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Modified intratympanic steroid therapy for sudden sensorineural hearing loss via tympanic tube and gelfoam as a salvage treatment

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A R T I C L E I N F O

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A B S T R A C T

Background: Sudden sensorineural hearing loss (SSNHL) is a prevalent emergency in ear, nose, and throat practice. Previous studies have demonstrated that intratympanic steroid therapy (IST) can serve as a salvage treatment for SSNHL after the failure of systemic steroid therapy (SST).
Objective: This study aimed to analyze the efficacy of modified IST involving the insertion of a tympanic tube and gelfoam as a salvage treatment for patients with SSNHL, and to explore its associated factors.
Methods: Totally, 74 patients who were aged 22–81 years with SSNHL were enrolled and allocated to either the control group ($n = 25$) or the treatment group ($n = 49$) based on their treatment modalities. All patients received SST lasting for at least 7 days. Subsequently, patients in the treatment group, after SST failure, underwent IST twice a week for 2–6 weeks, while the control group did not. Efficacy was assessed by the improvement in pure tone average at the affected frequency at the beginning and end of IST.
Results: Hearing improvement in all patients after IST in the treatment group was 9.71 ± 14.84 dB, with significant improvement at affected frequencies (250-8000 Hz) compared with the control group ($P < 0.05$). The findings indicated the duration from the onset of SSNHL to the beginning of IST as an independent factor for pure tone average improvement after treatment ($P = 0.002$), whereas age, duration of SST, and time of IST were not ($P > 0.05$).
Conclusion: The modified IST was demonstrated to be a safe and effective method as a salvage treatment for SSNHL. This study explored the efficacy of a modified IST approach, incorporating the utilization of tympanic tubes and gelfoam as key components. The findings underscore the advantages of gelfoam as a strategic drug carrier placed in the round window niche. By minimizing drug loss, extending action time, and increasing perilymph concentration, gelfoam enhances the therapeutic impact of IST, contributing to improved hearing outcomes in patients with SSNHL.

1. Introduction

Sudden sensorineural hearing loss (SSNHL) influences 5–27 individuals per 100,000 annually (Alexander and Harris, 2013) and poses a noticeable threat to auditory function, qualifying as a common emergency in otolaryngological practice. The predominant pathophysiological mechanisms often implicated involve vascular and viral etiologies (Murata, 2011). The American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) has published guidelines for SSNHL diagnosis, with audiometric criteria specifying a hearing decrease of ≥30 dB across at least 3 consecutive frequencies and an onset within a 72-h timeframe (Stachler et al., 2019). Notably, 32–65% of SSNHL cases exhibit spontaneous recovery. Systemic steroid therapy (SST) stands as the primary clinical intervention for SSNHL patients, owing to its anti-inflammatory and antioxidant effects (Marx et al., 2018; Haynes et al., 2007). However, SST is contraindicated for certain high-risk individuals, such as those experiencing pregnancy, diabetes, or severe hypertension, prompting the use of local intratympanic steroid therapy (IST) as an alternative. IST, further employed as a salvage treatment when SST proves ineffective (Yang et al., 2010), possesses

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advantages over SST by delivering steroids directly to the middle ear, promoting absorption into the inner ear through the round window membrane. This method not only mitigates the adverse effects associated with systemic administration, but also achieves higher perilymph concentrations in the inner ear (Parnes et al., 1999). Intratympanic steroids can be administered either directly through the tympanic membrane (TM) or via a ventilation tube (VT) (Stachler et al., 2019; Haynes et al., 2007). In recent years, IST has gained recognition as a salvage intervention for patients with SSNHL exhibiting suboptimal responses to SST. While various IST modalities exist, the present study concentrated on a modified approach involving the insertion of tympanic tubes and the strategic use of gelfoam. Gelfoam serves a crucial role as a carrier for steroids, strategically placed in the round window niche. This unique approach aimed to optimize drug delivery by reducing loss, extending the duration of action, and increasing steroid concentration in the perilymph, thereby enhancing the therapeutic efficacy of IST.

