

Effects of oral *N*-acetylcysteine combined with oral prednisolone on idiopathic sudden sensorineural hearing loss

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Abstract

Background: Idiopathic sudden sensorineural hearing loss (ISSNHL) is an acute condition that presents with sudden hearing loss, for which steroids remain the main treatment. *N*-acetylcysteine (NAC), as a precursor of glutathione, can reduce the production of reactive oxygen species to protect hair cells in the inner ear from damage. However, data regarding the therapeutic outcomes of oral steroid combined with oral NAC for ISSNHL are still limited. This study was performed to investigate this issue.

Methods: Between June 2016 and October 2021, 219 patients (219 ears) diagnosed with ISSNHL and treated with oral prednisolone were enrolled in this retrospective study. Oral NAC was prescribed to 94 of these patients (NAC group) but not to the remaining 125 patients (non-NAC group). The clinical and audiological findings were assessed.

Results: The NAC group showed a mean hearing level gain of 29.5±21.8 dB, speech reception threshold (SRT) gain of 26.2±34.4 dB, and speech discrimination score (SDS) gain of 25.5±30.4%. Although the NAC group had better mean hearing level, SRT, and SDS gains than the non-NAC group, the differences were not statistically significant (all $P > .05$). The only significant difference between the NAC and non-NAC groups was the posttreatment pure tone audiometry (PTA) thresholds at 8 kHz, which were 54.2±24.4 and 60.9±34.1 dB, respectively ($P = .046$).

Conclusions: This study demonstrated the effect of oral steroid combined with oral NAC for ISSNHL. Both the NAC and non-NAC groups showed obvious improvement in all PTA thresholds, as well as mean hearing level, SRT, and SDS gains. The NAC group showed significantly better PTA performance at a high frequency (8 kHz) than the non-NAC group. Therefore, for oral treatment of ISSNHL, we advocate concurrent use of oral prednisolone and oral NAC.

Abbreviations: CRP = C-reactive protein, ISSNHL = idiopathic sudden sensorineural hearing loss, NAC = N-acetylcysteine, PTA = pure tone audiometry, RNS = reactive nitrogen species, SDS = speech discrimination score, SRT = speech reception threshold

Keywords: idiopathic sudden sensorineural hearing loss, *N*-acetylcysteine, oral, prednisolone, steroid

1. Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is an acute condition that presents with sudden hearing loss of ≥30 dB within <3 days in at least 3 contiguous frequencies, with no obvious etiology.^[1,2] ISSNHL has an incidence of 5 to 27 cases per 100,000 annually.^[3,4] Although the principal cause of ISSNHL remains unclear, putative pathophysiological mechanisms include labyrinthine viral infection, inner ear vascular compromise, intracochlear membrane rupture, immune-mediated inner ear disease, and cellular stress.^[5,6]

N-Acetylcysteine (NAC) is a precursor of glutathione, which is a critical antioxidant in the human body.^[7-9] Reactive oxygen species (ROS), as oxygen-containing radicals, can damage auditory hair cells by activating apoptotic cell death programs,^[10]

and NAC can reduce the production of ROS to protect hair cells in the inner ear from damage.^[9,11] Thus, the mechanism of action of NAC in the treatment of ISSNHL is based on altering the oxidative status that contributes to cochlear injury.^[12]

Oral NAC combined with intravenous steroid treatment was confirmed to be useful in the treatment of ISSNHL.^[13]

However, data regarding the therapeutic outcome of oral NAC combined with oral steroid for ISSNHL are still limited. The present study was performed to examine the effects of oral NAC combined with oral steroid treatment in patients with ISSNHL.

2. Materials and Methods

This study retrospectively reviewed the medical records of 219 patients diagnosed with unilateral ISSNHL (219 ears) at Chang

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The authors have no funding and conflicts of interest to disclose.

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How to cite this article: Chen SL, Ho CY, Chin SC. Effects of oral *N*-acetylcysteine combined with oral prednisolone on idiopathic sudden sensorineural hearing loss. *Medicine* 2022;101:26(e29792).

Received: 5 January 2022 / Received in final form: 22 March 2022 / Accepted: 24 April 2022

<http://dx.doi.org/10.1097/MD.00000000000029792>

Gung Memorial Hospital, Linkou, Taiwan, between June 2016 and October 2021.

