

# Nimodipine and Steroid Combination Therapy for Idiopathic Sudden Sensorineural Hearing Loss

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**Objective:** To evaluate the treatment outcomes of nimodipine and steroid combination therapy for idiopathic sudden sensorineural hearing loss (ISSNHL).

**Study Design:** Retrospective case review.

**Setting:** Tertiary referral center.

**Patients:** Seventy-eight patients who were diagnosed with ISSNHL were divided into two groups based on the treatment strategies used: steroid+nimodipine (SN, n=36) and steroid only (SO, n=42) groups. Based on the level of hearing loss before treatment, subgroup analysis (<90 dB HL, SN-S versus SO-S groups; ≥90 dB HL, SN-P versus SO-P groups) was performed.

**Interventions:** Nimodipine+dexamethasone versus dexamethasone alone.

**Main Outcome Measures:** Hearing thresholds and complete/partial recovery rate after treatment.

**Results:** Hearing thresholds after treatment were not significantly different between the SN and SO groups ( $46.8 \pm 29.4$  versus  $54.8 \pm 27.6$  dB HL,  $p = 0.218$ ). However, the complete

recovery rate was significantly higher in the SN group than in the SO group (41.7% versus 16.8%,  $p = 0.014$ ). In subgroup analysis, the complete recovery rate was significantly higher in the SN-S group than in the SO-S group (60.9% versus 19.2%,  $p = 0.003$ ), whereas the difference between the SN-P and SO-P groups was not significant (7.7% versus 12.5%,  $p = 0.672$ ). The cumulative incidence of complete recovery was significantly higher in SN-S group than in the SO-S group ( $p = 0.005$ ); the mean recovery time was 4.4 weeks (95% confidence interval [CI], 2.8–6.1) in the SN-S group and 8.8 weeks (95% CI, 7.0–10.5) in the SO-S group.

**Conclusions:** The results of this study suggest that nimodipine and steroid combination therapy for ISSNHL results in a higher complete recovery rate than steroid alone in patients with moderate to severe hearing loss. **Key Words:** Hearing recovery—Nimodipine—Steroid—Sudden hearing loss.

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Sudden sensorineural hearing loss is sudden-onset hearing loss in one or both ears that is sensorineural in nature, occurs within a 72-hours, and meets audiological criteria (a decrease in hearing of  $\geq 30$  dB in at least three consecutive frequencies) (1). According to the clinical practice guideline for sudden hearing loss (1), initial treatment option for idiopathic sudden sensorineural hearing loss (ISSNHL) is systemic administration of corticosteroid. However, the treatment outcomes of

initial steroid therapy in ISSNHL have not been fully elucidated. In 2013, a Cochrane review reported that there was no clear evidence for greater efficacy of steroid therapy in patients with ISSNHL compared with placebo (2). Meta-analyses have shown similar results (3,4). The contradictory results regarding the effectiveness of initial steroid therapy might be due to the multifactorial etiology of ISSNHL.

The pathogenesis of ISSNHL has not been fully elucidated, and several hypotheses have been proposed in the literature, including vascular impairment, viral infection, and autoimmunity (5). The cochlear ischemia, due to a reduction in the blood supply to the inner ear, is one of the proposed mechanisms (6,7). A decrease in blood flow within the vertebrobasilar system has been reported on magnetic resonance imaging in patients with ISSNHL (8,9). In addition, alteration of blood viscosity and elevated plasma fibrinogen have each been reported in patients with ISSNHL (10). Associations have also been reported between ISSNHL and systemic cardiovascular

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diseases or related factors such as hypercholesterolemia (11), diabetes mellitus (12), myocardial infarction (13), stroke (14), smoking (15), increased alcohol consumption (15), and oxidative stress (16).

Several vasoactive agents that enhance cochlear blood flow have been assessed as treatment options for ISSNHL. Most studies of treatment with PGE1 (17–19), vitamins C and E (20), Ginkgo biloba (21), calcium antagonist (22,23), or dextran (24,25) failed to show more beneficial effects in patients with ISSNHL compared with steroid therapy. Nimodipine is a calcium channel blocker having higher selectivity for cerebral vasculature than for peripheral circulation and currently used for prevention of cerebral vasospasm and ischemia, which can be followed by subarachnoid hemorrhage. Moreover, protective effect of nimodipine to the hair cells and nerves of inner ear was documented in animal model (26). Therefore, we investigated the treatment outcome of nimodipine combined with steroid for ISSNHL; the results were compared with those of patients who were treated with steroid alone.

