were calculated to give 99.6 % power under the following assumptions: Patients were to get treatment or placebo randomly with probabilities $1/2$ and $1/2$. The treatment effect was estimated to be 20dB, which is 10dB better than stated in the null hypothesis, with standard deviation 15. All random components are assumed to be independent. With 100 patients, the corresponding power would be 85%. However, multiple regression analysis was from the beginning planned as the method for analysis. Since ISSNHL is an idiopathic disease and because this was an explorative study, any power calculation for multiple regression analysis would be an approximation. The power depends

Table 2. Categorization and findings of abnormal laboratory tests of patients included in modified ITT.

	Prednisolone group (n=47)	Placebo group (n=46)
“Arteriosclerosis associated variables”:	0 (0%)	0 (0%)
LDL-cholesterol / HDL-cholesterol ratio >3		
Total cholesterol >5mmol/L		
C- reactive protein (CRP) >3 mg/L in patients with or without earlier known cardiovascular disease		
“Inflammation/infection”:	16 (94%)	7 (78%)
CRP >10 mg/L		
Erythrocyte sedimentation rate >20 mm		
Leukocyte count >10 x 10 ⁹ ml/L		
Hemoglobin level <120 g/L		
Thrombocyte count >150 x 10 ⁹ ml/L		
Borrelia tests “positive” (IgG antibodies and IgM antibodies) in patients with or without ongoing clinical infection		
“Autoimmune variables”:	1 (6%)	2 (22%)
HSP-70		
Cardiolipin		
Antiphospholipid		
Anti-Neutrophilic Cytoplasmic Antibodies (ANCA)		
Antinuclear antibodies (ANA) “positive”		

on the distribution of each explanatory variable and how these correlate to each other. Such data were not available before the study and cannot be planned for in an observational study.

The analyses of primary and secondary endpoints were performed according to modified Intention-To-Treat (modified ITT) and Per Protocol (PP) with comparisons of the initial audiogram and the audiogram taken at the follow-up.

Multiple regression was used with selected variables (age, heredity for hearing loss, vertigo, tinnitus, time from onset of SSNHL to first ENT visit, prescribed rest or sick leave, affected frequency regions) which were forced into the model together with Prednisolone and placebo.

The first step in the multiple regression analysis was to study interactions between treatment and some selected variables. The interactions studied were between treatment & age, treatment & time from onset of SSNHL to first ENT-visit, treatment & affected frequency regions, treatment & baseline average change in hearing thresholds for the affected frequencies. The goal was to see if any of the selected interactions had a significant covariance with recovery. The interactions, which were not significant, were thereby removed from further analyses.

The second step in the multiple regression analyses was to include variables with stepwise forward method if $p < 0.05$ to see if any single variable had a significant covariance with recovery. Three dummy variables were created out of the four categories of frequency regions and used to indicate the absence or presence of some categorical effect that might be expected to shift the outcome. These three dummy variables were not tested individually in the stepwise forward process; the choice was between including none or all (partial F-test).

Single-sided null-hypothesis was used in testing the effect of Prednisolone and placebo because the purpose of the Prednisolone treatment is hearing improvement and not deterioration:

H_0 = the efficacy of Prednisolone on recovery $\leq 10\text{dB}$

H_1 = the efficacy of Prednisolone on recovery $> 10\text{dB}$

For the other variables, double-sided null-hypothesis was tested that the variable had no effect on recovery.

One-way ANOVA analysis was chosen to compare mean changes in recovery solely with respect to treatment.

A value of $p < 0.05$ was used for all tests to indicate statistical significance.

RESULTS

Fourteen ENT clinics contributed. The intention to include 200 patients between 2006 and 2008 was not fulfilled, therefore the study continued until September 2010. In four of the clinics, all patients who sought help for SSNHL during the time of the trial were registered. 57% of them were not eligible to be enrolled in the trial and thereby not analyzed. The most common causes for ineligibility were more than 7 days between the onset of hearing loss and first visit at the ENT clinics (47%), or patients wanting to have corticosteroid treatment (23%).

103 patients with ISSNHL were included, randomized evenly to treatment with either Prednisolone or placebo. Ten patients were excluded from the analyses: four in the treatment group and six in the placebo group. See Figure 1.