All patients had at least 30 dB hearing loss in three contiguous frequencies within a period of 3 days, which met the diagnostic criteria for ISSNHL. The general examination included detailed medical history-taking, physical and otoscopic examination, and laboratory tests. The audiological examination included pure tone audiometry (PTA), tympanometry, speech reception threshold (SRT), and speech discrimination score (SDS) tests. The hearing thresholds of patients were measured at 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz, and 8 kHz before and after treatment.

All ISSNHL patients were administered oral prednisolone (5 mg tablets, at a dose of 1 mg/kg/d, maximum 60 mg/d) for 7 days, followed by tapering within 7 days. The patients were retrospectively classified into NAC and non-NAC groups. In addition to oral prednisolone, the patients in the NAC group were prescribed oral NAC (600 mg per tablet, twice daily) for at least 1 month.¹⁴ Oral steroid and NAC was started simultaneously in the NAC group. In the NAC group, steroid and NAC were given together for the first 14 days, and NAC would continue to be taken until 1 month. All patients also received basic treatment for ISSNHL, aimed at improving vascular microcirculation and nerve function.

The mean hearing level was defined as the average hearing threshold at four frequencies (500 Hz, 1 kHz, 2 kHz, and 4 kHz).^{13,15} The mean hearing level gain, SRT gain, and SDS gain indicated improvement between the pretreatment and post-treatment mean hearing level, SRT, and SDS, respectively. For both groups, all patients underwent hearing tests before and 1 month after the onset of treatment.

We collected data on sex (male/female), side (left/right), age (<18, 18–65, >65 years), underlying diseases (hypertension and coronary artery disease), C-reactive protein (CRP), unaffected ear (PTA, tympanometry, SRT, and SDS), pretreatment of the affected ear (PTA, tympanometry, SRT, and SDS), and posttreatment of the affected ear (PTA, tympanometry, SRT, and SDS).

2.1. Exclusion criteria

We excluded patients with diabetes mellitus, chronic hepatitis, or a history of peptic ulcer (in whom high-dose systemic oral prednisolone is contraindicated). Patients with external auditory malformation, middle ear anomaly, hearing loss with a recognized genetic cause, Ménière disease, cochlear malformation, bacterial labyrinthitis, or previous aural surgery were excluded. We also used auditory brainstem response to exclude neurological deficit of hearing and applied otoacoustic emission to exclude hair cell lesion. In addition, we also excluded patients with multiple sclerosis or connective tissue disease like sarcoidosis. Further, we excluded patients with a disease onset time of >14 days, incomplete medical records, or inadequate follow-up. Patients who received an intratympanic injection of dexamethasone were also excluded. Finally, a total of 219 patients were enrolled in the study.

2.2. Ethics statement

This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (no. 202102033B0). As the data were collected retrospectively and anonymized before data analysis, the requirement for informed consent was waived.

2.3. Statistical analysis

All data were analyzed using MedCalc software (version 18.6; MedCalc Software, Ostend, Belgium). As the Kolmogorov–Smirnov test showed that the data were not normally distributed, we used the χ^2 test for analysis of categorical variables, and the Mann–Whitney *U* test and Wilcoxon test to compare continuous variables. In all analyses, *P* < .05 was taken to indicate statistical significance.

3. Results

The demographic and clinical data are shown in Table 1. A total of 219 patients with ISSNHL, consisting of 104 (47.4%)

Table 1
Clinicopathological characteristics of 219 patients with ISSNHL.