## MATERIALS AND METHODS

### Participants

A retrospective chart review was performed of patients who visited our clinic with hearing loss and were diagnosed with ISSNHL from January 2014 through October 2018. The ISSNHL was defined as unilateral sensorineural hearing loss of more than or equal to 30 dB at three contiguous frequencies occurring over a 72-hour period (1). The degree of certainty regarding the ISSNHL diagnosis was “very certain” (based on previous audiometric evaluation) or “certain” (no previous otologic history and normal premonitory hearing level) (1). Patients with conductive hearing loss, bilateral sudden hearing loss, previous episodes of hearing loss, fluctuating hearing loss, or focal neurological symptoms/signs were excluded. The absence of retrocochlear pathology was confirmed by brain magnetic resonance imaging or evaluation of the auditory brainstem response. At the initial visit, related otologic symptoms (tinnitus, dizziness) and underlying disease (diabetes mellitus, hypertension) were evaluated.

A total of 78 patients (34 men, 44 women) with ISSNHL were enrolled in this study. The mean age was  $50.5 \pm 14.0$  years (range, 19–77 yr). The mean time between onset of hearing loss and start of treatment was  $3.7 \pm 3.7$  days (range, 1–20 d).

All procedures performed in studies involving the participants were in accordance with the ethical standards of the institutional review board of Soonchunhyang University College of Medicine, Cheonan Hospital for research involving human subjects (No. 2019–05-014), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Audiological Evaluation

Audiometry was performed with earphone (TDH50P, Telephonics, NY) on a diagnostic audiometer (Audiostar pro, Grason-Stadler, MN), calibrated yearly to standard specifications for diagnostic audiometers (ANSI S3.6-2010; ISO389-1, 1998). Pure tone audiometry was performed at the initial visit and then followed for up to 12 weeks (1, 2, 4, 8, 12 weeks after start of treatment). We evaluated the bone conduction and air-

conduction thresholds at frequencies of 0.25, 0.5, 1, 2, 3, 4, and 8 kHz. The average air conduction pure tone threshold was calculated across frequencies of 0.5, 1, 2, and 4 kHz (PTA in decibel). The speech discrimination score was evaluated using Korean standard monosyllabic word lists (KS-MWL) with a sound 30 dB higher than speech recognition thresholds. The degree of hearing loss was defined as the difference in PTA between the affected and unaffected sides at each frequency. Follow-up periods varied among patients because those who recovered completely did not require further follow-up, and some other patients were lost to follow-up. Thus, the follow-up period ranged from 1 to 12 ( $5.2 \pm 3.4$ ) weeks. The follow-up period up to the final audiological evaluation did not significantly differ between the steroid + nimodipine (SN) and steroid only (SO) groups ( $5.1 \pm 3.6$  and  $5.4 \pm 3.3$  weeks, respectively,  $p = 0.726$ ).

The complete recovery was defined as the difference of less than 10 dB in PTA between the affected and unaffected ears (1). A partial recovery was defined as more than or equal to 10 dB improvement and serviceable hearing level ( $<50$  dB HL) in PTA after treatment (1,27).

### Treatment Protocol

The two clinicians (the co-authors of this study) applied different treatment strategies for ISSNHL; one prescribed a high-dose steroid only (dexamethasone, 10 mg per day, intravenously) for 5 days (SO group), and the other prescribed nimodipine (10 mg per day, continuous infusion intravenously) and dexamethasone (10 mg per day, intravenously; SN group) for 5 days simultaneously. After high-dose steroid administration, the dose of steroid was tapered for 10 days in both groups. Based on the level of PTA before treatment, subgroup analysis was performed. Patients with moderate to severe hearing loss (PTA,  $<90$  dB HL) were included in the steroid + nimodipine-severe (SN-S) or steroid only-severe (SO-S) group. Patients with profound hearing loss (PTA,  $\geq 90$  dB HL) were included in the steroid + nimodipine-profound (SN-P) or steroid only-profound (SO-P) group.

