*The Journal of Laryngology & Otology (2017)*, ***131***, *404–410*.

doi:10.1017/S0022215117000548

**MAIN ARTICLE**

# Intratympanic methylprednisolone perfusion as a salvage treatment for profound idiopathic sudden sensorineural hearing loss

Y DAI[1,2], L LU[2], J HOU[2], X YANG[2], H LI[2], Y YANG[2], W SHE[1,2]

[1]*Department of Otolaryngology – Head and Neck Surgery, Nanjing Drum Tower Hospital, Clinical College of Nanjing Medical University and* [2]*Department of Otolaryngology – Head and Neck Surgery, Nanjing Drum Tower Hospital, Affiliated Hospital of Nanjing University Medical School, People's Republic of China*

## Abstract

*Objective*: This study aimed to examine the effectiveness of intratympanic methylprednisolone perfusion as salvage treatment for profound idiopathic sudden sensorineural hearing loss.

*Methods*: A retrospective clinical study of 97 patients with unilateral profound idiopathic sudden sensorineural hearing loss was performed. In all, 83 patients who received salvage intratympanic methylprednisolone perfusion plus conventional treatment (except for steroids) as the second-line therapy were assigned to the study group, while 14 patients who received conventional treatment alone were assigned to the comparison group.

*Results*: In the study group, treatments in patients with a shorter interval from disease onset to intratympanic methylprednisolone perfusion (up to 15 days) had significantly greater improvements in the overall effective rate and pure tone average compared with patients with a longer interval (over 15 days). For patients with a short interval from disease onset to intratympanic methylprednisolone perfusion, those in the study group had significantly greater improvements in the overall effective rate and pure tone average compared with those in the comparison group. In both the study and comparison groups, hearing improvements were greater at low frequencies than at medium and high frequencies.

*Conclusion*: The interval from disease onset to intratympanic methylprednisolone perfusion was the major factor affecting hearing recovery. Early second-line salvage intratympanic methylprednisolone perfusion significantly improved the degree of hearing recovery in profound idiopathic sudden sensorineural hearing loss patients after failure of systemic steroid treatment.

**Key words:** Hearing Loss; Perfusion, Methylprednisolone; Salvage Therapy

## Introduction

Idiopathic sudden sensorineural hearing loss (SNHL) is commonly defined as hearing loss of more than 30 dB over at least three contiguous frequencies, occurring over a period of up to three days.[1] As the term idiopathic suggests, the aetiology and pathophysiology of idiopathic sudden SNHL are largely unknown. Possible causes include vascular compromise, viral infection and autoimmune disease.[1] Owing to its possible multifactorial origin, various treatment protocols for improving hearing recovery in idiopathic sudden SNHL patients have been proposed. Since the double-blind clinical trial conducted by Wilson *et al.* in the early 1980s,[2] systemic steroids have been widely accepted as a first-line treatment within these protocols. However, steroids can be directly applied to affected ears using an intratympanic approach, which has been used to treat various inner-ear disorders, including idiopathic sudden SNHL. Indeed, intratympanic steroids were initially used by Schuknecht to control vertigo in Ménière's disease in the 1950s.[3] Animal experiments suggest that intratympanic steroid perfusion delivers a significantly higher steroid concentration to the perilymph, with lower or no systemic steroid absorption compared with systemic administration.[4,5] Intratympanic steroids are usually used in three treatment protocols for idiopathic sudden SNHL: (1) as an initial treatment without systemic steroids[6,7]; (2) as an adjunct treatment concomitant with systemic steroids[8,9]; and (3) as a salvage treatment after failure of systemic steroids.[10–13] Salvage intratympanic steroid perfusion has been used to treat idiopathic sudden SNHL in Nanjing Drum Tower Hospital since 2007.[14]

Dexamethasone and methylprednisolone are the steroids most commonly used for intratympanic delivery.