Characteristics	N = 219 (%)
Gender	
Male	104 (47.4)
Female	115 (52.6)
NAC	
Yes	94 (42.9)
No	125 (57.1)
Side	
Left	110 (50.3)
Right	109 (49.7)
Age, yr ± SD	47.7 ± 16.5
<18 yr	12 (5.4)
18–65 yr	168 (76.8)
>65 yr	39 (17.8)
Duration of onset of hearing loss, d ± SD	2.3 ± 0.7
Underlying diseases	
Hypertension	41 (18.7)
Coronary artery disease	14 (6.3)
CRP, mg/L ± SD	1.4 ± 1.7
Unaffected ears	
250 Hz, dB ± SD	16.7 ± 14.0
500 Hz, dB ± SD	17.0 ± 11.3
1k Hz, dB ± SD	19.7 ± 12.2
2k Hz, dB ± SD	20.9 ± 15.6
4k Hz, dB ± SD	23.1 ± 22.4
8k Hz, dB ± SD	25.1 ± 24.9
Mean hearing level, dB ± SD	20.4 ± 15.3
Tympanometry type A	219 (100.0)
Tympanometry type B	0 (0.0)
Tympanometry type C	0 (0.0)
SRT, dB ± SD	17.1 ± 11.2
SDS, % ± SD	97.0 ± 9.5
Pretreatment of affected ears	
250 Hz, dB ± SD	70.9 ± 23.2
500 Hz, dB ± SD	76.9 ± 21.3
1k Hz, dB ± SD	80.3 ± 20.6
2k Hz, dB ± SD	75.9 ± 23.4
4k Hz, dB ± SD	79.7 ± 23.8
8k Hz, dB ± SD	80.3 ± 22.6
Mean hearing level, dB ± SD	77.3 ± 19.3
Tympanometry type A	214 (97.7)
Tympanometry type B	5 (2.3)
Tympanometry type C	0 (0.0)
SRT, dB ± SD	73.6 ± 24.6
SDS, % ± SD	44.6 ± 19.8
Posttreatment PTA of affected ears	
250 Hz, dB ± SD	38.2 ± 24.6
500 Hz, dB ± SD	42.2 ± 25.1
1k Hz, dB ± SD	52.5 ± 26.3
2k Hz, dB ± SD	54.2 ± 26.7
4k Hz, dB ± SD	56.2 ± 29.3
8k Hz, dB ± SD	58.0 ± 30.4
Mean hearing level, dB ± SD	50.2 ± 23.1
Tympanometry type A	219 (100.0)
Tympanometry type B	0 (0.0)
Tympanometry type C	0 (0.0)
SRT, dB ± SD	51.5 ± 28.0
SDS, % ± SD	68.8 ± 28.1
Mean hearing level gain, dB ± SD	27.1 ± 22.0
SRT gain, dB ± SD	22.0 ± 33.4
SDS gain, % ± SD	24.2 ± 30.3

CRP = C-reactive protein, ISSNHL = idiopathic sudden sensorineural hearing loss, mean hearing level = average pure tone audiometry (PTA) at 500, 1k, 2k, and 4k Hz, N = numbers, NAC = N-acetylcysteine, SD = standard deviation, SDS = speech discrimination score, SRT = speech reception threshold.

males and 115 (52.6%) females, were included in this study. The NAC group consisted of 94 (42.9%) patients treated with oral prednisolone and NAC, while the non-NAC group consisted of 125 (57.1%) patients treated with oral prednisolone alone. The left ear was affected in 110 cases (50.3%) and the right ear was affected in 109 cases (49.7%). The study population consisted of 12 (5.4%) patients aged <18 years, 168 (76.8%) patients aged 18 to 65 years, and 39 (17.8%) patients aged >65 years; the mean age was 47.7 ± 16.5 years. The mean duration of onset of hearing loss was 2.3 ± 0.7 days. Underlying diseases included hypertension in 41 cases (18.7%) and coronary artery disease in 14 cases (6.3%). The mean level of CRP was 1.4 ± 1.7 mg/L.

In PTA of all unaffected ears, the mean thresholds were 16.7 ± 14.0 dB at 250 Hz, 17.0 ± 11.3 dB at 500 Hz, 19.7 ± 12.2 dB at 1 kHz, 20.9 ± 15.6 dB at 2 kHz, 23.1 ± 22.4 dB at 4 kHz, and 25.1 ± 24.9 dB at 8 kHz. The mean hearing level (average PTA at 500, 1 kHz, 2 kHz, and 4 kHz) was 20.4 ± 15.3 dB. All 219 (100%) unaffected ears were classified as type A on tympanometry. The mean SRT was 17.1 ± 11.2 dB and the mean SDS was $97.0 \pm 9.5\%$.