In the present study, it was attempted to retrospectively analyze data of SSNHL patients admitted to Beijing Tsinghua Changgung Hospital (Beijing, China) between 2015 and 2022, in order to develop an appropriate therapeutic strategy. Those patients exhibiting incomplete recovery post-SST underwent a modified IST as a salvage treatment following primary treatment failure. The procedure involved the placement of a VT and gelfoam through otoendoscopy. Subsequently, improvements before and after the intervention were compared.

2. Methods

2.1. Patients

Patients with SSNHL admitted to Beijing Tsinghua Changgung Hospital (Beijing, China) between June 2015 and June 2022, who did not fully recover after SST, were enrolled based on the following criteria:

1. Age range: 22–81 years, regardless of gender.
2. Audiometric criteria: Hearing loss of ≥30 dB affecting at least three consecutive frequencies, with an onset within 72 h. Enrollment occurred within 12 weeks following the onset of SSNHL. Patients with SSNHL were included if they did not fully recover after SST, with the affected ear's recovery not reaching within 10 dB HL of the unaffected ear.
3. No contraindications: Absence of contraindications for the use of steroids.
4. Exclusion criteria: Patients without conductive hearing loss and other inner ear diseases.
5. Informed consent: The necessity of signing written informed consent forms before IST.

Totally, 74 patients who were aged 22–81 years old were selected for inclusion in this study, with a gender distribution of female (45.9%) and male (54.1%). The identification and recruitment of patients involved a comprehensive assessment of medical records and clinical evaluations during their admission to Beijing Tsinghua Changgung Hospital. The mean duration of SST upon admission, ranging from 7 to 19 days, was documented for each patient. The criteria for inclusion further considered the rationale behind a 10 dB difference between the affected and healthy ear, ensuring a standardized approach to participants' selection. Additionally, metabolic and cerebrovascular conditions were thoroughly taken into account during the screening process to provide a comprehensive overview of the study cohort. IST was initiated, on average, 24.1 days from the onset of SSNHL (range, 8–56), with an average of 6.16 IST (range, 3–11) sessions. To align with the principles of intention-to-treat study design, it was attempted to recognize the significance of employing a comparable treatment group. In this study, clarity regarding the treatment modalities administered to both the control and treatment groups was provided. The control group received standard SST as the primary treatment for SSNHL. In contrast, the treatment group underwent the modified IST protocol following the failure of SST.

Table 1 presents patients' characteristics. It is essential to acknowledge the retrospective nature of this study, which inherently involved certain limitations, including the absence of randomization. The assignment of patients into the control and treatment groups was based on treatment modalities rather than a randomized process. While this design allowed for the examination of real-world treatment outcomes, the potential of selection bias is noteworthy.

2.2. Treatment

All patients underwent otologic examinations upon hospitalization and initially received SST: 0.9% sodium chloride (250 ml) + methylprednisolone 40 mg/day, administered intravenously for a minimum of 7 days. Subsequently, patients in the treatment group underwent salvage treatment with a VT using an otoendoscope, following these steps: The patient was placed in a supine position with the affected ear angled upward. After local or general anesthesia, myringotomy was conducted in the anteroinferior quadrant of the TM. Two pieces of gelfoam (2*2 mm^2 each) were placed, one in the direction of the ostium tympanum and the other in the round window niche, to minimize steroid loss and enable slow release, as illustrated in Fig. 1. After VT placement, 1 ml of steroid (10 mg/ml, methylprednisolone) was injected into the tympanum through the tube. The patient's position was stabilized for 30 min. IST was administered twice a week for a total course duration of 2–6 weeks. The VT was removed after completing the course. The control group did not receive IST treatment.

