

Original Article

Exploration of gradable treatments in patients with idiopathic sudden sensorineural hearing loss

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Abstract: There is no instructional treatment algorithm for idiopathic sudden sensorineural hearing loss (ISSNHL). Steroids, hyperbaric oxygen (HBO₂) and vasodilator infusion are the accepted treatments. In this retrospective study, 163 patients with unilateral ISSNHL were recruited based on their pure tone audiogram (PTA). CT or MRI was performed for some patients to exclude other diseases. The patients were divided into four groups (Groups 2-5) based on the hearing level (Grades 2-5). Four kinds of treatments were applied to these patients, including vasodilator, corticosteroid, HBO₂ and combination. Total recovery rate was 53.37%, and patients in group 4 (Grade 4) had the best recovery (71.79%). HBO₂ was better in group 3 hearing loss patients (62.5%), steroid or combination treatment was better for Group 4 (more than 70%). Age is an influencing factor in the treatment choice. Based on our results, corticosteroids and HBO₂ are the two main treatments for ISSNHL patients. Larger sample sizes and further research will be helpful to find potential gradable treatments for ISSNHL patients with different hearing loss levels, ages and other contraindications.

Keywords: Sudden sensorineural hearing loss, recovery rate, corticosteroids, hyperbaric oxygen therapy, vasodilator infusion

Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is a common problem in ENT clinics and emergency departments, of which the incidence is about 5 to 60.9 per 100,000 people annually [1, 2]. The etiology of ISSNHL is unclear, and the treatment is still controversial. The most accepted spontaneous recovery rate is 35%-39% [3]. Corticosteroids and hyperbaric oxygen (HBO₂) are the two most popular therapeutic methods. Though corticosteroid treatment is advised by some research as the first choice for ISSNHL, definite evidence is still lacking, and the pharmacological mechanism is obscure. For the intravenous vasodilator, there is not any evidence demonstrating its efficacy [1]. Combination treatment with steroids, HBO₂ and/or vasodilator was recommended by some researchers and better treatment efficiency was found in patients with severe to profound ISSNHL [4, 5]. Nowadays,

hearing loss severity and interval time from onset to treatment determines the recovery of ISSNHL [2, 6]. Other factors such as age, accompanied vertigo or tinnitus, types of audiogram also influence the treatment effect [5-8].

Many reported factors affect the treatment and prognosis of ISSNHL, thus targeted or gradable treatments are needed [2]. In this retrospective study, the data of 163 adults with ISSNHL were reviewed, and all of them were hospitalized within 14 days after the attack of ISSNHL. The patients were allocated into 4 groups (Groups 2-5) according to the hearing loss level (Grades 2-5). They were further divided into 4 subdivisions based on diverse treatments. Vasodilation was applied in all four groups, and the other 3 groups received corticosteroids and/or HBO₂. The effect was compared between groups to identify the best treatments for ISSNHL individuals. This study was approved by our institutional review board with the number UFHIRB. E2021-003.

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Table 1. Criteria for pre-treatment hearing grades and hearing recovery outcomes

Levels of pre-treatment hearing grades (Modified Siegel's grade)	
Grade 1	Average threshold value ≤ 25 dB HL
Grade 2	Average threshold value 25-45 dB HL
Grade 3	Average threshold value 45-75 dB HL
Grade 4	Average threshold value 75-90 dB HL
Grade 5	Average threshold value > 90 dB HL
Levels of hearing recovery outcomes (Siegel's grade)	
Complete recovery	Final hearing level ≤ 25 dB or same degree of unaffected side
Partial recovery	More than 15 dB hearing gain and final hearing level 25-45 dB
Slight improvement	More than 15 dB hearing gain and final hearing level 45-75 dB
No improvement	Less than 15 dB hearing gain or final hearing level > 75 dB

Materials and methods

Subjects

Patients with sudden hearing loss complaint in our hospitals from January 2010 to June 2018 were included. The inclusion criteria: hearing loss more than 30 decibels (dB) over 3 consecutive frequencies; unilateral hearing loss; older than 18 years; less than 14 days after onset; denied previous unusual hearing loss history (persons with presbycusis were included). The exclusion criteria: less than 18 years old; previous unilateral or bilateral hearing loss history; bilateral sudden hearing loss; hearing loss caused by other reasons; more than 14 days after onset.