93 patients were analyzed by modified ITT; 47 received Prednisolone and 46 placebo. For eight of ninety-three patients, the change in hearing thresholds was evaluated by comparison of an audiogram taken within two years before the ISSNHL. Six of these had been treated with placebo.

87/93 (94%) patients were analyzed by per protocol analysis, those had followed the protocol regarding the first eight days of treatment; 45 belonged to the treatment group and 42 placebo. Fourteen of those 87 patients either should have continued taking the study drug up to 30 days or did continue, but not according the protocol.

73/93 (78%) patients who did take the study drug according to the protocol were analyzed as Total per Protocol (total PP); 38 belonged to the treatment group and 35 placebo (Figure 1).

Characteristics of the included patients

The baseline characteristics data and hearing improvement of 93 patients included in the modified ITT analyses are described in Table 3. Hearing loss occurred in the right ear for 46 patients and in the left ear for 47. None was bilaterally affected.

The hearing of the 93 patients was evaluated at the first visit and after eight days treatment. Audiograms were missing for four of them at final follow-up. Those missing were not included in the analysis—two had gotten Prednisolone. Another 25 patients had their final follow-up later than three months; thirteen of those were treated with Prednisolone. Sixteen came within four months, seven had received Prednisolone. The latest follow-up was after nine months (one placebo).

Table 3. Baseline characteristics and hearing improvement of 93 patients included in a modified Intention-To Treat analysis

Variables		Prednisolone (n=47)	Placebo (n=46)	<i>p</i> -value
Gender	Female	23	17	0.297
	Male	24	29	
Age	Mean $\pm$ SD (years)	56.8 $\pm$ 12.7	53.8 $\pm$ 13.5	0.281
	Range (years)	26 – 80	26 – 79	
Affected ear	Left	25	22	0.680
	Right	22	24	
Initial average change of hearing threshold for the affected frequencies (dB)	Mean $\pm$ SD	66.2 $\pm$ 21.2	63.5 $\pm$ 16.9	0.507
	Range	32 – 110	32 – 100	
Affected frequency regions	Low frequency region	14	13	0.573
	Mid frequency region	22	24	
	High frequency region	10	6	
	“Flat” loss	1	3	
Prevalence of associated symptoms	Tinnitus	30	38	0.061
	Vertigo	11	14	0.490
	No associated symptoms	10	6	0.411
Days from onset to treatment	Mean $\pm$ SD	3 $\pm$ 1,9	3,2 $\pm$ 2,3	0.660
	Median	3	2	
	Range	0 - 7	0 - 7	
Improvement (dB) at day 8	Mean $\pm$ SD	25.5 $\pm$ 27.1	26.4 $\pm$ 26.2	0.863*
	Range	-40 to +87	-32 to +75	
Improvement (dB) at day 90	Mean $\pm$ SD	39 $\pm$ 20.1	35.1 $\pm$ 38.3	0.484*
	Range	-5 to +87	-17 to +84	

* ONEWAY ANOVA

Figure 1: Trial profile

Of 93 patients in modified ITT analysis, 50 had one or more laboratory tests taken. Blood screenings varied from a simple screening test to a complete analysis covering most hypotheses concerning SSNHL such as C-reactive protein (CRP), HSP70, Anti-Neutrophilic Cytoplasmic Antibodies (ANCA) tests and Borrelia tests. One or more pathological findings were discovered in 17/26 with laboratory work-up in the Prednisolone group compared with 9/24 in the placebo group. Almost all of the patients with abnormal findings had “inflammations markers”. See Table 2.

MRI or CT was done on 40 patients in modified ITT analysis. Abnormal findings were seen in 13 of 22 patients with MRI or CT in the Prednisolone group compared with 10/18 in the placebo group. The majority of the findings (18/21) were different vascular abnormalities. Acoustic neuroma was found in one patient.

Adverse events occurred for 26 patients, 15 who received Prednisolone and 11 placebo. Gastrointestinal complaints were the most common. No serious adverse events were reported.

Primary endpoint: effect of treatment

Audiogram at the first follow-up (after eight days treatment)

No significant difference of hearing recovery was observed at day eight between the Prednisolone group and placebo group regarding the effect of treatment, either when using multiple regression or one-way ANOVA. See Table 5.