2.3. Outcome assessment

Pure tone audiometry was conducted weekly before and after treatment, assessing the air conduction threshold at frequencies of 250, 500, 1,000, 2,000, 4,000, and 8000 Hz. Additionally, the bone conduction threshold was measured at 500, 1,000, 2,000, and 4000 Hz. The pure tone average (PTA) of the affected frequency was calculated. Evaluation of efficacy was based on the improvement in PTA at both the initiation and end of IST.

2.4. Statistical analysis

The SPSS 21.0 software (IBM, Armonk, NY, USA) was used to analyze the data. The enumerated data were presented as the number of cases

Table 1
Patients' baseline characteristics.

Characteristics	Value
Number of cases	74
Age (years)	
$\bar{x} \pm s$	53.8 ± 16.2
min-max	22–81
Side	
Left	39(52.7%)*
Right	35(47.3%)
Gender	
Female	34(45.9%)
Male	40(54.1%)
Duration of SST (days)	
$\bar{x} \pm s$	10.0 ± 3.5
min-max	7–19
Duration from the onset of SSNHL to the beginning of IST (days)	
$\bar{x} \pm s$	24.1 ± 13.7
min-max	8–56
Time of IST (times)	
$\bar{x} \pm s$	6.2 ± 2.3
min-max	3–11

*% indicates the percentage of total number of patients.

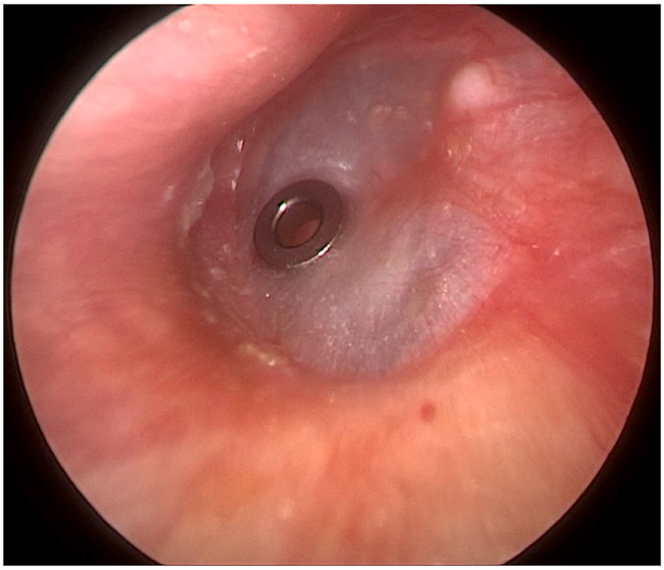

Fig. 1. A ventilation tube under an otoendoscope.

and percentage (%), and measurement data were expressed as mean (min, max). Independent-samples *t*-test was employed to compare the data. Spearman's rank correlation coefficient was used to analyze the correlation. Multivariate logistic regression analysis was performed by a multivariate linear regression model, and factors with $P < 0.1$ were evaluated by the univariate analysis. $P < 0.05$ was considered statistically significant.

3. Results

3.1. PTA improvement at affected frequencies

In Table 2, the results revealed that PTA at affected frequencies (250-8000 Hz) was significantly improved after IST treatment compared with that in the control group (P = 0.015, 0.002, 0.001, 0.003, 0.000, and 0.001, respectively), indicating that the difference in PTA between the control and treatment groups was statistically significant.

3.2. PTA improvement in different genders

In the present study, the efficacy of IST for SSNHL in different genders was assessed (Table 3). The results revealed that in the treatment group, the mean PTA improvement in men and women was 10.59 (−11.25, 46.67) and 8.86 (−10, 40.83), respectively. There was no significant difference in hearing improvement between the control and treatment groups (control group, male *vs.* female, $P = 0.34$; treatment group, male *vs.* female, $P = 0.992$). Meanwhile, the mean PTA improvement in the treatment group was 9.71 ± 14.84 dB, and 21 (42.9%) patients experienced >10 dB improvement.