### Statistical Analysis

The evaluation of audiological results and statistical analysis were performed by otolaryngologist in an independent institution, and he had no preconceptions about the effectiveness of the nimodipine and steroid combination therapy. All results are presented as means  $\pm$  standard deviation. Statistical analyses were performed using SPSS software (ver. 18.0; SPSS Inc., Chicago, IL).  $P$  values  $<0.05$  were considered to indicate statistical significance.  $t$  Tests and Mann–Whitney  $U$  test were used to evaluate differences in hearing levels. The  $\chi^2$  test were used to evaluate differences in complete/partial recovery ratios. The comparison of the change of PTA after treatment between SO and SN groups was performed using repeated measure analysis of variance (ANOVA). Kaplan–Meier analysis was used to plot the cumulative incidence of complete recovery; the log-rank test was used to compare complete recovery between the SO-S and SN-S groups. The time to complete recovery was defined as the survival time. If the hearing level did not show complete recovery during the follow-up period or the patient was lost to follow-up, the data were coded as censored. Multivariate Cox proportional-hazards models were used to assess the effects of clinically relevant factors on the time taken for complete recovery, and the results are presented as odds ratios with 95% confidence intervals (CIs). Regression model assumptions were checked with residual plots and histograms.

TABLE 1. Clinical characteristics of participants

	SN Group (n = 36)	SO Group (n = 42)	P-Value
Age, mean (SD) (y)	48.1 (11.8)	52.6 (15.4)	0.161 <sup>a</sup>
Sex (M:F), No.	19:17	15:27	0.130 <sup>b</sup>
Period to diagnosis, mean (SD) (d)	3.2 (2.6)	4.2 (4.3)	0.210 <sup>a</sup>
Affected ear, (Right: Left), No.	18:18	19:23	0.675 <sup>b</sup>
Hearing thresholds of unaffected side (dB)	16.7 ± 11.2	17.5 ± 9.9	0.737 <sup>a</sup>
HTN, No. (%)	6 (16.7)	12 (28.6)	0.213 <sup>b</sup>
DM, No. (%)	12 (33.3)	12 (28.6)	0.650 <sup>b</sup>
Dizziness, No. (%)	16 (44.4)	16 (38.1)	0.570 <sup>b</sup>
Tinnitus, No. (%)	24 (66.7)	23 (52.4)	0.201 <sup>b</sup>

<sup>a</sup>*p* value from *t* test.

<sup>b</sup>*p* value from  $\chi^2$  test.

d indicates day; dB, decibel; DM, diabetes mellitus; F, female; HTN, hypertension; M, male; No., number; SD, standard deviation; SN group, steroid + nimodipine group; SO group, steroid only group.

## RESULTS

Thirty-six patients were classified as the SN group and 42 as the SO group. There were no significant differences in age, sex, time between onset and diagnosis, side of involvement, hearing threshold on the unaffected side, underlying disease (hypertension or diabetes mellitus), or presence of associated symptoms (tinnitus or dizziness) between the SN and SO groups (Table 1).

Before treatment, initial PTA in the SN and SO groups were  $83.2 \pm 23.2$  dB HL and  $82.9 \pm 23.8$  dB HL, respectively; there was no significant difference between the two groups ( $p = 0.959$ ; Fig. 1). The SN group showed greater improvement in PTA than the SO group at 1 week after the start of treatment (from  $83.2 \pm 23.2$  to  $53.0 \pm 32.8$  dB HL versus from  $82.9 \pm 23.8$  to  $67.2 \pm 28.3$  dB HL); the difference between the two groups was

statistically significant (*t* test,  $p = 0.053$ ; RM-ANOVA,  $p = 0.033$ ; Fig. 1). At the final audiological evaluation, the PTA of the SN group was qualitatively lower than that of the SO group ( $46.8 \pm 29.4$  versus  $54.8 \pm 27.6$  dB HL), but the difference between the two groups was not statistically significant (*t* test,  $p = 0.218$ ; RM-ANOVA,  $p = 0.128$ ; Fig. 1).