The estimated treatment efficacy on the day eight audiogram was -3.1 dB for the 93 patients in modified ITT analysis, meaning that patients receiving Prednisolone recovered insignificantly less than the placebo group.

For PP analysis (87 patients), the estimated treatment efficacy at the eight day audiogram was -2.48 dB and for the total PP analysis (73 patients) based on the eight day audiograms -2.91 dB, meaning that patients receiving Prednisolone recovered insignificantly less than the placebo group. Total recovery occurred in 20 patients after eight days of medication with the study drugs, eleven of those had received Prednisolone (ns).

The improvement in the Prednisolone group was 25.5 ± 27.1 dB and for placebo was 26.4 ± 26.2 dB ($p=0.863$). See Table 3.

Audiogram at the final follow-up (three months)

No significant difference of hearing recovery was observed after 90 days between the Prednisolone group and placebo group regarding the effect of treatment.

The estimated treatment efficacy at 90 days was -0.83 dB for the 93 patients in modified ITT analysis, meaning that patients receiving Prednisolone recovered insignificantly less than the placebo group.

For PP analysis (87 patients), the estimated treatment efficacy at 90 days was -0.18 dB and for the total PP analysis (73 patients) -0.06 dB. For comparison of means, see Table 3.

At the final follow-up (three months), 36 patients had total recovery, 18 of those had received Prednisolone (ns). These thirty-six patients with total recovery are presented in Table 4.

Twelve of them had a change in hearing thresholds <50 dB, six in each group. The range of the change in hearing thresholds for the remaining twenty-four patients was 52–90 dB.

Twenty-six patients had a decrease in hearing thresholds in the low frequency regions.

Thirteen of those had complete recovery, seven had received placebo and six had Prednisolone. Twenty-four patients had a mean decrease of hearing thresholds of the three most affected contiguous frequencies <50 dB. Twelve of them had no or moderate recovery and of them seven had gotten Prednisolone and five placebo.

Secondary endpoints: prognostic factors

The prognostic efficacy of the variables in the CRF was evaluated both at day eight of treatment and final follow-up.

Predictive factors at the first follow-up (after eight days treatment)

In the day eight audiogram, three factors were significantly related to outcome regardless of treatment: vertigo, abnormal findings of radiological investigations and abnormal findings of laboratory work-ups. See Table 5.

Presence of vertigo at the onset of ISSNHL was associated with less hearing improvement regardless of treatment. The effect of vertigo was -15.7 dB ($p=0.008$) for the 93 patients in the modified ITT analysis, -13.7 dB ($p=0.032$) in the 87 patients in the PP analysis and -14.5 dB ($p=0.041$) in the 73 patients in the total PP analysis.

Abnormal radiological findings were associated with a negative effect on hearing improvement (regardless of treatment). This effect was -22.5 dB ($p=0.000$) in the 93 patients

Table 4. Prognostic factors at the first and final follow-up on 93 patients in modified Intention-To Treat analysis.

Predictor	First follow-up			Final follow-up		
	Coef.	SE Coef	P-value	Coef.	SE Coef	P-value
Constant	46.80	21.47		39.22	25.76	
Treatment	-3.114	5.361	0.563*	-0.827	5.807	0.887*
Age	-0.256	0.189	0.180	-0.346	0.203	0.093
Heredity for hearing loss	10.287	6.013	0.091	8.700	6.397	0.178
Vertigo	-15.706	5.749	0.008	-18.526	6.252	0.004
Tinnitus	4.233	5.788	0.467	-1.764	6.163	0.776
Time from onset of SSNHL to the first at the ENT clinics	0.350	1.218	0.775	1.509	1.326	0.259
Prescribed rest or sick leave	0.166	6.565	0.980	-3.367	7.414	0.651
Frequency regions			0.262 !			0.524 !
Abnormal findings of radiological investigations	-22.462	6.148	0.000			ns
Abnormal findings of laboratory work-ups	15.178	5.628	0.009	14.424	5.928	0.018

* A single-sided null-hypothesis, that there is less than 10 dB difference of treatment efficacy between the Prednisolon and placebo group was used.

! p-value refers to the partial F-test where null hypothesis is that there is no difference between regions.

Table 5a. Patients with total recovery in Prednisolone group.
Frequency regions, Baseline average change of hearing thresholds and improvement at day 90.