Table 2
Comparison of PTA at different frequencies between control and treatment groups.

Frequency (Hz)	Control group[a] (dB)	n1	Treatment group[a] (dB)	n2	P
250	2.3(-5.0,15.0)	20	14.2(-20.0, 75.0)	44	0.015
500	−0.7(-10.0,5.0)	21	17.9(-15.0,85.0)	43	0.002
1000	−2.6(-10.0,5.0)	21	10.7(-20.0,50.0)	41	0.001
2000	−3.6(-10.0,0.0)	22	7.3(-25.0,65.0)	40	0.003
4000	−4.6(-10.0,5.0)	23	7.8(-10.0,60.0)	43	0.000
8000	−4.8(-15.0,0.0)	23	4.5(-20.0,35.0)	42	0.001

[a] PTA of control/treatment group is presented as mean (min, max); n1 = Control, n2 = Treatment.

Table 3
PTA improvement in male and female participants (mean, min-max).

Factors		PTA improvement[a] (dB)	
Sex		Control group	Treatment group
	Female	−1.02(-9.17,10.0)	8.86(-10,40.83)
	Male	−2.63 (−8.33,0.83)	10.59(-11.25, 46.67)
	P	0.34	0.687
Total		−2.13 ± 4.72	9.71 ± 14.84

[a] The improvement in PTA is expressed as the mean paired difference between pre- and post-treatment at various frequencies.

3.3. PTA improvement and the influential factors

To analyze the correlation between PTA improvement after treatment and influential factors, the Spearman rank correlation test was utilized. Table 4 shows that the PTA improvement in the treatment group was negatively correlated with the duration of SST (Rs = −0.306, $P = 0.033$) and the duration of IST from the onset of SSNHL (Rs = −0.483, $P = 0.000$), while there was no significant correlation between PTA improvement and time of IST ($P > 0.05$).

3.4. The multivariate logistic regression analysis of influential factors

To further investigate the correlation between influential factors in the treatment group and PTA improvement after treatment in the univariate analysis (Table 5), the multivariate logistic regression analysis was conducted. PTA improvement was selected as a dependent variable, and 4 influential factors (age, duration of SST, duration from the onset of SSNHL to the beginning of IST, and time of IST) were selected as independent variables. Table 5 indicates that there was a negative correlation between the duration from SSNHL onset to IST initiation and PTA improvement following treatment ($P < 0.05$), in which the shorter duration, the greater PTA improvement. However, age, duration of SST, and time of IST were not independent factors of PTA improvement ($P > 0.05$). It is noteworthy that all patients experienced no infection or overflow after myringotomy. Additionally, all TMs were healed without perforation after tube removal.

4. Discussion

4.1. The modified IST

The present study introduced a modified IST approach, leveraging the advantages of gelfoam as a key element in the treatment of SSNHL. The placement of gelfoam in the round window niche serves as a strategic drug carrier, providing distinct benefits over conventional IST methods. By minimizing drug loss, extending the duration of steroid action, and increasing perilymph concentration, gelfoam enhances the overall efficacy of IST. In recent years, various studies, such as the research conducted by Choung et al. (2006), which utilized a spinal needle, a syringe, and a two-puncture technique for ventilation and

Table 4
Correlation analysis between PTA improvement after treatment and influential factors.

Influential factors	PTA improvement (dB)	
	Rs	P
Age (years old)	−0.244	0.091
Duration of SST (days)	−0.306	0.033
Duration from the onset of SSNHL to the beginning of IST (days)	−0.483	0.000
Time of IST (times)	0.261	0.071

*Analysis was performed using Spearman rank correlation test.

Table 5
Assessment of the correlation between PTA improvement after treatment and influential factors.