Prior to treatment, the mean thresholds of all affected ears were 70.9 ± 23.2 dB at 250 Hz, 76.9 ± 21.3 dB at 500 Hz, 80.3 ± 20.6 dB at 1 kHz, 75.9 ± 23.4 dB at 2 kHz, 79.7 ± 23.8 dB at 4 kHz, and 80.3 ± 22.6 dB at 8 kHz. The mean hearing level was 77.3 ± 19.3 dB. On tympanometry, 214 (97.7%) ears were classified as type A and 5 (2.3%) were classified as type B. The mean SRT was 73.6 ± 24.6 dB, and the mean SDS was $44.6 \pm 19.8\%$.

After treatment, the mean thresholds of all affected ears were 38.2 ± 24.6 dB at 250 Hz, 42.2 ± 25.1 dB at 500 Hz, 52.5 ± 26.3 dB at 1 kHz, 54.2 ± 26.7 dB at 2 kHz, 56.2 ± 29.3 dB at 4 kHz, and 58.0 ± 30.4 dB at 8 kHz. The mean hearing level was 50.2 ± 23.1 dB. On tympanometry, all 219 (100%) ears were classified as type A after treatment. The mean SRT was 51.5 ± 28.0 dB, and the mean SDS was $68.8\% \pm 28.1\%$. The mean hearing level gain was 27.1 ± 22.0 dB, the SRT gain was 22.0 ± 33.4 dB, and the SDS gain was 24.2 ± 30.3 dB.

As shown in Table 2, both the NAC and non-NAC groups showed obvious improvement of PTA at all frequencies, and the mean hearing level, after treatment (all $P < .001$). In addition, both the NAC and non-NAC groups showed obvious improvements in SRT and SDS after treatment (all $P < .001$).

As shown in Table 3, there were no significant differences between the NAC and non-NAC groups with regard to gender, side, age, duration of onset of hearing loss, underlying diseases, CRP, the results of audiological examination of unaffected ears,

or the results of pretreatment audiological examinations of affected ears (all $P > .05$). The only significant difference was found in the posttreatment PTA of affected ears at 8 kHz, which showed a threshold at 8 kHz of 54.2 ± 24.4 dB in the NAC group and 60.9 ± 34.1 dB in the non-NAC group ($P = .046$).

The differences between pretreatment and posttreatment hearing thresholds at each frequency were statistically significant at all frequencies in both the NAC and non-NAC groups (Fig. 1A and B). The only significant difference in posttreatment hearing thresholds between the NAC and non-NAC groups was found at 8 kHz on PTA (Fig. 1C).

4. Discussion

In this cohort study, both the NAC and non-NAC groups showed obvious improvements in all frequencies on PTA, mean hearing level gain, SRT gain, and SDS gain. The only difference between the groups was in the high-frequency range (8 kHz) on PTA. For oral treatment of ISSNHL, this study showed the effect of the combination of oral steroid and oral NAC.

ISSNHL is one of the most common audiological emergencies encountered in clinical practice, and its incidence is increasing around the world. Impaired cochlear perfusion is a major risk factor for ISSNHL because the terminal vasculature of the cochlea is extremely sensitive to anoxia and hypoxia.^[16,17]

Due to uncertainty regarding the cause of ISSNHL, there are a variety of treatment strategies, including oral corticosteroids, plasma expanders, antiviral agents, antioxidants, intratympanic steroid injection, hyperbaric oxygen therapy, calcium channel blockers, and traditional Chinese approaches.^[12,14] Steroid treatment is generally used as the first-line treatment of ISSNHL.^[3,18,19] Steroids have strong antiinflammatory, antitoxic, and immunoregulatory effects. Some studies have reported that glucocorticoids can protect hair cells from a variety of adverse factors, such as noise and inflammation.^[20,21] Battaglia et al^[22] reported that patients treated with intratympanic dexamethasone alone had an average PTA improvement of 31 dB, while those treated with a combination of intratympanic dexamethasone and oral prednisone had an average improvement of 40 dB. The therapeutic effect of steroids differs among studies.^[23] There is evidence that increasing the amount and duration of use of steroids in the inner ear can significantly improve ISSNHL.^[24–26] However, steroid treatment can have side effects and complications, and high-dose, intensive steroid administration can cause gastritis, insulin resistance, acute hepatitis, and even psychosis.^[14]