Accepted for publication 24 December 2016 First published online 14 March 2017

Although both have anti-inflammatory effects on the cochlea, Parnes and colleagues reported that methylprednisolone reaches a higher concentration and is present for longer than dexamethasone in the perilymph and endolymph.[5] In addition, Trune and Kempton demonstrated that methylprednisolone can also regulate sodium transport or/and reabsorption in the cochlea, which is important for the cochlear function, but that dexamethasone may not.[15] Based on these reports, methylprednisolone was selected for intratympanic perfusion in the present study.

The World Health Organization classification of hearing impairment defines profound idiopathic sudden SNHL as a pure tone average (PTA) of more than 80 dB at 0.5, 1.0, 2.0 and 4.0 kHz.[16] The disease has a relatively poor prognosis and a poor response to initial systemic steroid treatment.[17,18] Most patients who received salvage intratympanic methylprednisolone perfusion after failure of initial systemic steroids at the Department of Otolaryngology – Head and Neck Surgery, Nanjing Drum Tower Hospital, had been diagnosed with profound idiopathic sudden SNHL. To determine the efficacy of salvage intratympanic methylprednisolone perfusion for profound idiopathic sudden SNHL, the present study reviewed and analysed clinical data from all profound idiopathic sudden SNHL patients treated in Department of Otolaryngology – Head and Neck Surgery from April 2007 to January 2015.

## Materials and methods

### *Patient groups*

All protocols used in the present study were approved by the Ethics Committee of Nanjing Drum Tower Hospital and complied with their ethical standards on human experimentation. Data were collected from the medical records for all hospitalised unilateral profound idiopathic sudden SNHL patients (PTA ≥ 81 dB at 0.5–4 kHz) in the Department of Otolaryngology – Head and Neck Surgery between April 2007 and January 2015.

Within a week of disease onset, all patients had received first-line conventional treatment for at least 10 days. After failure of the first-line treatment, patients received second-line treatment comprising either a second 10-day regimen of conventional treatment (comprising vasodilators and thrombolytic anticoagulant) or intratympanic methylprednisolone perfusion plus conventional treatment (comprising vasodilators and thrombolytic anticoagulant). These treatments were administered as previously reported.[14,19] PTA findings at 0.25–8.0 kHz were used to evaluate hearing levels. A PTA gain of less than 15 dB was defined as failure of the first-line treatment.

For second-line treatments, patients in the study group received intratympanic methylprednisolone perfusion plus conventional treatment, while patients in the comparison group received a second round of conventional treatment only.

### *Hearing assessment and follow up*

Hearing was assessed by pure tone audiometry after disease onset, before and after first-line conventional treatment and second-line treatment, and at three months after the second treatment. Hearing thresholds were recorded as the maximum output value plus 5 dB if the patient had no response to the maximum audiometric output. All data were collected and recorded by the same clinician.

The change in PTA (i.e. PTA after onset minus PTA at three months after treatment) was used to evaluate hearing outcome. A final PTA of within 10 dB of the hearing level in the contralateral ear was defined as complete hearing recovery. Significant, partial and no recovery were defined as changes in the PTA of at least 30, 15–29 and less than 15 dB, respectively. Complete, significant and partial recovery were considered effective outcomes and used for calculating the overall effective rate.

### *Statistical analysis*

Data were analysed using IBM SPSS Statistics software version 19.0 (Armonk, New York, USA) and expressed as means ± standard deviation (SD). Data from patient groups were compared using the Student's *t*-test or the Mann–Whitney *U*-test. The Mann–Whitney *U*-test was used for non-normally distributed data. Qualitative data were analysed using the $\chi^2$ test. A $p$ value less than 0.05 was considered statistically significant.

## Results

### *Clinical characteristics of the study and comparison groups*

A total of 97 patients with profound idiopathic sudden SNHL were included in the study: 83 were assigned to the study group and 14 to the comparison group. There were no significant differences in sex, average age, ear laterality, or the presence of dizziness or tinnitus between the study and comparison groups. However, there were significant between-group differences in the mean initial PTA values (i.e. after disease onset) and the interval from disease onset to second-line treatment. Hearing loss after disease onset was slightly greater in the comparison group than in the study group ($p$ = 0.047), while the interval from disease onset to second-line treatment was significantly longer in the study group than in the comparison group ($p$ = 0.000; Table I).

