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An Analysis of Systemic Steroid Dosage in Idiopathic Sudden Sensorineural Hearing Loss

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ABSTRACT

Objective: We retrospectively investigated whether the dosage of prednisolone (PSL) affects the response rate in patients with idiopathic sudden sensorineural hearing loss (ISSNHL).

Design: Retrospective.

Methods: A total of 159 patients diagnosed with initial ISSNHL and hospitalized between April 2007 and March 2021 at Yokosuka Kyosai Hospital were treated with systemic steroid therapy (SST) as a primary therapy and evaluated by pure-tone audiometry once a month. The cohort was comprised of 82 males and 77 females, with a mean age of 60.9 years old (range 16-83), consisting of 76 and 83 right and left ears, respectively. A total of 135 and 24 patients received SST with PSL dosage at 200 mg/day for 3 days with a 6-day taper and at 100 mg/day for 3 days with a 6-day taper, respectively.

Results: In grades 1-2, there were no significant differences in the therapeutic response rates between the 2 groups; however, in grades 3-4, the response rate in the 200 mg PSL dosage group was significantly higher. We extracted dosage of PSL, age, time from onset to treatment, and vertigo as variables affecting the recovery rate, which was defined as the sum of the rate of complete recovery and marked improvement. Multivariate logistic regression analysis identified age and vertigo as significant variables influencing the recovery rate.

Conclusion: Systemic steroid therapy with more than 100 mg/day of PSL with a taper for ISSNHL may not increase therapeutic efficacy in a dose-dependent manner.

Keywords: Idiopathic sudden sensorineural hearing loss, systemic steroid therapy, prednisolone, primary therapy, multivariate logistic regression analysis

Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as sensorineural hearing loss in at least 3 consecutive frequencies in pure-tone audiometry, which develops within 72 hours. Wilson et al[1] reported that systemic steroid therapy (SST) was more effective than a control group in the treatment of ISSNHL, and subsequently, SST has become a standard treatment worldwide. However, although multiple protocols for SST have been examined, there have been no reports showing significance in terms of dosage, route, period, and type of steroid in prospective studies.[2-6] Thus, a concrete protocol of SST has not yet been established. Therefore, SST is defined as an optional therapy for sudden hearing loss in the clinical practice guidelines of the American Academy of Otolaryngology—Head and Neck Surgery Foundation.[6] In our basic treatment protocol, we hospitalize ISSNHL patients and administer SST (200 mg/day of prednisolone [PSL] with a taper). Patients who are elderly or suffering from complications, such as diabetes mellitus and hypertension, receive SST at a reduced PSL dosage of 100 mg/day with a taper under the supervision of the responsible attending physicians.

In this study, we retrospectively investigated the differences in therapeutic efficacy between basic and reduced dosage groups.

Methods

Cases

We included patients who were hospitalized between April 2007 and March 2021 at Yokosuka Kyosai Hospital for initial ISSNHL within 14 days from the onset and were treated

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by SST. This study was approved by Ethics Committee of Yokosuka Kyosai hospital, (Approval No: 22-23, Date: 5th September 2022).

Treatments

All patients were hospitalized and received SST with PSL (200 mg/day for 3 days with a 6-day taper or 100 mg/day for 3 days with a 6-day taper). Due to complications such as heart disease, heart failure, post-myocardial infarction, post-cerebral infarction, chronic kidney disease, poorly controlled diabetes mellitus, a history of cancer, and advanced age, 100 mg/day was selected under the responsibility of the attending physician. A proton pump inhibitor was also prescribed to prevent gastric ulcers.