Table 2

Comparison between the pretreatment and posttreatment values in patients with ISSNHL

Characteristics	NAC, N = 94 (%)			Non-NAC, N = 125 (%)		
	Pretreatment	Posttreatment	P value	Pretreatment	Posttreatment	P value
250 Hz, dB \pm SD	69.7 \pm 24.6	35.3 \pm 21.7	<.001*	71.8 \pm 22.2	40.3 \pm 26.5	<.001*
500 Hz, dB \pm SD	74.8 \pm 22.7	37.6 \pm 20.0	<.001*	78.6 \pm 20.1	45.7 \pm 27.9	<.001*
1k Hz, dB \pm SD	77.6 \pm 20.6	48.2 \pm 20.4	<.001*	82.3 \pm 20.4	55.6 \pm 29.7	<.001*
2k Hz, dB \pm SD	74.6 \pm 22.1	51.2 \pm 23.6	<.001*	76.8 \pm 24.4	56.4 \pm 28.7	<.001*
4k Hz, dB \pm SD	79.1 \pm 21.8	53.9 \pm 23.9	<.001*	80.2 \pm 25.3	58.0 \pm 32.7	<.001*
8k Hz, dB \pm SD	81.7 \pm 18.6	54.2 \pm 24.4	<.001*	79.3 \pm 25.2	60.9 \pm 34.1	<.001*
Mean hearing level, dB \pm SD	76.3 \pm 18.4	46.7 \pm 16.3	<.001*	78.1 \pm 20.0	52.8 \pm 26.9	<.001*
Tympanometry type A	92 (97.8)	94 (100.0)	.497	122 (97.6)	125 (100.0)	.247
Tympanometry type B	2 (2.2)	0 (0.0)	.497	3 (2.4)	0 (0.0)	.247
Tympanometry type C	0 (0.0)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	1.000
SRT, dB \pm SD	74.5 \pm 23.4	48.2 \pm 22.7	<.001*	72.9 \pm 25.6	54.0 \pm 31.2	<.001*
SDS, % \pm SD	44.4 \pm 21.3	70.0 \pm 27.0	<.001*	44.7 \pm 18.7	68.0 \pm 29.0	<.001*

ISSNHL = idiopathic sudden sensorineural hearing loss, mean hearing level = average pure tone audiometry (PTA) at 500, 1k, 2k, and 4k Hz, N = numbers, NAC = N-acetylcysteine, SD = standard deviation, SDS = speech discrimination score, SRT = speech reception threshold.

* $P < .05$.