Patient code	Prednisolone group		
	Frequency regions	Baseline (dB)	Improvement (dB) at 90 days
009	Low	45	50
040	Low	80	85
112	Low	38	35
124	Low	35	33
178	Low	32	32
211	Low	38	48
001	Mid	32	30
023	Mid	68	68
090	Mid	53	50
092	Mid	78	76
102	Mid	80	73
108	Mid	52	50
113	Mid	75	73
125	Mid	90	87
207	Mid	63	54
003	High	58	50
027	High	85	87
192	“Flat loss”	72	81
Mean ± SD		59.7 ± 20	59 ± 19.8

Table 5b. Patients with total recovery in placebo group.
Frequency regions, baseline average change of hearing thresholds and improvement at day 90.

Patient code	placebo group		
	Frequency regions	Baseline	Improvement (dB) at 90 days
010	Low	68	70
012	Low	47	42
029	Low	80	72
083	Low	33	29
153	Low	38	38
213	Low	40	38
241	Low	45	37
016	Mid	84	84
026	Mid	78	75
035	Mid	68	65
036	Mid	47	45
058	Mid	63	63
084	Mid	72	70
154	Mid	68	65
193	Mid	78	80
215	Mid	75	68
236	Mid	65	60
121	High	47	40
Mean ± SD		60.1 ± 16.5	57.8 ± 17

in modified ITT analysis, -24.3 dB ($p=0.001$) in the 87 patients in the PP analysis and -29.7 dB ($p=0.001$) in the 73 patients in the total PP analysis.

Abnormal laboratory findings were associated with better prognosis for hearing improvement (regardless of treatment). This effect was $+15.2$ dB ($p=0.009$) in the 93 patients in modified ITT analysis, $+16.4$ dB ($p=0.008$) in the 87 patients in the PP analysis and $+17.3$ dB ($p=0.031$) in the 73 patients in the total PP analysis.

Predictive factors at the final follow-up (three months)

After three months, modified ITT analysis and PP analysis showed slightly different prognostic factors for recovery than after eight days:

Significantly related to outcome, were vertigo, baseline average change in hearing thresholds for the affected frequencies and abnormal findings of laboratory work-ups regardless of treatment. See Table 5.

After three months, presence of vertigo at the onset of ISSNHL was associated with poorer hearing improvement regardless of treatment. The effect of vertigo was -18.5 dB ($p=0.004$) for the 93 patients in modified ITT and -20.0 dB ($p=0.003$) for the 87 patients in the PP analysis.

The baseline average change in hearing thresholds for the affected frequencies influenced the recovery independently of treatment. The effect was $+0.4$ dB ($p=0.014$) for the 93 patients in modified ITT analysis and $+0.4$ dB ($p=0.025$) for the 87 patients in the PP analysis, meaning that after 90 days, the mean hearing gain was 40% of the initial decrease.

Patient with abnormal findings of laboratory work-up had significantly better hearing improvement regardless of treatment. The effect was $+14.4$ dB ($p=0.018$) for the 93 patients in modified ITT analysis and $+15.4$ dB ($p=0.016$) for the 87 patients in the PP analyses.

Total PP analysis of 73 patients who did take the study drug according to the protocol showed that the only factor affecting the outcome was presence of vertigo. The ability to recover dropped with 20.5 dB ($p=0.007$) for patients with vertigo.

DISCUSSION

The present paper is the first investigation in which it has been possible to demonstrate in a RCT that corticosteroids orally, in a high tapering dosage, have no effect in the treatment of ISSNHL. Because the number of patients who recovered completely was the same in the Prednisolone as in the placebo group after 8 days and no significant difference was observed between the groups with respect to recovery after 90 days, the null-hypothesis was not rejected.

The change in hearing caused by the ISSNHL has been the main focus for the study as well as the improvement by treatment. This is to be recommended instead of use of PTA to make comparisons possible in future studies regarding treatment of ISSNHL

Most patients belonged to the mid-frequency region followed by the low frequency region. That can have explained the slightly higher total recovery rate in the present study compared to others, as better prognosis has been stipulated for these frequencies irrespective of treatment (14,17).