Although significant hearing improvement at three months after second-line treatment was recorded in most patients in the study group, there was no significant difference in the overall effective rate or in PTA improvement between the study and comparison groups ($p$ = 0.066 and $p$ = 0.053, respectively; Table I). In this preliminary analysis, all patients in the study group were compared with all patients in the comparison group. However, this simple approach could not fully evaluate the therapeutic effects of salvage intratympanic

https://doi.org/10.1017/S0022215117000548 Published online by Cambridge University Press

TABLE I
STUDY AND COMPARISON GROUPS: GENERAL CLINICAL CHARACTERISTICS AND THERAPEUTIC EFFECTS

| Characteristic | SG ($n = 83$) | CG ($n = 14$) | Statistical value | $p$ value |
|---|---|---|---|---|
| Sex (M:F) | 41:42 | 7:7 | $\chi^2 = 0.002$ | 0.967* |
| Average age (y) | 44.40 ± 13.51 | 43.57 ± 17.66 | $t = 0.203$ | 0.839† |
| Ear laterality (L:R) | 41:42 | 8:6 | $\chi^2 = 0.287$ | 0.592* |
| Dizziness | 56 | 9 | – | 1.000‡ |
| Tinnitus | 82 | 13 | – | 0.269‡ |
| Initial PTA (dB) | 94.40 ± 6.44 | 97.05 ± 6.49 | $z = -1.984$ | 0.047** |
| Interval from disease onset to second-line treatments (d) | 24.43 ± 19.10 | 12.86 ± 1.56 | $z = -3.500$ | 0.000** |
| Overall effective rate (%) | 39.80 | 14.29 | $\chi^2 = 3.370$ | 0.066* |
| ΔPTA (dB) | 15.30 ± 15.67 | 6.69 ± 12.17 | $t = 1.957$ | 0.053† |

Data are means ± standard deviation. *Pearson $\chi^2$ test. †Independent-samples $t$-test. ‡Fisher's exact test. **Mann–Whitney $U$-test. SG = study group; CG = comparison group; M = male; F = female; y = years; L = left; R = right; PTA = pure tone average; d = days; ΔPTA = change in pure tone average

TABLE II
STUDY AND COMPARISON GROUPS: HEARING RECOVERY

| Patient group* | $n$ | Overall effective rate (%) | Recovery status† | | | |
|---|---|---|---|---|---|---|
| | | | Complete | Significant | Partial | No |
| SG | | | | | | |
| – Short interval | 39 | 62 | 1 | 13 | 10 | 15 |
| – Medium interval | 28 | 21 | 0 | 2 | 4 | 22 |
| – Long interval | 16 | 19 | 1 | 0 | 2 | 13 |
| CG with short interval | 14 | 14 | 0 | 1 | 1 | 12 |

Data are $n$. *Interval between disease onset to second-line treatment: short, up to 15 days; medium, 16–30 days; long, at least 31 days. †See main text for definitions. SG = study group; CG = comparison group

methylprednisolone perfusion on profound idiopathic sudden SNHL. A more detailed analysis identified a significantly longer interval from disease onset to second-line treatment in the study group than in the comparison group (Table I). Patients in the study group had varying intervals from disease onset to intratympanic methylprednisolone perfusion and were therefore classified into three subgroups according to interval length: up to 15 days, 16–30 days and over 30 days. The overall effective rates at three months after two treatment courses in the comparison group and the three study subgroups are listed in Table II.