Detailed history and physical examination was collected in all enrolled patients. Pure tone audiogram (PTA) and acoustic impedance were performed, and auditory brainstem response (ABR) was checked for some patients. Temporal computed tomography (CT) and magnetic resonance imaging (MRI) were applied to most patients, especially those with moderate to severe hearing loss. Hearing level for all decreased frequencies was recorded, and mild to profound level was scaled according to modified Siegel's pretreatment grade (**Table 1**) [9]. Informed consent was given from each patient included in the study.

Treatments

Intravenous vasodilator or vasoactive substances were applied to all patients, including extract of ginkgo biloba leaves (Dr. Willmar Schwabe GmbH & Co. KG, Germany), thrombolytics and/or mecobalamin.

Corticosteroids and HBO₂ were used separately or combined. Dexamethasone was injected intravenously for less than 14 days, 5-10 mg according to the weight. Oral prednisone with tapering for another 1 week was applied if there's no improvement after intravenous application. HBO₂ treatment was started within 3 days after admission with the standard protocol for 5-20 days, even if the patients were discharged from hospitals.

The inpatient treatment lasted for about 2 weeks. The factors such as patient's condition, contraindications of medication or HBO₂, and accessibility of HBO₂ determined the treatments. The intravenous corticosteroid treatment was applied for at least 7 days or until PTA showed acceptable recovery. HBO₂ treatment was applied for more than 5 days. Patients given oxygen inhalation outside of the hyperbaric oxygen chamber or HBO₂ treatment less than 5 days were assigned to the groups without HBO₂ treatment.

PTA was performed every 7 days after treatment or when the patient reported a significant recovery. Hearing improvement classification was based on Siegel's grade [10]: complete recovery, partial recovery, slight improvement and no improvement (**Table 1**).

Patients were followed-up for 6 months after they were discharged.

Statistical analysis

Hearing levels at all decreased frequencies was compared. Complete recovery, partial recovery and slight improvement were regarded as effective treatment. IBM SPSS Statistics

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Table 2. The demography of the ISSNHL patients in four groups based on the hearing level

Parameters	Group 2 (n=18)	Group 3 (n=64)	Group 4 (n=39)	Group 5 (n=42)	P value
Age (years)	43.00±13.00	50.27±15.50	48.23±15.34	50.79±15.54	0.276
Male/Female	5/13	33/31	22/17	17/25	0.151
Side (R/L)	8/10	35/29	24/15	22/20	0.662
Interval days (d)	5.50±4.42	4.25±3.22	3.97±2.77	4.17±3.63	0.441
Inpatient days (d)	9.22±2.84	11.23±2.53*	12.03±2.33*	13.71±3.71*,&,†	0.010

Data are presented as mean ± standard deviations. *P<0.05 versus Group 2; &P<0.05 versus Group 3; †P<0.05 versus Group 4.

Table 3. Statistical data of treatment results of different therapeutic methods

Treatment	Steroid (n=40)	Combined (n=89)	HBO ₂ (n=15)	Infusion (n=19)	Total (n=163)	P value
Age (years)	53.30±14.66	44.73±15.00*	50.13±13.77	60.00±11.18&,†	49.11±15.27	0.000
Complete recovery	10 (25.00%)	20 (22.47%)	6 (40.00%)	5 (26.31%)	41 (25.15%)	
Partial recovery	7 (17.50%)	19 (21.35%)	4 (26.67%)	2 (10.53%)	32 (19.63%)	
Slight improvement	6 (15.00%)	6 (6.74%)	0	2 (10.53%)	14 (8.59%)	
No improvement	17 (42.50%)	44 (49.44%)	5 (33.33%)	10 (52.63%)	76 (46.63%)	
Recovery rate	57.50%	50.56%	66.67%	47.37%	53.37%	0.594

Data are presented as mean ± standard deviations for ages; *P<0.05 versus Steroid treatment group; &P<0.05 versus Combined treatment group; †P<0.05 versus HBO₂ treatment group.