Speech discrimination score was not significantly different between the SN and SO groups before treatment at affected side ( $21.9 \pm 28.5$  versus  $25.0 \pm 36.6\%$ ,  $p = 0.677$ ) and at unaffected side ( $98.7 \pm 4.0$  versus  $98.9 \pm 4.7\%$ ,  $p = 0.856$ ). After treatment, the SN group showed greater improvement in speech discrimination score than SO group at final evaluation (from  $21.9 \pm 28.5$  to  $43.2 \pm 38.8\%$  versus from  $25.0 \pm 36.6$  to  $31.2 \pm 33.7\%$ ; RM-ANOVA,  $p = 0.049$ ).

To assess the effect of combination therapy for SSNHL, based on hearing level before treatment, we stratified patients according to degree of hearing loss: severe (PTA,  $<90$  dB HL; SN-S and SO-S groups) or profound (PTA,  $\geq 90$  dB HL; SN-P and SO-P groups). The SN-S group ( $n = 23$ ) showed qualitatively higher improvement in hearing level than the SO-S group ( $n = 26$ ) at 1 week after treatment (from  $68.8 \pm 13.9$  to  $38.8 \pm 25.1$  dB HL versus from  $68.1 \pm 16.2$  to  $51.5 \pm 22.5$  dB HL) (*t* test,  $p = 0.074$ ; RM-ANOVA,  $p = 0.073$ ; Fig. 2A). At the final evaluation, the PTA of the SN-S group was also qualitatively higher than that of the SO-S group ( $32.8 \pm 21.9$  versus  $45.7 \pm 25.1$  dB HL) (*t* test,  $p = 0.064$ ; RM-ANOVA,  $p = 0.052$ ; Fig. 2A). The PTAs of the SN-P ( $n = 13$ ) and SO-P ( $n = 16$ ) groups were not significantly different before treatment ( $108.6 \pm 10.9$  versus  $107.0 \pm 11.0$  dB HL,  $p = 0.698$ ), 1 week after treatment ( $85.8 \pm 23.9$  versus  $92.3 \pm 15.8$  dB HL,  $p = 0.335$ ), or at the final evaluation ( $71.7 \pm 24.3$  versus  $69.8 \pm 25.6$  dB HL,  $p = 0.976$ ; Fig. 2B).

The complete recovery rate, indicative of hearing threshold recovery to less than 10 dB of the unaffected ear, was significantly higher in the SN group ( $n = 15/36$ , 41.7%) than in the SO group ( $n = 7/42$ , 16.7%) ( $p = 0.014$ ) (Table 2), whereas the complete/partial