### *Effect on hearing recovery of interval length from disease onset to intratympanic methylprednisolone perfusion*

For analysing the impact of interval length on hearing recovery, the study group was classified into two subgroups according to interval length: an interval from disease onset to intratympanic methylprednisolone perfusion of up to 15 days (shorter interval) was recorded in 39 patients and an interval of more than 15 days (longer interval) was recorded in 44 patients. There was no significant difference between these subgroups regarding sex, average age, ear laterality, presence of dizziness or tinnitus, initial PTA, or the PTA after first-line treatment. However, there were significant differences in both the overall effective rate and the change in PTA between subgroups. Patients with shorter intervals showed a significantly greater improvement in the overall effective rate and a significantly greater PTA change after all treatments ($p_{\text{Overall effective rate}} = 0.000$, $p_{\text{PTA improvement}} = 0.008$; Table III).

### *Outcomes of second-line treatments in patients with shorter treatment intervals in the study and comparison groups*

Since the mean interval from disease onset to second-line treatment was significantly longer in the study group than in the comparison group, hearing outcomes were compared in patients who had a short treatment interval (up to 15 days). No significant statistical differences in the initial PTA and in the PTA after first-line conventional treatment were found between patient subgroups ($p > 0.05$ for both). However, improvements in the overall effective rate and in the PTA after second-line treatment were significantly greater for patients in the study group than for those in the comparison group ($p = 0.006$ for both; Table IV).

### *Effects of PTA improvement after first-line conventional treatment on final hearing recovery in the study group*

Although all 39 patients with a short treatment interval (up to 15 days) in the study group had significantly better hearing recovery after second-line therapy, a detailed analysis revealed that these patients had

https://doi.org/10.1017/S0022215117000548 Published online by Cambridge University Press

TABLE III
STUDY GROUP: EFFECT OF INTRATYMPANIC METHYLPREDNISOLONE PERFUSION TREATMENT INTERVAL ON HEARING RECOVERY

| Variable | Interval ≤ 15 days ($n = 39$) | Interval > 15 days ($n = 44$) | Statistical value | $p$ value |
|---|---|---|---|---|
| Sex (M:F) | 16:23 | 25:19 | $\chi^2 = 2.063$ | 0.151* |
| Average age (y) | 46.97 ± 13.50 | 42.18 ± 13.57 | $t = 1.609$ | 0.111† |
| Ear laterality (L:R) | 20:19 | 21:23 | $\chi^2 = 0.105$ | 0.746* |
| Dizziness | 25 | 31 | $\chi^2 = 0.380$ | 0.538* |
| Tinnitus | 38 | 44 | – | 0.470‡ |
| PTA (dB) | | | | |
| – Initial | 94.19 ± 6.73 | 94.59 ± 6.26 | $t = -0.283$ | 0.778† |
| – After first-line treatment | 91.26 ± 8.64 | 90.91 ± 9.00 | $t = 0.179$ | 0.859† |
| – Change | 19.77 ± 15.51 | 10.64 ± 14.86 | $t = 2.738$ | 0.008† |
| Overall effective rate (%) | 61.54 | 20.45 | $\chi^2 = 14.570$ | 0.000* |

Data are means ± standard deviation. *Pearson $\chi^2$ test. †Independent-samples $t$-test. ‡Fisher's exact test. M = male; F = female; y = years; L = left; R = right; PTA = pure tone average

TABLE IV
STUDY AND COMPARISON GROUPS: PTA BEFORE SECOND LINE TREATMENT AND CHANGE AFTER SECOND LINE TREATMENT FOR A SHORT TREATMENT INTERVAL

| Variable | SG, interval of ≤15 days ($n = 39$) | CG, interval of ≤15 days ($n = 14$) | Statistical value | $p$ value |
|---|---|---|---|---|
| PTA (dB) | | | | |
| – Initial | 94.19 ± 6.73 | 97.05 ± 6.49 | $t = -1.375$ | 0.175* |
| – After first-line treatment | 91.26 ± 8.64 | 96.20 ± 5.93 | $t = -1.975$ | 0.054* |
| – Change | 19.77 ± 15.51 | 6.69 ± 12.17 | $t = 2.851$ | 0.006* |
| Overall effective rate (%) | 61.54 | 14.29 | $\chi^2 = 7.411$ | 0.006† |

Data are means ± standard deviation. *Independent-samples $t$-test. †Pearson $\chi^2$ test. SG = study group; CG = comparison group; PTA = pure tone average; PTA = pure tone average

different responses to first-line treatment. Of these, 24 patients with PTA improvements of 15 dB or more at three months after all treatments were assigned to the effective study subgroup, while the other 15 patients with PTA improvements of less than 15 dB were assigned to the ineffective study subgroup. Although there was no statistical difference in the initial PTA between these subgroups, hearing recovery after first-line treatment was better in the effective study subgroup ($p = 0.024$; Table V).