Table 3**Comparison between the NAC and non-NAC groups.**

Characteristics	NAC, N = 94 (%)	Non-NAC, N = 125 (%)	P value
Gender			.171
Male	50 (53.1)	54 (43.2)	
Female	44 (46.9)	71 (56.8)	
Side			.133
Left	53 (56.4)	57 (45.6)	
Right	41 (43.6)	68 (54.4)	
Age, yr	48.1 ± 17.9	47.4 ± 15.5	.745
<18 yr	7 (7.6)	5 (4.0)	.233
18–65 yr	67 (71.2)	101 (80.8)	
>65 yr	20 (21.2)	19 (15.2)	
Duration of onset of hearing loss, d	2.2 ± 0.8	2.4 ± 0.6	.145
Underlying diseases			.387
Hypertension			
Yes	15 (15.9)	26 (20.8)	
No	79 (84.1)	99 (79.2)	
Coronary artery disease			.589
Yes	7 (7.4)	7 (5.6)	
No	87 (92.6)	118 (94.4)	
CRP, mg/L ± SD	1.6 ± 1.9	1.2 ± 1.6	.378
Unaffected ears			
250 Hz, dB ± SD	14.2 ± 9.4	18.5 ± 16.4	.055
500 Hz, dB ± SD	15.3 ± 7.6	18.2 ± 13.4	.519
1k Hz, dB ± SD	17.7 ± 8.8	21.4 ± 14.1	.264
2k Hz, dB ± SD	19.0 ± 12.6	22.3 ± 17.4	.226
4k Hz, dB ± SD	20.1 ± 18.7	25.3 ± 24.7	.230
8k Hz, dB ± SD	22.9 ± 21.5	26.7 ± 27.1	.324
Mean hearing level, dB ± SD	18.2 ± 11.2	22.0 ± 17.7	.432
Tympanometry type A	94 (100.0)	125 (100.0)	1.000
Tympanometry type B	0 (0.0)	0 (0.0)	1.000
Tympanometry type C	0 (0.0)	0 (0.0)	1.000
SRT, dB ± SD	14.8 ± 6.2	18.8 ± 13.6	.202
SDS, % ± SD	97.8 ± 6.2	96.3 ± 11.4	.334
Pretreatment of affected ears			
250 Hz, dB ± SD	69.7 ± 24.6	71.8 ± 22.2	.768
500 Hz, dB ± SD	74.8 ± 22.7	78.6 ± 20.1	.338
1k Hz, dB ± SD	77.6 ± 20.6	82.3 ± 20.4	.093
2k Hz, dB ± SD	74.6 ± 22.1	76.8 ± 24.4	.514
4k Hz, dB ± SD	79.1 ± 21.8	80.1 ± 25.3	.452
8k Hz, dB ± SD	81.7 ± 18.6	79.3 ± 25.2	.977
Mean hearing level, dB ± SD	76.3 ± 18.4	78.1 ± 20.0	.428
Tympanometry type A	92 (97.8)	122 (97.6)	1.000
Tympanometry type B	2 (2.2)	3 (2.4)	1.000
Tympanometry type C	0 (0.0)	0 (0.0)	1.000
SRT, dB ± SD	74.5 ± 23.4	72.9 ± 25.6	.679
SDS, % ± SD	44.4 ± 21.3	44.7 ± 18.7	.926
Posttreatment PTA of affected ears			
250 Hz, dB ± SD	35.3 ± 21.7	40.3 ± 26.5	.389
500 Hz, dB ± SD	37.6 ± 20.0	45.7 ± 27.9	.063
1k Hz, dB ± SD	48.2 ± 20.4	55.6 ± 29.7	.075
2k Hz, dB ± SD	51.2 ± 23.6	56.4 ± 28.7	.165
4k Hz, dB ± SD	53.9 ± 23.9	58.0 ± 32.7	.093
8k Hz, dB ± SD	54.2 ± 24.4	60.9 ± 34.1	.46*
Mean hearing level, dB ± SD	46.7 ± 16.3	52.8 ± 26.9	.073
Tympanometry type A	94 (100.0)	125 (100.0)	1.000
Tympanometry type B	0 (0.0)	0 (0.0)	1.000
Tympanometry type C	0 (0.0)	0 (0.0)	1.000
SRT, dB ± SD	48.2 ± 22.7	54.0 ± 31.2	0.206
SDS, % ± SD	70.0 ± 27.0	68.0 ± 29.0	.732
Mean hearing level gain, dB ± SD	29.5 ± 21.8	25.3 ± 22.1	.086
SRT gain, dB ± SD	26.2 ± 34.4	18.8 ± 32.4	.090
SDS gain, % ± SD	25.5 ± 30.4	23.2 ± 30.4	.563

CRP = C-reactive protein, mean hearing level = average pure tone audiometry (PTA) at 500, 1k, 2k, and 4k Hz, N = numbers, NAC = *N*-acetylcysteine, SD = standard deviation, SDS = speech discrimination score, SRT = speech reception threshold.

* $P < .05$.