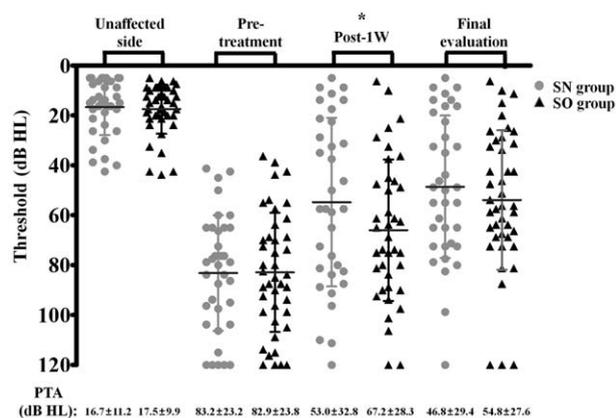
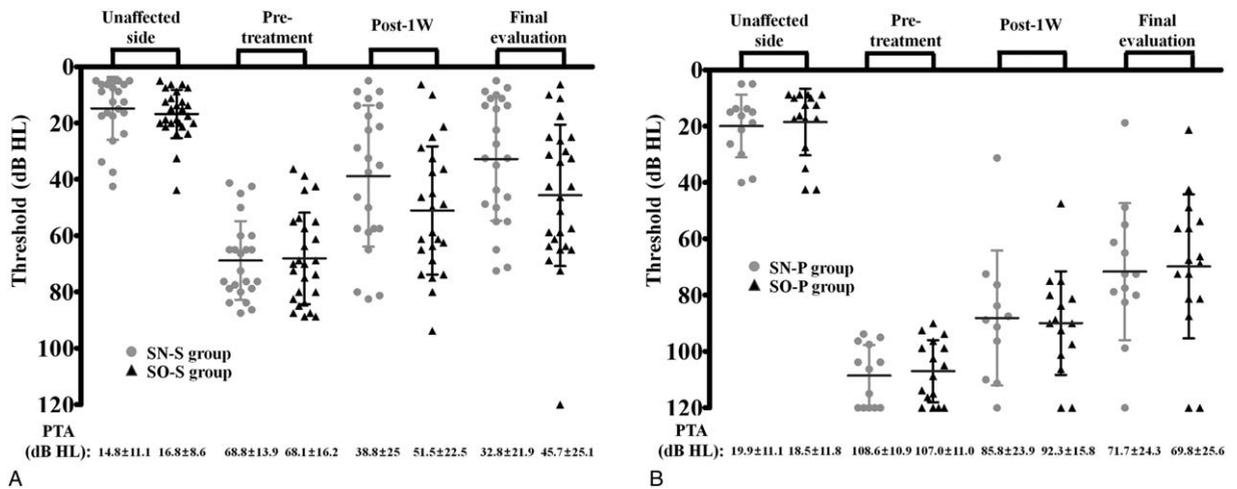


FIG. 1. Comparison of the changes in hearing thresholds after treatment between the steroid + nimodipine (SN) and steroid only (SO) groups. Before treatment, hearing thresholds on the affected side do not differ between the SN (grey circle) and SO (black triangle) groups. At 1 week after treatment, the SN group showed better improvement in hearing threshold than the SO group (\*), but the difference in hearing threshold between the two groups was not significant at the final evaluation after treatment. PTA indicates the average pure tone thresholds  $\pm$  standard deviation. \*,  $p < 0.05$ , RM-ANOVA.



**FIG. 2.** Comparison of the changes in hearing thresholds after treatment, based on the hearing level before treatment. *A*, In patients with moderate to severe hearing loss before treatment (the average pure tone thresholds [PTA] < 90 dB HL), the hearing level of those who were treated with nimodipine and steroid combination therapy (SN-S group, grey circle) showed qualitatively higher improvement at 1 week after treatment and at the final evaluation compared with the level of patients with steroid only therapy (SO-S group, black triangle). *B*, In patients with profound hearing loss before treatment (PTA ≥ 90 dB HL), the PTA was not significantly different between the patients who were treated with nimodipine and steroid combination therapy (SN-P group, grey circle) and those with steroid only therapy (SO-P group, black triangle) before treatment, at 1 week after treatment, or at the final evaluation. PTA indicates the average pure tone thresholds ± standard deviation.

recovery rate was not significantly different between the SN and SO groups (52.8% versus 38.1%,  $p = 0.194$ ). In subgroup analysis, 60.9% ( $n = 14/23$ ) of patients in the SN-S group showed complete recovery, compared with only 19.2% ( $n = 5/26$ ) of patients in the SO-S group (Table 2 and Fig. 3); the ratio of patients with complete recovery at the final evaluation was significantly higher in the SN-S group than in the SO-S group ( $p = 0.003$ ; Table 2). In contrast, the treatment outcome was extremely poor in patients with profound hearing loss before treatment. The complete recovery rate was only 7.1% ( $n = 1/13$ ) in the SN-P group and 12.5% ( $n = 2/16$ ) in the SO-P group; there was no significant difference between the two groups at the final evaluation ( $p = 0.672$ ).