### *Comparisons of pure-tone improvement at different frequencies*

Patients in the study and comparison groups had similar responses to second-line treatment at different frequencies. In the study group, the mean (± SD) improvement in PTA after second-line treatment at low (0.25 and 0.5 kHz), medium (1.0 and 2.0 kHz) and high (4.0 and 8.0 kHz) frequencies were 21.30 ± 19.66, 14.52 ± 18.37 and 9.46 ± 14.26 dB, respectively. Hearing recovery was significantly different at the three frequency ranges: hearing improvement at low frequencies was greater than that at medium frequencies, and hearing improvement at the medium frequency range was better than at high frequencies (Figure 1).

In the comparison group, mean (± SD) improvement in PTA after the second-line conventional treatment at low, medium and high frequencies were 12.14 ± 19.63, 5.71 ± 11.74 and 2.14 ± 6.27 dB, respectively. The difference in hearing improvement was significant between the low and medium frequencies but not between the medium frequencies and high frequencies (Figure 2).

## Discussion

Although vascular compromise, viral infection and autoimmune diseases may be involved in the aetiology of idiopathic sudden SNHL, direct causes are thought to be thrombosis and embolism of the cochlear artery or spiral modiolar artery.[20] Based on these theoretical

TABLE V
STUDY GROUP: PURE TONE AVERAGE IMPROVEMENT AFTER FIRST-LINE CONVENTIONAL TREATMENT

| Variable | ESG ($n = 24$) | ISG ($n = 15$) | Statistical value | $p$ value |
|---|---|---|---|---|
| Initial PTA (dB) | 92.78 ± 6.43 | 96.45 ± 6.79 | $t = -1.696$ | 0.098* |
| PTA improvement after first-line treatment (dB) | 4.18 ± 5.46 | 0.78 ± 1.79 | $z = -2.263$ | 0.024† |

Data are means ± SD. *Independent-samples $t$-test. †Mann–Whitney $U$-test. ESG = effective study subgroup; ISG = ineffective study subgroup; PTA = pure tone average

https://doi.org/10.1017/S0022215117000548 Published online by Cambridge University Press

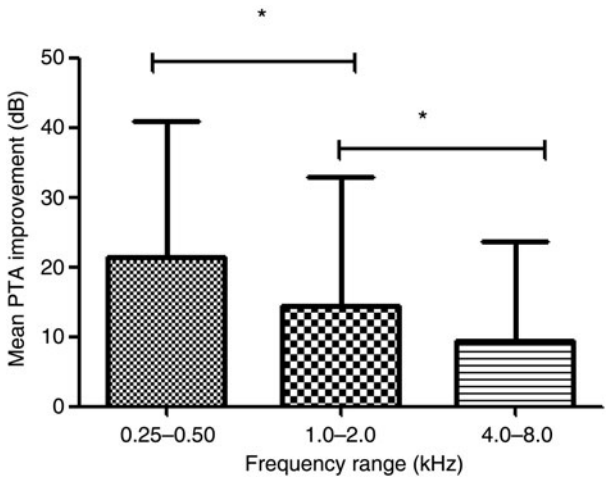


FIG. 1

Graph showing the pure tone average (PTA) improvement at different frequencies in the study group. Data are means ± standard deviation. $^{*}p < 0.01$.