Version 19 (IBM Corp., Armonk, New York, U.S.) was used for the statistical analysis. Demographic data and hearing outcomes was expressed as mean ± standard deviation (SD) or n%. Normality of data distribution was measured with the Kolmogorov-Smirnov test. One way ANOVA was used to analyze normally distributed continuous variables. When allowed by the homogeneity of variance, post hoc test by LSD was performed for the comparison among groups; for the data not allowed, Games-Howell was used to evaluate the differences. For the enumeration data, including the gender, sides and case numbers, chi squared was performed for groups' comparisons. Results were evaluated using a confidence interval of 95 percent, and a two-sided P<0.05 was considered significant.

Results

Demographic data comparison between groups

One hundred and sixty-three patients were included in the study, they were divided into four groups (Groups 2-5) according to the corresponding pre-treatment hearing levels (Grades 2-5). The data of ages and inpatient days showed homogeneity, while the interval days

between disease onset and treatment was adverse. There were no significant differences among the four groups in ages, gender, affected side and interval time (P>0.05). For the length of hospital stay, group 3 and 4 had no differences with each other (P=0.177), while Group 2 and 5 showed significant differences when compared with other groups (P<0.05). Group 2 had the shortest inpatient stay, and Group 5 had the longest stay (**Table 2**).

Recovery of the patients based on different treatments

Age and efficacy of different treatment between groups was also analyzed (**Table 3**). The age data had homogeneity of variance. There were significant differences among groups regarding ages, the combined group had differences with the steroid group (P=0.02) and the infusion group (P=0.00), the HBO₂ group had differences with the infusion group (P=0.049). Patients in the infusion group had the highest age and the combined group had the youngest averaged age. For the treatment efficacy, the HBO₂ group showed the highest recovery rate (66.67%), the infusion only group had the lowest effect (47.37%), but there were no differences between these groups (P=0.594). The recovery rate of the 144 patients who accept-

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Table 4. Statistical data of treatment results of different hearing levels

Groups (cases)	Treatments	Complete recovery	Partial recovery	Slight improvement	No improvement	Recovery rate	Summary rate
Group 2 (n=18)	steroid	1			1	50%	10/18 (55.56%)
	combined	5			5	50%	
	HBO ₂	3				100%	
	infusion	1			2	33.33%	
Group 3 (n=64)	steroid	5	4		7	56.28%	35/64 (54.69%)
	combined	8	8		16	50%	
	HBO ₂	2	3		3	62.5%	
	infusion	2	2	1	3	62.5%	
Group 4 (n=39)	steroid	2	2	3	3	70%	28/39 (71.79%)
	combined	6	10	2	6	75%	
	HBO ₂	1			1	50%	
	infusion	1		1	1	66.67%	
Group 5 (n=42)	steroid	2	1	3	6	50%	14/42 (33.33%)&,†
	combined	1	1	4	17	26.09%	
	HBO ₂		1		1	50%	
	infusion	1			4	20%	
Total (n=163)		41	32	14	76	53.37%	

&P<0.05 versus Group 3; †P<0.05 versus Group 4.

ed treatment of steroids combined with HBO₂ was 54.17% (78/144 cases), which was a little higher than the total recovery rate (53.37%).

Recovery of the patients based on hearing level

Four different kinds of treatments were applied and each hearing loss group (Groups 2-5) could be classified as four subdivisions: corticosteroid + vasodilator (steroid treatment group), corticosteroid + vasodilator + HBO₂ (combined treatment group), HBO₂ + vasodilator (HBO₂ treatment group) and vasodilator infusion only (infusion treatment group). Recovery rate was based on the ratio of patients with improvement/patients accepted corresponding treatment (**Table 4**).