During the 12-week follow-up period, the cumulative incidence of complete recovery was significantly higher in the SN-S group than in the SO-S group (log-rank test,  $p = 0.005$ ; Fig. 4); the mean recovery time was 4.4 weeks (95% CI, 2.8–6.1) in the SN-S group and 8.7 weeks (95% CI, 7.0–10.5) in the SO-S group. In Cox proportional hazard regressions analysis (using stepwise forward selection) of the cumulative incidence of complete recovery, a prediction model including group (SN-S versus SO-S) as a factor was significant ( $p = 0.011$ ). Age, latency to starting treatment, diabetes mellitus, hypertension, presence of tinnitus, and dizziness were excluded from this model by stepwise forward selection method. The adjusted odds ratio of complete recovery was 3.486-fold (95% CI, 1.248–9.742;  $p = 0.017$ ) for the SN-S group compared with the SO-S group.

**TABLE 2.** The ratio of a complete and partial recovery after treatment with steroid only (SO group) and combination of steroid and nimodipine (SN group)

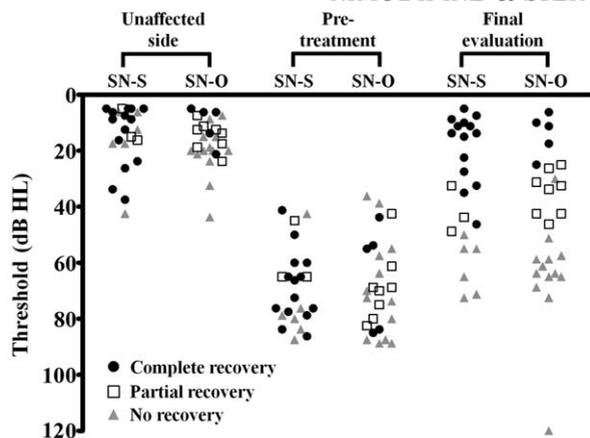
Initial Hearing Threshold	Classification	SN Group No. (%)	SO Group No. (%)	P-Value
Total	Complete recovery	15 (41.7%)	7 (16.7%)	0.014 <sup>a,c</sup>
	Partial recovery	4 (11.1%)	9 (21.4%)	0.194 <sup>b</sup>
	No recovery	17 (47.2%)	26 (61.9%)	
<90 dB	Complete recovery	14 (60.9%)	5 (19.2%)	0.003 <sup>a,c</sup>
	Partial recovery	3 (13.0%)	8 (30.8%)	0.086 <sup>b</sup>
	No recovery	7 (26.1%)	14 (50.0%)	
≥90 dB	Complete recovery	1 (7.1%)	2 (12.5%)	0.672 <sup>a</sup>
	Partial recovery	1 (7.1%)	1 (6.3%)	0.811 <sup>b</sup>
	No recovery	11 (84.6%)	13 (81.3%)	

<sup>a</sup>Comparison of complete versus partial/no recovery rate between SN and SO groups ( $\chi^2$  test).

<sup>b</sup>Comparison of complete/partial versus no recovery rate between SN and SO groups ( $\chi^2$  test).

<sup>c</sup> $p < 0.05$ .

dB, decibel; No, number; SN group, steroid + nimodipine group; SO group, steroid only group.



**FIG. 3.** Comparison of complete and partial recovery rates after treatment in patients with moderate to severe hearing loss between the steroid + nimodipine-severe (SN-S) and steroid only-severe (SO-S) groups. The hearing threshold distribution (complete recovery, black circle; partial recovery, white square; and no recovery, gray triangle) was similar between the SN-S and SO-S groups before treatment on the unaffected and affected sides. After treatment, the SN-S group showed a higher rate of complete recovery than the SN-P group. SN-S indicates nimodipine and steroid combination therapy; SO-S, steroid only therapy.

During the period of nimodipine administration in SN group, side effects or complication such as decreased blood pressure, abnormal liver function test, skin rash, or

gastrointestinal symptoms were not reported in any patients.