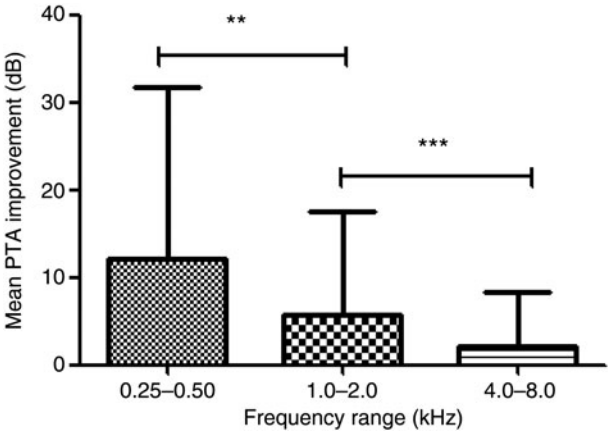


FIG. 2

Graph showing the pure tone average (PTA) improvement at different frequencies in the comparison group. Data are means ± standard deviation. $^{**}p < 0.05$, $^{***}p > 0.05$.

causes, thrombolytics, *Ginkgo biloba* and systemic steroids were recommended as treatments for profound idiopathic sudden SNHL by a Chinese multicentre clinical study group for idiopathic sudden SNHL and by the German Society of Otorhinolaryngology – Head and Neck Surgery.[17,20] However, patients with profound idiopathic sudden SNHL have a relatively poor response to this first-line treatment programme and exhibit high morbidity. Intratympanic steroid perfusion has been recommended as salvage treatment for idiopathic sudden SNHL by the American Academy of Otolaryngology Head and Neck Surgery since 2012.[21] In line with these recommendations, thrombolytics, *G biloba* and systemic steroids comprised the first-line conventional treatment and intratympanic methylprednisolone perfusion was second-line salvage treatment in the present study.

The interval from idiopathic sudden SNHL onset to treatment is regarded as the most important factor affecting hearing outcome. In the present study, most patients in the study group had a long treatment interval (more than 15 days) from disease onset to intratympanic methylprednisolone perfusion, while all patients in the comparison group had a short interval (up to 15 days) from disease onset to the second-line treatment. To exclude the influence of interval length on the analysis, hearing outcomes were only compared between patients with a similar treatment interval (up to 15 days). These patients had a similar initial PTA at disease onset, but those who underwent salvage intratympanic methylprednisolone perfusion within 15 days of disease onset had much better hearing recovery compared with those who did not.

To investigate the benefits of prompt intratympanic methylprednisolone perfusion, therapeutic outcomes were compared between patients with shorter and longer treatment intervals in the study group. As expected, the overall effective rate and degree of PTA improvement were better in patients with a shorter treatment interval. Therefore, early intratympanic methylprednisolone perfusion plus conventional treatment is strongly recommended for profound idiopathic sudden SNHL patients for whom the conventional treatment regimen has failed. The administration of higher steroid concentrations in the cochlea via early intratympanic methylprednisolone perfusion may help prevent the development of irreversible auditory pathological changes. Banerjee and Parnes demonstrated significantly better hearing improvement in patients treated with intratympanic steroids within 10 days of idiopathic sudden SNHL onset compared with those treated after 10 days.[22] However, some patients have shown a positive response to delayed intratympanic methylprednisolone injections[11]; a similar response was observed in the present study. A female profound idiopathic sudden SNHL patient who did not respond to systemic steroids and received combined intratympanic methylprednisolone perfusion and conventional treatment 36 days after disease onset had completely recovered three months after intratympanic methylprednisolone perfusion. Therefore, delayed treatment incorporating intratympanic methylprednisolone perfusion can also be effective.