Outcomes

Pure-tone audiometry was performed before the treatment, prior to discharge, and 1 month after discharge. If the patient achieved complete recovery before discharge, a patient was classified as complete recovery without performing the 1-month follow-up audiogram. The severity criteria of pure tone averages (PTA) were defined as the average of 5 thresholds at 250, 500, 1000, 2000, and 4000 Hz, as defined by the Sudden Deafness Research Committee of the Ministry of Health, Labour and Welfare (MHLW), Japan (2015): grade 1: PTA < 40 dB; grade 2: 40 dB ≤ PTA < 60 dB; grade 3: 60 dB ≤ PTA < 90 dB; and grade 4: 90 dB ≤ PTA.[7] The outcomes were classified as complete recovery, marked improvement, slight improvement, and no change by MHLW[7] and analyzed at the initial and 1-month audiogram in each threshold (250, 500, 1000, 2000, and 4000 Hz and PTA).

Statistical Analysis

All quantitative variables were compared using the Student's *t*-test. All qualitative variables were compared using the χ^2 test. Multivariate analysis was performed by logistic regression analysis. Statistical processing was performed with GraphPad Prism version 7.02 (GraphPad Software, La Jolla, CA) and JMP® 15 Pro (SAS Institute Inc., USA). For all comparisons, $P < .05$ was considered significant.

Results

General Characteristics

Of 193 enrolled ISSNHL patients enrolled, 159 were included in the analyses. Patients with contralateral hearing loss, second ISSNHL, missing 1-month follow-up, and treatment discontinuation were excluded(see consort diagram in Figure 1). Two patients who terminated the treatment and were discharged within 8 days prematurely were not followed up at 1 month. The cohort was comprised of 82 males and 77 females with a mean age of 60.9 years old (range 16-83), and there were 76 right and 83 left ears. One hundred thirty-five patients received 200mg of PSL dosage SST with a taper and 24 patients received 100 mg of PSL dosage SST with a taper.

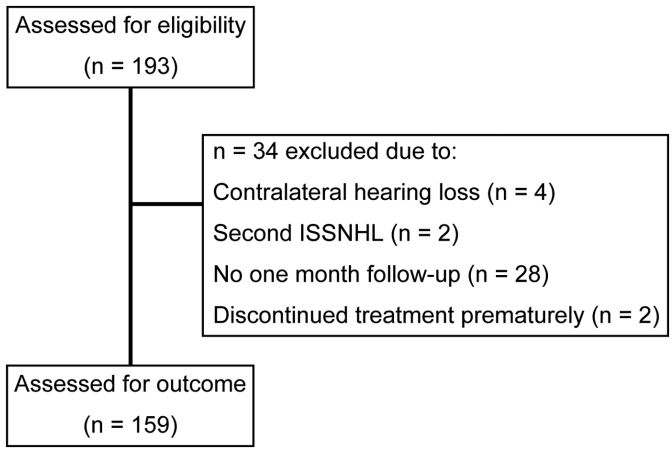

Figure 1. Consort flow diagram for the ISSNHL patients. ISSNHL: idiopathic sudden sensorineural hearing loss.

Hearing Recovery

In the 200 mg PSL group, the rates of complete recovery, marked improvement, slight improvement, and no change were 56.3%, 14.8%, 16.3%, and 12.6%, respectively. In the 100 mg PSL dosage group, the rates of complete recovery, marked improvement, slight improvement, and no change were 37.5%, 8.3%, 16.7%, and 37.5%, respectively. The response rates were significantly higher in the 200 mg than the 100 mg PSL dosage group ($P = .0213$; Figure 2a). In addition, we investigated the response rates in grades 1-2 and grades 3-4. The response rates were not significantly different between the 200 mg and 100 mg PSL dosage groups in grades 1-2 (77.4%, 0.0%, 9.4%, and 13.2% vs. 80.0%, 0.0%, 20.0%, and 0.0%; $P = .5606$; Figure 2b), whereas in grades 3-4, the response rates in the 200 mg PSL dosage group were significantly higher than the 100 mg PSL dosage group (42.7%, 24.4%, 20.7%, and 12.2% vs. 26.3%, 10.5%, 15.8%, and 47.4%; $P = .0052$; Figure 2c).