Total recovery rate of all patients was 53.37%. Patients in Group 4 showed the highest summary recovery rate (71.79%), Group 2 and 3 also had a good recovery regardless of the treatments (55.56% and 54.69% respectively). HBO₂ and vasodilator infusion showed a better effect for patients in Group 3 (62.5%), and steroid or combination treatment for Group 4 patients (≥70%). For Group 5, the recovery was disappointing (≤50%), and it presented significant differences with Group 3 (P=0.031) and 4

(P=0.001). When compared the recovery rates among these groups (Groups 2-5) accepting 3 kinds of treatments (steroid, combined and HBO₂), differences was found between Group 4 and 5 only (P=0.001), and the respective recovery rates were 72.22% (26/36 cases) and 35.14% (13/37 cases). There was no further comparison for some subdivisions which contained a small sample of patients.

Discussion

In this study, the recovery rate of ISSNHL was 54.17% for the patients accepting treatments of steroid and/or HBO₂, combined with vasodilator infusion. For those who accepted only intravenous vasodilator treatment, the recovery rate was 47.37%. Group 4 patients (severe hearing loss) had the best recovery rate, and HBO₂ with vasodilator showed good efficacy on most ISSNHL patients.

Evaluation criteria of hearing level before and after treatment was variable [2, 6, 9, 10], and it is difficult to compare the hearing outcomes between reports. Some authors used the hearing level within 20 dB of unaffected ear as total improvement measurement [2], the recovery rate should be higher than those with strict criteria. Siegel's criteria provides the hearing level

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and gain, and it is widely used to evaluate the treatment outcomes. The modified Siegel's pretreatment criteria is matched to the items of Siegel's criteria and make it comparable [9]. For the post treatment evaluation, the complete hearing recovery should be not only limited to less than 25 dB, but also reached the unaffected side or hearing level before the loss [6], especially for some seniors. The patients in this study denied previous hearing problems, so the complete improvement item should be the same degree as in the unaffected ear. For the analytical frequencies of hearing loss, some reports used 0.5k, 1k and 2k Hz, some added 4k Hz. In this paper, we used the hearing level of all the decreased frequencies, so there were at least 3 frequencies that were compared, and 6k/8k Hz generally had less recovery than other frequencies. Above post treatment criteria and compared frequencies caused the recovery rate (53.37%) in this cohort of patients to be less than some reports. For persons with hearing level more than 90 dB after treatment, we classified them into the group without improvement. This makes it easy to compare the effect of different treatment protocols.

The effects of infusion medication like antivirals, thrombolytics, vasodilators, or vasoactive substances were not proved, and they are not recommended by the guidelines [1]. While according to some reports, prostaglandin E1, Ginkgo biloba extract, heparin and Vitamin had additional effects to the hearing level or speech discrimination, especially to those with severe to profound hearing loss [2, 11, 12]. In this study, pure placebo treatment was not performed, and the recovery rate of patients in the vasodilator infusion group who accepted Ginkgo biloba extract and other non-steroidal medications was only 47.37%, which was a little higher than the acknowledged spontaneous recovery rate [3]. Our study also showed that the vasodilator infusion still had good results for the Group 3 and 4 patients, nearly the same effect as steroid treatment when compared between different hearing level groups.