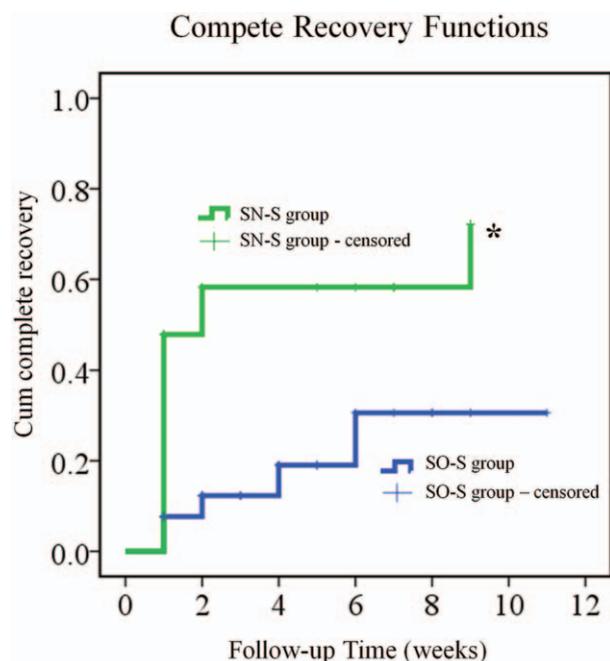
**DISCUSSION**

In this study, we evaluated the treatment outcome of nimodipine and steroid combination therapy for ISSNHL. To the best of our knowledge, this study is the first to show a synergistic effect of nimodipine and steroid treatment (22,23,28). Nimodipine and steroid combination therapy had a higher complete recovery rate than steroid alone; moreover, the mean time for complete recovery was shorter in the SN group than in the SO group in patients with moderate to severe hearing loss.

Nimodipine is a 1,4-dihydropyridine calcium channel blocker that was originally developed as an anti-hypertensive drug. Nimodipine inhibits the influx of calcium in smooth muscle cells by stabilizing voltage-gated calcium channels, thereby preventing smooth muscle contraction and subsequent vasoconstriction. Compared with other calcium channel blockers, nimodipine has higher selectivity for cerebral vasculature than for peripheral circulation. Therefore, nimodipine is currently used primarily for prevention of cerebral vasospasm and ischemia, which can be followed by subarachnoid hemorrhage (29–31). Putative mechanisms by which nimodipine influences the outcome of subarachnoid hemorrhage include prevention of irreversible neuronal damage by calcium influx (32,33), induction of an anticonvulsant effect (34,35), dilation of small arterioles (36), or inhibition of ischemia by fibrinolytic activity (37).

Intra-labyrinthine hemorrhage has been identified as a cause of ISSNHL (38,39), and the presence of intra-labyrinthine hemorrhage was reportedly associated with poor prognosis of ISSNHL (40). In addition to intra-labyrinthine hemorrhage, other putative mechanisms of ISSNHL pathophysiology include altered vascular supply, atherosclerosis, and ischemia (41,42). Therefore, nimodipine could also contribute to the treatment of SSNHL in a subset of patients with SSNHL in whom the presumed etiology includes a vascular component. Considering the absence of tools to differentiate causes of SSNHL, a cocktail regimen combining putative drugs, such as a vasoactive drug and steroid, might be an effective strategy for treating idiopathic SSNHL.

In previous studies, the complete recovery rate of steroid therapy was reported as approximately 15%, and the outcome was similar to that of the SO group in our study (16.7%; Table 2) (43). In contrast, the SN group showed a markedly higher complete recovery rate (41.7%) than reported in previous studies that used steroid alone (43). Fetterman et al. (44) demonstrated a possible cumulative effect of vasodilators, and reported that patients who were treated with both steroid and vasodilators showed better prognosis. Although no previous clinical studies regarding the effectiveness of nimodipine for ISSNHL have been reported, the effects of nimodipine on cochlear blood flow were studied in an



**FIG. 4.** Kaplan–Meier curves showing the cumulative incidence of complete recovery in the SN-S group and SO-S group. The SN-S group showed significantly higher cumulative incidence of complete recovery and shorter mean recovery time than the SO-S group (\*). \*,  $p < 0.05$ , log-rank test. SN-S indicates nimodipine and steroid combination therapy; SO-S, steroid only therapy.

animal model (26,45). In that study, significant increases in cochlear blood flow were identified during intra-arterial infusion of nimodipine in guinea pigs. In another study, nimodipine showed a protective effect against reduction of cochlear blood flow due to salicylate ototoxicity (46). In addition to the vasodilatory effect of nimodipine, stabilization of calcium channels, and protection against inner ear cell damage due to calcium influx might be putative mechanisms by which nimodipine mediates its effects in ISSNHL (26,32,33).