Patient Characteristics in Grades 3-4

As shown in Table 1, the age and number of patients with hypertension and diabetes mellitus were significantly higher in the 100 mg PSL dosage group than the 200 mg PSL dosage group.

Univariate Analysis

All thresholds and PTA were significantly improved in the 200 mg PSL dosage group than in the 100 mg PSL dosage group (38.5 dB at 250 Hz, 45.6 dB at 500 Hz, 39.7 dB at 1000 Hz, 32.1 dB at 2000 Hz, 26.1 dB at 4000 Hz, and 36.4 dB in PTA vs. 22.4 dB at 250 Hz, 25.8 dB at 500 Hz, 21.1 dB at 1000 Hz, 19.5 dB at 2000 Hz, 15.3 dB at 4000 Hz, and 20.8 dB in PTA, Figure 3).

Recovery rate was defined as the sum of the rates of complete recovery and marked improvement. To investigate variables

Main Points

- We investigated whether the dosage of prednisolone (PSL) affects the response rate in patients with idiopathic sudden sensorineural hearing loss (ISSNHL).
- In univariate analysis, all thresholds and pure tone averages were significantly improved in the 200 mg compared to the 100 mg PSL group. In multivariate logistic regression analysis, the significant variables influencing the recovery rate were age and vertigo; however, the dose of PSL was not significant.
- Systemic steroid therapy with more than 100 mg/day of PSL with a taper for ISSNHL may not increase the therapeutic efficacy in a dose-dependent manner.

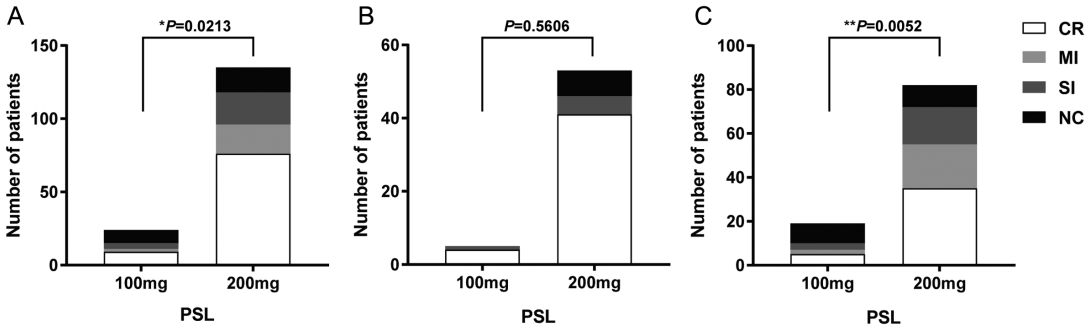

Figure 2. Comparison of therapeutic efficacy (A. grades 1-4, B. grades 1-2, C. grades 3-4). The response rates were significantly higher in the 200 mg than the 100 mg PSL dosage group in grades 1-4 and grades 3-4. CR: complete recovery, white column; MI: marked improvement, light gray column; SI: slight improvement, dark gray column; NC: no change, black column. *$P < .05$, **$P < .01$.

Table 1. Patient's Characteristics in Grades 3-4 (n = 101)

	PSL 100 mg (N = 19)	PSL 200 mg (N = 82)	*P*	Statistical Analysis
Average age (mean, years)	72 (± 6.8) (SD)	60 (± 15.3) (SD)	**.0012	Student's *t*-test
Average of the initial hearing level (dBHL)	81.0 (± 17.9) (SD)	80.5 (± 13.8) (SD)	.7164	Student's *t*-test
Average time between onset to treatment (day)	4.0 (± 2.2) (SD)	4.0 (± 2.4) (SD)	.3236	Student's *t*-test
Severity			.2691	χ^2 test
Grade 3	12	62		
Grade 4	7	20		
Vertigo			.0615	χ^2 test
Yes	9	21		
No	10	61		
Hypertension			**.0046	χ^2 test
Yes	14	31		
No	5	51		
Diabetes			***<.0001	χ^2 test
Yes	12	13		
No	7	69		

Age and number of the patients with hypertension and diabetes mellitus were significantly higher in the 100 mg than the 200 mg PSL dosage group. PSL, prednisolone.**$P < .01$.***$P < .001$.