Though the targeted treatment for ISSNHL is still undefined, steroids and HBO₂ are recommended mostly because of the supposed effect of controlling the inflammatory response

and improving the oxygen level in the inner ear. There are 3 kinds of application routines for steroids, including oral, intravenous and intra-tympanic injection. Oral and intravenous ways are considered as systemic treatment, and the intra-tympanic way is local treatment. Nowadays, systemic treatment is widely used. According to Ahmadzai's review, any application methods of steroids could improve the PTA compared to placebo [13], and the combination of systemic and intra-tympanic steroid was recommended by some reports in light of the higher recovery rate [13, 14]. HBO₂ was also used as initial treatment by some doctors. Our previous study of 56 patients with Grade 3 hearing loss (moderate level) showed HBO₂ and vasodilator infusion presented excellent outcomes [15]. Steroid and HBO₂ can be applied separately or jointly, and combination treatment confers a significant additional therapeutic benefit compared to individual treatment, and it is recommended by some doctors for severe to profound ISSNHL patients [4, 5]. In this text, HBO₂ with vasodilator showed highest recovery rate (66.67%) compared to other treatments (**Table 3**), and it showed more benefit for Group 2 (3 cases only), while it was not that helpful for Group 4 and 5 (severe to profound level). For Group 5, HBO₂ treatment still presented the same efficacy (50%) as steroid combined with vasodilator. This was diverse to Sevil's report, which showed the HBO₂ with systemic steroid treatment had higher recovery on profound hearing loss patients [16]. There is no result of intra-tympanic steroid treatment in this report, as we performed the procedure as a salvage treatment only for several cases. According to the previous reports, early treatment combined with intra-tympanic steroid had significant and stable response [9, 14]. One recent animal study showed intravenous and intra-tympanic therapy could deliver more drugs into the inner ear, with a longer therapeutic window, and were more effective than intravenous or trans-tympanic injection alone [17].

The pathogenesis of ISSNHL is still unclear. Reports from Germany consider that lower frequency hearing loss is correlated with the labyrinthine hydrops, while profound hearing loss is from thrombus formation. Treatments based on the hearing frequency loss level are advised though the theory is obscure [18]. According to

the recovery rates in this study, Group 4 patients (severe hearing loss) had the best recovery rate, which was higher than Groups 2 and 3, and steroid infusion treatment provided a fantastic effect. This result was contradictory to the conventional idea that the mild and moderate hearing loss should have better recovery. Of course, some of the mild or moderate hearing loss patients had quick recovery after treatment and were not included in the study. The Group 5 patients (profound hearing loss) had the lowest recovery compared to other hearing loss groups, even with the same treatments in some circumstance, and the infusion treatment was not helpful with a recovery rate of 20%. This disappointing recovery might be caused by more damage in the inner ear, or different reasons for the hearing loss, and the current medication could not rescue the function of the inner ear.

The time interval from onset to treatment, hearing loss severity, audiogram type and vestibular involvement were accepted as factors that affect prognosis [6, 7]. Whether age and systemic diseases affect the recovery is still controversial [6, 19, 20], but they can influence the choice of treatments. Older patients have more combined diseases, steroid and HBO₂ application should be used cautiously, and sometimes vasodilator infusion becomes a good choice. Based on the present results, the combination group patients had the youngest ages, the vasodilator infusion only patients had the highest age, and there are differences of therapeutic results among the different treatment groups. If intra-tympanic steroid was performed as the initial treatment, the age and systemic diseases would not be contraindications for steroids.

Prognosis of ISSNHL is a multi-factorial problem, treatment can depend on individual conditions, including age, hearing loss level and contraindications. One review in 2019 showed an algorithm for ISSNHL had benefits when choosing suitable treatments [2]. In this study, we tried to formulate a gradable treatment for ISSNHL that is practical, so recovery of patients with mild to profound sudden hearing level were compared, and therapeutic effect of different treatments were also analyzed. According to the present data, steroid treatment was advised for most patients; HBO₂ with

vasodilator had good efficacy and it's recommended for those who refuse steroid treatment and those with mild to moderate hearing loss. For data comparison, patients were divided into four diverse treatment groups based on some objective items, so it is not based on random distribution, and the ages and some systemic diseases may affect the treatment options and result analysis. Also the sample of patients was not large enough. All these were limits of this retrospective report. Further comparison with larger samples and different grades are helpful to find the potential regularity of ISSNHL treatment, and an algorithm should be established.

Disclosure of conflict of interest

None.

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