The predicted 200 patients would have been achieved without the hard truth of Lasagna's law (18). That patients came too late for inclusion was the most common reason not to be eligible. Since ISSNHL is a "non-painful disease", both a patient-delay and a doctor-delay were common. When initially seeking help, patients often thought an obstructing earwax plug caused the symptoms. Not rarely, the condition was then misdiagnosed as a serous otitis media. Therefore, it was often too late to participate in the trial when a referral was finally made to the ENT clinic. Since the present study indicates that Prednisolone in high tapering dose does not influence outcome, perhaps no medical harm was done to these patients.

Another reason not to be included in the trial was doctor and patient bias. Many doctors at the contributing clinics already had firm opinions about the effect of corticosteroids and therefore had difficulties in answering patients' common question: "How would you treat it if you got this disease, Doc?" That made it difficult to recruit patients to the study. Patients today have often studied Internet even before the first visit and have a clear opinion about which treatment they want; in this case, they wanted corticosteroids.

The prevalence of patients to treat for ISSNHL seemed to be declining over the study period at all fourteen contributing clinics. This could be due in part to decreasing interest for the trial.

No reason is evident for a real decrease in incidence. Other studies have shown the opposite: an increasing prevalence of ISSNHL (19).

A higher awareness of ISSNHL among referring doctors and patients prevailed earlier when the patients occupied beds in ENT clinics with either Dextran 40 therapy (20) for five days or were treated surgically with patching of the round window (21). These treatments were later shown not to have better effect than placebo (6,22,23) and fell into disrepute to the benefit for corticosteroid therapy already before the trial period (15).

Demographics for patients included in the study were very similar to those for patients included earlier in the Swedish database for Idiopathic Sudden Sensorineural Hearing Loss (400 patients) (15,16). It is therefore most unlikely that further recruitment up to a total of 200 patients in the present study would have given different results. The present placebo-controlled study was intended to confirm/reject earlier findings from the database where no effect of corticosteroids had been observed (15,16).

A number of treatments tried for ISSNHL, have been evaluated in Cochrane reports (12,24,25), none showing evidence in support of steroid efficacy. Over the last ten years, local administration of steroids into the affected ear has more and more been the focus for research (26), although the basis for how the corticosteroids work in the ear is not clear.

For vestibular neuritis (27), and more so in Bell's palsy (28), corticosteroids tested in RCT's have recently been shown to exert a beneficial effect. These diseases are the other two idiopathic conditions causing harm to the neurological tissue within the inner ear canal. A similar positive effect might therefore have been expected for ISSNHL in the present trial where doses of corticosteroids of equal size were used.

Receptors for corticosteroids have recently been found in the inner ear (29). However, since the pathogenesis for ISSNHL is unknown, a possible effect for excessive corticosteroid in the labyrinth is difficult to predict and may even be damaging. The receptors within the labyrinth are known to up-regulate by noise stimulation and seem to influence the ear's sensitivity to acoustic trauma (30).

The known negative effect on the cardiovascular system of high endogenous cortisol levels (31) seems to be contradictory to a treatment of ISSNHL with exogenous administered corticosteroids. To reduce stress by rest, aiming thereby to decrease intrinsic cortisol level has not been tested in RCT's, but has been shown to favor recovery in the recently published Swedish database for ISSNHL (16).

The introduction of corticosteroids for Sudden Deafness during the 70's was based on the hypothesis that it would relieve unknown infections/inflammations. However, neither proven presence of herpes virus or positive Borrelia findings concomitant with ISSNHL have shown to yield better outcome after treatment with corticosteroids (32,33). Interestingly, patients with "inflammatory sign" in the present trial had a better prognosis for hearing improvement, independently of treatment. This finding requires further clarification and might be a reason for apparent effects of steroids in other non-RCT studies (8,9,34).

The prognostic negative effect of vertigo at onset of ISSNHL on hearing improvement in this study is earlier well known (17,35) and was not influenced by treatment.

The prognostic negative effect of unspecific white substance changes on MRI or CT at the day eight recovery that did not reach significance after the three months might indicate a slower recovery rate for patients with cerebrovascular disease and has not to our knowledge been shown earlier.

CONCLUSION

Based on data in the present study, no therapeutic effect for oral corticosteroids can be supported in the treatment of ISSNHL. Spontaneous recovery is as common among placebo treated patients. Further meta-analysis of treatment data is necessary before change of treatment policy can be recommended.

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