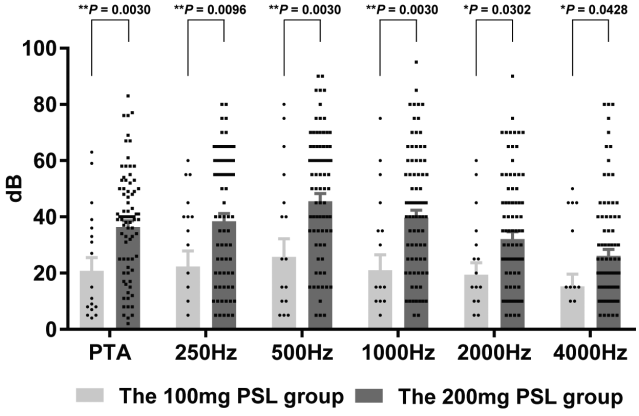

Figure 3. Degree of improvement in each frequency and PTA. All thresholds and PTA attained significant improvement in the 200 mg compared to the 100 mg PSL dosage group. The 100 mg PSL group: light gray column; the 200 mg PSL group: dark gray column. *$P < .05$, **$P < .01$.

affecting recovery rate, we performed univariate analysis using variables such as age, time from onset to treatment, treatment, sex, vertigo, diabetes mellitus, and hypertension. The significant negative variables were higher age, longer time from onset to treatment, the 200 mg PSL group, and vertigo ($P < .0001$, $P = .0007$, $P = .0147$, $P = .0009$, respectively, Table 2).

Multivariate Logistic Regression Analysis

A multivariate logistic regression analysis was performed using the 4 variables extracted by the univariate analysis as explanatory variables and the recovery rate as the objective variable. Age and vertigo were identified as significant variables influencing the recovery rate ($P = .0016$, odds ratio (OR) = 0.9229; 95% CI, 0.8780-0.9701, $P = .0003$, OR = 8.4326; 95% CI, 2.6654-26.6785, respectively, Table 3).

Complications

No serious adverse events occurred, and no patients discontinued treatments due to the adverse events of SST.

Table 2. Univariate Analysis of the Recovery Rates

Factors	Recovery (n = 62)	Non Recovery (n = 39)	*P*	Statistical Analysis
Average age (mean ± SD)	58.1 ± 16.7	68.8 ± 7.8	***<.0001	Student's *t*-test
The time between onset to treatment (mean ± SD)	3.9 ± 1.8	4.7 ± 3.0	***.0007	Student's *t*-test
Average of the initial hearing level (dBHL)	82.0 ± 13.5	81.0 ± 16.3	.1879	Student's *t*-test
Treatment				χ^2 test
100 mg PSL	7	12	*.0147	
200 mg PSL	55	27		
Sex				χ^2 test
Male	33	17	.3457	
Female	29	22		
Vertigo			***.0009	χ^2 test
Yes	11	19		
No	51	20		
Diabetes mellitus			.5237	χ^2 test
Yes	14	11		
No	48	28		
Hypertension			.1362	χ^2 test
Yes	24	21		
No	38	18		

Recovery was defined as the sum of complete recovery and marked improvement. Higher age, the 200 mg PSL group, longer time from onset to treatment, and vertigo were significant negative variables.PSL, prednisolone.*$P < .05$. ***$P < .001$.

Table 3. Multivariate Logistic Regression Analysis

Explanatory Variables	*P*	Odds	95% CI
200 mg prednisolone	.8359	1.1392	0.3320-3.9091
Age	**.0016	0.9229	0.8780-0.9701
The time between onset to treatment	.0653	0.8304	0.6817-1.0118
Vertigo	***.0003	8.4326	2.6654-26.6785

Age and vertigo were identified as significant variables that influence the recovery rate. **$P < .01$.***$P < .001$.