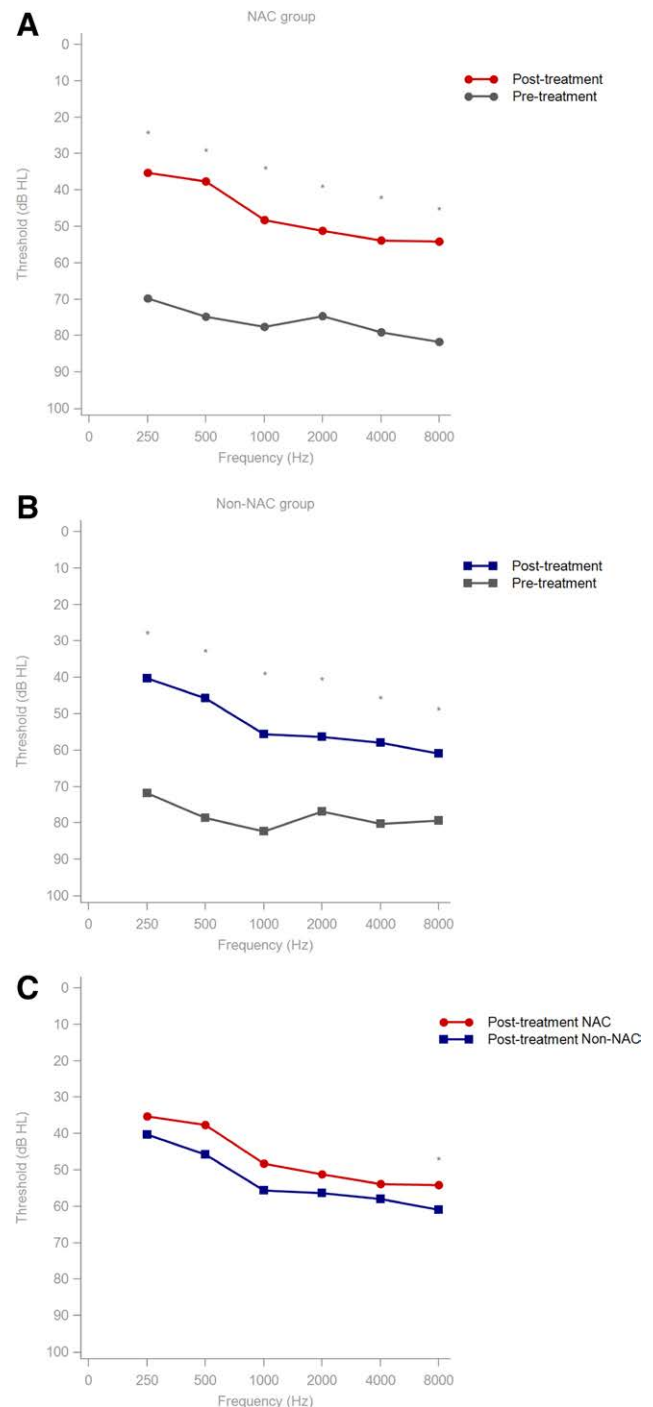


Figure 1. Pretreatment and posttreatment hearing thresholds at each frequency of ears with idiopathic sudden sensorineural hearing loss in (A) the *N*-acetylcysteine (NAC) group and (B) non-NAC group. (C) Comparison of posttreatment hearing thresholds between the NAC and non-NAC groups. * $P < .05$.

NAC is a precursor of glutathione, which is the main antioxidant in the cell.^[27,28] Oral supplementation with NAC can increase intracellular glutathione levels.^[12]

Some clinical trials are being conducted to assess the efficacy of NAC for the prevention of noise-induced sensorineural hearing loss.^[8,29] Feldman et al^[30] also showed that NAC prevented gentamicin-induced hearing loss in hemodialysis patients. However, there is still controversy regarding the mechanism underlying the effect of NAC on ISSNHL.^[12]

The cochlea responds to inflammation, ototoxic drugs, noise, and vascular trauma by generating ROS and reactive nitrogen species (RNS), which are responsible for oxidative intracellular damage; the accumulation of ROS and RNS would activate the programmed cell death pathway in auditory hair cells and non-sensory cells within the cochlea, resulting in hearing loss.^[10,31–34]

Capaccio et al^[35] reported that patients with ISSNHL had higher serum levels of ROS. As ROS and RNS production are associated with many noxious stimuli, the use of antioxidants has been hypothesized to inactivate or reduce the generation of free radicals causing damage to cells.^[36] There is a great deal of evidence from *in vitro* studies and animal models of deafness that NAC, used as an antioxidant, can attenuate hair cell degeneration or deafness.^[37–39] NAC has also been shown to be clinically effective as a single therapy for the treatment of ISSNHL.^[14] Since animal studies have shown an antiapoptotic effect of steroid^[31] and NAC may potentiate the antiapoptosis,^[12] we considered simultaneous administration of NAC and steroid is effective to treat ISSNHL.