	β	SE	β	t	P	95%CI	
						upper	lower
Factors	19.753	12.242		1.614	0.114	−4.919	44.426
Age (years old)	−0.162	0.128	0.165	1.263	0.213	−0.419	0.096
Duration of SST (days)	−0.043	0.669	0.009	0.064	0.949	−1.392	1.306
Duration from the onset of SSNHL to the beginning of IST (days)	−0.553	0.171	0.431	3.229	0.002	−0.897	−0.208
Time of IST (times)	1.777	0.995	0.238	1.785	0.081	−0.229	3.783

perfusion, have confirmed the efficacy of IST for patients with SSNHL, particularly for those refractory to oral steroid therapy. Gianoli and Li (2001) highlighted IST as an alternative for SSNHL patients who failed SST or found it barely tolerable. Banerjee et al. (Banerjee and Parnes, 2005) reported the safe and effective use of IST by inserting a ventilation tube for steroid delivery in the middle ear.

In the present study, otoendoscopic surgery was employed for tympanic membrane puncture, incision, and tube and gelfoam placement. This approach possesses advantages, such as a clearer visual field, closer observability, better illumination, and more flexible operation. These benefits contribute to improved intraoperative identification of important anatomical structures, enhancing the accuracy and safety of tube and gelfoam placement (Lai et al., 2017; Wang et al., 2021).

A novel aspect of the present study was the placement of gelfoam in the round window niche and on the tympanic orifice of the Eustachian tube as a carrier for steroids. This innovative technique reduces steroid loss, extends its action time, and increases steroid concentration in the perilymph, holding significant clinical implications for the treatment of inner ear diseases (Tang et al., 2010). The results of the current study revealed that salvage treatment of SSNHL by placing gelfoam and injecting steroids significantly improved hearing loss.

In the present study, steroid was directly injected through a V T (Li et al., 2015). Although the AAO-HNSF guidelines recommended spinal needles with narrow gauge for injection into the middle ear, it was also advised to consider VT insertion if multiple injections were planned (Stachler et al., 2019). This approach avoids repeated punctures, reduces patient discomfort, and lowers the risk of non-healing TM perforation post-treatment. Simultaneous placement of a ventilation tube with gelfoam was carried out based on animal experiments, suggesting that steroid injection with gelfoam is easily absorbed by the round window, resulting in higher perilymph concentrations compared with conventional IST. The reason for this difference remains elusive and may be associated with electric charge, concentration, molecular weight, and molecular size carried by the solution (Taha et al., 2019).

According to the AAO-HNSF guidelines, the recommended dose for IST is 0.4–0.8 ml dexamethasone (16–24 mg/ml (compound) or 10 mg/ml (reserve)) or methylprednisolone (30–40 mg/ml) (Stachler et al., 2019). Previous randomized controlled trials (RCTs) have mainly utilized 2–4 mg dexamethasone or 20–80 mg methylprednisolone (Li et al., 2015). In the present study, 10 mg methylprednisolone was administrated every day until patients perceived the bitterness of the solution.

4.2. Efficacy of IST

In a study conducted by Dallan et al. (2010), 27 patients with SSNHL who exhibited poor recovery after SST were treated with IST for 30 days, resulting in hearing improvement in 55.6% of patients. Gianoli et al. (Gianoli and Li, 2001) reported a 44% improvement in patients with an average gain of 15.2 dB. Taha et al. (2019) a 59% hearing improvement of approximately 4.5 dB in their study. Similarly, in our study, patients in the treatment group exhibited a mean pure tone average (PTA) improvement of 9.71 ± 14.84 dB, with 42.9% of patients experiencing an improvement above 10 dB at the affected frequency, aligning with findings in related studies. The results of our study indicated improved hearing across different frequencies (250-8000 Hz), with improvement more pronounced at lower frequencies, a trend consistent with Belhassen et al.'s findings (Belhassen and Saliba, 2014). Despite the expectation that steroids reach the basal turn first through the round window, studies have suggested that hearing improvement is more frequent at low frequencies, potentially due to the basal turn's increased vulnerability to free radicals and structural abnormalities following ischemia (Seggas et al., 2011).