Discussion

Comparison Between the 200 mg and 100 mg Prednisolone Dosage Groups

The 200 mg PSL dosage group had higher therapeutic efficacy than the 100 mg PSL dosage group in univariate analysis. However, the dosage of PSL was not a significant variable in multivariate logistic regression analysis. Therefore, regarding SST with more than 100 mg/day of PSL with a taper for ISSNHL, the observed therapeutic response may not be related to increased PSL dosage.

Comparison of Results Between Previous Reports and Our Study

In prospective studies, the improvement of PTA in the 200 mg PSL dosage group was 36.4 dB, which was about 5 dB higher than the control group, who received 60 mg/day of PSL with a taper.[8,9] Although direct comparison is not possible due to different backgrounds, 200 mg/day PSL with a taper may have more therapeutic efficacy than 60 mg/day PSL with a taper.

Dosage of Steroid

Prednisolone has glucocorticoid and mineralocorticoid activities. Glucocorticoids exert immunosuppressive, anti-inflammatory, and anti-allergic effects on primary and secondary immune responses. These actions have 2 major effects. Genomic action is a complex in which glucocorticoids bind to glucocorticoid receptors present in the cytoplasm, which are translocated into the nucleus and promote transcription of protein synthesis through binding to steroid-specific elements present in DNA. This action takes several hours. On the other hand, nongenomic action is carried out with a latency of several minutes to respond with steroid receptors on the cell membranes of cells and tissues. Nongenomic action changes the excitability and ion permeability of cell membranes, increases sensitivity to neurotransmitters and hormones, and has the effect of prompting responses to stimuli in combination with medium- and long-term actions.[10] The genomic action saturates the steroid receptors in the body at 100 mg of PSL, whereas the non-genomic action exerts a dose-dependent effect even at more than 100 mg of PSL.[11] Therefore, administration of more than 100 mg of PSL is expected to have additional effects, and steroid pulse therapy at doses exceeding 100 mg of PSL is used for treatment of various diseases, including rheumatoid arthritis, SLE, nephrotic syndrome, and mucocutaneous lymph node syndrome.[12,13] Although this additional effect may be expected

for ISSNHL, we did not observe it in the present study. In the inner ears, mineralocorticoid receptors are present in the organ of corti, stria vascularis, spiral ligament, and spiral ganglion.[14] Mineralocorticoids, especially, exert stria vascularis to regulate electrolytes in the endolymph.[15,16] Therefore, mineralocorticoids may exert effects for endolymphatic hydrops or endolymphatic deficiency in the cochleae to be secondarily occurred by ISSNHL.

Potential Etiologies

Atherosclerosis was associated with a higher incidence of hearing impairment in middle-aged adults, indicating that vascular events can affect the inner ear.[17,18] Although we investigated including a medical history of hypertension and diabetes mellitus, which are risk factors for vascular events, they did not contribute to prognostic factors. These results were the same as the previous report.[19] Simões also reported that meta-analysis results indicated an increased risk of ISSNHL for patients with not hypertension and diabetes mellitus but hypertriglyceridemia and high levels of total cholesterol.[20] Therefore, hypertension and diabetes mellitus may not be exacerbating factors. Inflammation was also associated with an incidence of hearing impairment compared to the neutrophil-to-lympho cyte ratio (NLR) or inflammatory markers.[21-23] High NLR was reported to be a risk of prognostic and recurrent factors.[24,25] As mentioned, vascular events and inflammation in the inner ears are assumed to be the etiological and risk factors. As of yet, there are no reports that the prognosis differs between ISSNHL caused by inflammation and ISSNHL caused by vascular events.