Although the complete recovery rate was significantly higher in our SN group than in the SO group (41.7% versus 16.7%; Table 2), average hearing thresholds at the final evaluation were not significantly different between the SN and SO groups ( $46.8 \pm 29.4$  versus  $54.8 \pm 27.6$  dB HL,  $p = 0.218$ ; Fig. 1). The proportion of patients with “no recovery” status at the final evaluation was similar between the SN ( $n = 17/37$ , 47.2%) and SO groups ( $n = 26/42$ , 61.9%) (Table 2); thus, the rate of poor prognosis did not significantly differ between the two groups. Accordingly, the difference in average hearing threshold between SN and SO groups might be minimal, such that the effectiveness of nimodipine and steroid combination therapy could be obscured.

Among patients with complete/partial recovery in the SN group ( $n = 19$ ), 15 patients (78.9%) showed complete recovery, whereas only 7 of 16 (43.8%) showed complete recovery in the SO group (Table 2). Therefore, nimodipine might have an additive effect with steroid treatment, such that the degree of improvement is augmented in patients with an at least partial recovery. The SN-S group also showed shorter mean complete recovery time (4.4 wk) than the SO-S group (8.7 wk) (Fig. 4). Therefore, nimodipine increased the complete recovery rate and accelerated hearing recovery in ISSNHL when combined with steroid.

The initial hearing level before treatment is reportedly related to poor prognosis of ISSNHL (47,48). Only two patients in our SN-P group (14.2%) and three in the SO-P group (12.5%) showed complete/partial recovery, consistent with previous studies (7–30%) (48,49). Therefore, our findings showed that nimodipine did not have a synergistic effect with steroid treatment in patients with profound hearing loss. Severe pathologic damage in the inner ear, representing profound hearing loss, could be cured with steroid treatment alone only in limited cases, and the vasoactive and protective effect of nimodipine would be not effective in those circumstances.

In Cox regression analysis to identify factors related to complete recovery in patients with moderate to severe hearing loss, only one factor (group; SN-S versus SO-S) was identified. Interestingly, hypertension (7,12,42) and dizziness (44,49), which are well-known factors related to the prognosis of ISSNHL, were excluded from our predictive model because the factors were not significantly related with complete recovery rate. The exclusion of previously identified factors from our predictive model might have resulted from the exclusion of patients

with profound hearing loss in this analysis. We performed regression analysis on patients with moderate to severe hearing loss only, because the complete recovery rate was extremely poor in patients with profound hearing loss and did not significantly differ between the SN-P and SO-P groups (Table 2). The proportion of patients with hypertension was significantly higher in the profound hearing loss group ( $n = 12/33$ , 36.4%) than in the moderate to severe hearing loss group ( $n = 8/49$ , 16.3%) ( $p = 0.038$ ). In addition, the incidence of dizziness was also higher in patients with profound hearing loss ( $n = 19/33$ , 57.6%) than in patients with moderate to severe hearing loss ( $n = 14/49$ , 28.6%) ( $p = 0.009$ ). Therefore, the presence of dizziness and hypertension might both be related to the initial level of hearing loss; these factors were eliminated from the Cox regression analysis after excluding the patients with profound hearing loss.

The patients in this study were enrolled retrospectively, and there may have been a selection bias. Furthermore, the follow-up periods varied among patients, and the timing of the final audiological evaluation varied from 1 to 12 weeks. In addition, the number of participants was not sufficient to confirm the therapeutic effectiveness of nimodipine on ISSNHL. To confirm the effectiveness of nimodipine and steroid combination therapy, a randomized, double-blind prospective study with large sample size should be followed in the future.

## CONCLUSION

We demonstrated that nimodipine and steroid combination therapy were associated with a better ISSNHL prognosis than steroid alone in terms of the complete recovery rate among patients with moderate to severe hearing loss. In addition, treatment response was accelerated with nimodipine and steroid combination therapy. Considering the limited effectiveness of steroid treatment in patients with ISSNHL, nimodipine, and steroid combination therapy might serve as a novel and effective treatment strategy for ISSNHL.

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