As shown in Table 1, the average age of our patients was 47.7 ± 16.5 years, consistent with previous studies.^[12,14] The mean hearing level in this cohort was 77.3 ± 19.3 dB, classified as “severe” (71–90 dB) hearing loss.^[40] The posttreatment mean hearing level in our cohort was 50.2 ± 23.1 , similar to a previous study.^[13]

Both our NAC and non-NAC groups showed obvious improvements in mean hearing level on PTA at all frequencies, as well as SRT and SDS (all $P < .001$) (Table 2). The therapeutic effects of steroids, taken orally or administered by intratympanic injection, are widely known, so recovery of hearing in both the NAC and non-NAC groups was expected. Chen et al^[15] also reported that steroids have potent anti-inflammatory effects, so effective improvement in the hearing threshold of the affected ear after steroid treatment was not surprising.

Table 3 shows posttreatment comparisons between the NAC and non-NAC groups. The mean hearing level gain in the NAC group was 29.5 ± 21.8 , similar to the results reported by Angeli et al,^[12] and the mean hearing level and SDS gains in our non-NAC group were also similar to the results of Battaglia et al.^[22] In this study, although the NAC group had better mean hearing level, SRT, and SDS gains than the non-NAC group, these differences were not statistically significant. In fact, as steroids can significantly improve hearing, it is not easy to enhance the treatment effect by adding another drug.

The only significant group difference in the present study was that the NAC group had better PTA performance at 8 kHz than the non-NAC group. This was consistent with the results of Bai et al,^[13] whose NAC group (which received concurrent intratympanic steroid injection therapy and oral NAC) showed a significant hearing gain at 8 kHz in comparison to the control group treated with intratympanic steroid injection therapy alone. Chen et al^[15] reported that the hearing threshold of the affected ear improved after steroid therapy at all frequencies, except 8 kHz, in patients with obstructive sleep apnea, which also confirmed the damaging effect of hypoxia on high-frequency hearing. The association between the use of the antioxidant NAC and hearing gain at higher frequencies suggests region-specific susceptibility to oxidative stress in the cochlea. Sha et al^[41] suggest that the vulnerability of the basal coil outer hair cells responsible for high-frequency hearing compared with the apical coil outer hair cells can be explained by differences in their intrinsic defense system against oxidative stress. However, 8 kHz does not contribute to the “hearing level” in a person. Thus, how the improving of 8 kHz alone will actually contribute to patients, which remains to be explored in future studies.

Although oral prednisolone and oral NAC are convenient for patients, Eftekhari et al^[42] reported that the addition of

NAC increased glucocorticoid sensitivity in a mouse model of steroid-resistant asthma. Our patients did not show such side effects, but we still suggest that each patient should be followed up closely during treatment of ISSNHL.

4.1. Limitations of the article

This study had some limitations. First, it used a retrospective design, which gave rise to an insufficient data collection and a certain attrition rate. The study may also have been biased due to the relatively small sample size and lack of stratification by confounders such as severity of coronary artery disease. Furthermore, the decision to prescribe NAC to patients in this cohort was made at the discretion of different physicians.

Although this research displayed an improvement of 8 kHz via NAC using, 8 kHz does not contribute to hearing level in a person and how does this 8 kHz improvement alone improve the patient’s subjective perception of hearing is still an issue. Prospective randomized controlled studies and larger sample sizes with long-term follow-up are required to reduce above biases.

5. Conclusion

In this study, both the NAC and non-NAC groups showed obvious improvements in PTA at all frequencies, as well as in mean hearing level, SRT, and SDS gains, following treatment. The NAC group showed better PTA performance at a high frequency (8 kHz) than the non-NAC-group. For oral treatment of ISSNHL, we advocate concurrent oral prednisolone and oral NAC.

Acknowledgments

The authors thank all of the members of Department of Otorhinolaryngology-Head and Neck Surgery, Chang Gung Memorial Hospital, Linkou, for their invaluable help.

Author contributions

Conceptualization: C.-Y.H. and S.-L.C.

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All authors have read and agreed to the published version of the manuscript.

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