Prognostic Factor

Age, onset to treatment, severity of hearing loss, shape of the audiogram, and vertigo have been reported as prognostic factors for ISSNHL.[26] In our study, age, the time between onset to treatment, and vertigo were candidates of explanatory variables in the univariate analysis, and age and vertigo were prognostic factors in the multivariate logistic regression analysis. Especially, vertigo was found to be a strong prognostic factor with a high OR, which was similar to previous reports.[27-29] Since the proportion of vertigo in grade 4 was higher than that in grade 3, ISSNHL with vertigo may consequently have a poor prognosis (Supplementary Figure 1).

Limitations

This study had several limitations. First, since the study was retrospective and not randomized, the 2 groups differed significantly in terms of cardiovascular risk factors and age, which can have a significant confounding effect on the results. Second, a large additional effect cannot be expected because the improvement of PTA in the 200 mg PSL dosage group was only 5 dB higher than the control groups who received 60 mg/day PSL with a taper[8,9]; therefore, the differences between the 2 groups would be expected to be approximately 5 dB, even if biases, such as age and complications, are excluded. Third, the number of patients in the 100 mg PSL group was small. A larger number of cases would be necessary for a statistically rigid study.

Treatment Approach

We have introduced intratympanic steroid injections (ITSI) since 2010 and provided ITSI to patients who wish it to salvage. Intratympanic steroid injections and SST have been performed in combination since 2014, except for patients who refuse ITSI. Therefore, the number of patients treated with SST alone has been so small since 2014 and most of the patients who received SST with PSL 100 mg/day followed a taper alone were hospitalized between 2007 and 2011 (data not shown). Nowadays, as ITSI is a recommendation for salvage therapy in clinical practice guideline, ITSI may be prioritized for treatment instead of SST with PSL 100 mg/day with a taper in order to decrease the side effects of SST.[6]

We retrospectively investigated whether the dosage of PSL affects the response rate in patients with ISSNHL who were hospitalized and treated at Yokosuka Kyosai Hospital. In univariate analysis, all thresholds and PTA were significantly improved in the 200 mg compared to the 100 mg PSL group. In multivariate logistic regression analysis, the significant variables influencing the recovery rate were age and vertigo; however, the dose of PSL was not significant. Systemic steroid therapy with more than 100 mg/day of PSL with a taper for ISSNHL may not increase the therapeutic efficacy in a dose-dependent manner.

Ethics Committee Approval: This study was approved by Ethics Committee of Yokosuka Kyosai hospital, (Approval No: 22-23, Date: 5th September 2022).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.H.; Design – H.H.; Supervision – H.H.; Materials – H.H., S.F., Y.A., Y.M., K.S., K.S.; Data Collection and/or processing – H.H., S.F., Y.A., Y.M., K.S., K.S.; Analysis and/or interpretation – H.H.; Literature Review – H.H., M.N.; Writing – H.H., M.N.; Critical Review – M.N.

Declaration of Interests: The authors have no conflict of interest to declare.

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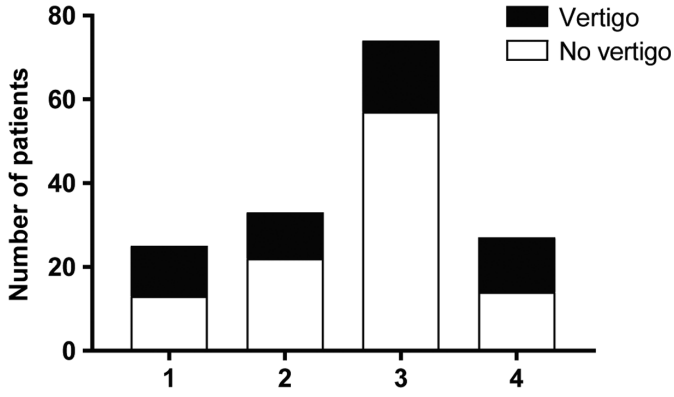

Supplementary Figure 1. The number of patients with vertigo or without vertigo in each grade.