The majority of patients in the present study experienced noticeable hearing improvement. Some patients exhibited slight changes in hearing, while very few had hearing loss. Potential factors contributing to these outcomes included salvage treatment, where patients were diagnosed with SSNHL within 3 months, possibly missing the optimal treatment period. Additionally, long-term follow-up (more than 6 months) revealed some patients with progressive hearing loss, tinnitus, and vertigo, who were eventually diagnosed with Meniere's disease. Although such cases were excluded, there might be undiagnosed patients with similar symptoms, leading to short-term improvement, whereas unsatisfactory results in the middle and long term. Furthermore, some patients might be unsure about the onset of SSNHL, potentially underestimating the duration. Despite these considerations, the results of the present study remain reliable.

4.3. Influential factors of IST

Numerous factors influence the prognosis of patients with SSNHL. Evaluating the efficacy of IST for SSNHL is challenging due to the variable self-recovery rate and differing evaluation criteria. In the present study, it was revealed that hearing improvement, when IST was employed as a salvage treatment for SSNHL, was not correlated with age and the number of IST sessions. Previous studies have generally reported no significant correlation between age and prognosis (Haynes et al., 2007), although some suggested a trend of better hearing recovery in younger individuals (Banerjee and Parnes, 2005), which lacked statistical significance. The weak correlation coefficient of −0.306 for the duration of SST indicated that it is not an independent factor. Furthermore, the present study identified the duration of IST from the onset of SSNHL as an independent factor, which is consistent with previous research (Stachler et al., 2019; Yu et al., 2015; Ho Ahn et al., 2008), which emphasized the greater efficacy of early treatment. Timely initiation of salvage treatment, especially when the primary treatment proves ineffective, is essential. However, this might also be influenced by the natural self-recovery process in patients at an early stage of SSNHL.

It is pertinent to acknowledge studies within the literature that have investigated the efficacy of interventions, such as ventilation tubes and steroid eardrops in the context of SSNHL. Previous research has reported comparable outcomes with these modalities. The present study aimed to underscore the distinctiveness of the modified IST approach. The study proposed a novel aspect by employing tympanic tubes and gelfoam as integral components of the treatment protocol. The utilization of tympanic tubes allows for precise delivery of steroids, while gelfoam serves as a unique drug carrier within the round window niche. These elements collectively contribute to the safety and efficacy of the modified IST, differentiating it from interventions utilizing ventilation tubes and steroid eardrops.

The present study's retrospective design represents a notable limitation, as the absence of randomization introduces the possibility of selection bias. The decision to assign patients to the control or treatment group was contingent on treatment modalities rather than a randomized allocation. This design choice, while reflective of real-world clinical scenarios, might impact the internal validity of the findings. We acknowledge the importance of randomization in clinical trials to mitigate bias and confounding variables. Moving forward, prospective RCTs are warranted to validate the results of this study and provide robust evidence supporting the efficacy of the modified IST as a salvage treatment for SSNHL.

In conclusion, it was revealed that, following high-dose dexamethasone in patients with incomplete recovery after SST, the majority of patients experienced improvement in the affected frequency, and closer proximity of IST to the onset time was correlated with greater hearing improvement. The key outcomes of this study can be summarized as follows: 1) We used the affected frequency of PTA compared with other studies that covered all frequencies of PTA. In contrast to studies that encompassed all frequencies of PTA, the present study specifically concentrated on the affected frequency. It enabled us to draw precise comparisons related to the efficacy of the modified IST for SSNHL. 2) Gelfoam placement in the round window niche and the tympanic orifice of the eustachian tube as a drug carrier, despite the absence of an RCT design, demonstrated potential benefits by reducing drug loss, ensuring slow drug release, and increasing action time. These findings shed light on the potential of gelfoam-assisted IST as a safe and efficacious strategy for SSNHL, suggesting insights for further exploration and validation in the future RCTs.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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