In the present study, patients with a higher PTA gain after first-line conventional treatment had significantly better hearing recovery at the final follow up. Therefore, greater hearing gain after first-line treatment may help predict the prognosis after intratympanic methylprednisolone perfusion. Consistent with this observation, Ito and colleagues reported a time-course of hearing improvement in idiopathic sudden SNHL patients, demonstrating that the hearing improvement rate at 1–2 weeks after treatment could predict their long-term prognosis.[23] For this reason, a combination of intratympanic methylprednisolone perfusion and conventional therapy is strongly recommended for patients with greater hearing gain after first-line treatment.

https://doi.org/10.1017/S0022215117000548 Published online by Cambridge University Press

A spontaneous hearing recovery rate of 30–60 per cent within two weeks of idiopathic sudden SNHL onset regardless of medical treatment has been reported.[24–27] However, spontaneous improvement was also reported to be rare in patients with severe-to-profound hearing loss.[28] In the present study, all patients had profound hearing loss. Therefore, a hearing gain after the first-line treatments is unlikely to be due to spontaneous recovery: other factors, such as sensitivity to steroids, may also contribute to initial hearing recovery. A greater hearing gain after first-line systemic steroid treatment suggests higher sensitivity to steroids and thus a better response to intratympanic methylprednisolone perfusion.[14,19] Intratympanic methylprednisolone perfusion effectively increases intra-cochlear steroid concentrations, improves cochlear blood flow,[29] protects the inner ear from inflammation and maintains cochlear ion gradients,[30] resulting in greater hearing recovery.

Theoretically, intratympanic perfusion should yield a higher steroid concentration in the basal turn than in the apical turn of the cochlea.[31] Consequently, hearing improvement should be better within the high frequency region. However, regardless of the treatment strategy, hearing improvement was better at the low frequencies in the present study. Similarly, better hearing recovery at low frequencies was previously reported for idiopathic sudden SNHL patients after salvage intratympanic perfusion.[11] This result may be explained by the basal turn of the cochlea being more vulnerable to free radical damage and basal turn injuries being more difficult to treat compared with those in the apical turn.[32,33]

- **The efficacy of salvage intratympanic methylprednisolone perfusion for profound idiopathic sudden sensorineural hearing loss was investigated**
- **Early salvage intratympanic methylprednisolone perfusion may improve hearing recovery after systemic steroid failure**
- **Greater hearing gain after first-line systemic steroids predicts a better prognosis after salvage intratympanic methylprednisolone perfusion**
- **All patients had better hearing improvement at low frequencies regardless of the second-line therapy**

In the present study, prompt salvage intratympanic methylprednisolone perfusion after failure of first-line systemic steroid treatment significantly improved hearing outcomes in profound idiopathic sudden SNHL patients. Intratympanic steroid administration is likely to achieve higher local concentrations in the inner ear without systemic side effects. However, disadvantages include possible ineffectiveness against systemic inflammatory disorders if inflammation extends beyond the inner ear. Moreover, the round window niche could be obstructed by pseudomembranes, which may impede steroid diffusion into the inner ear.[34] As there is evidence for the efficacy of both systemic and intratympanic steroids, a combination of the two treatment strategies (i.e. first-line systemic steroids and early intratympanic steroids if the initial treatment fails) should be considered to maximise anti-inflammatory effects inside and outside the inner ear.

In the present study, far fewer patients were included in the comparison group than in the study group because most patients preferred to undergo combined intratympanic methylprednisolone perfusion and conventional treatment after failure of first-line treatment. Thus, an imbalance in the sample sizes of study and comparison groups was a limitation of the present study. Long-term or multicentre studies are needed to overcome this problem.

## Conclusion

Early intratympanic methylprednisolone perfusion combined with a conventional treatment regimen without systemic steroids may improve final hearing recovery in profound idiopathic sudden SNHL patients after failure of systemic steroid treatment. A greater PTA gain after first-line systemic steroid treatment may indicate a better prognosis for hearing after second-line treatment. Regardless of the second-line treatment strategy, hearing recovery was better at low frequencies than at medium and high frequencies.

## Acknowledgements

The authors would like to thank Dr H Zhu for assistance with the statistical analysis and Drs M West and X Du for their invaluable comments in preparing the manuscript. This work was supported by the National Natural Science Foundation of China (W She, grant number 81271074); the Medical Science and Technology Development Foundation of Nanjing Department of Health (Y Dai, grant number YKK13054), the Clinical Medicine Foundation of the Science and Technology Department of Jiangsu Province, China (W She, grant number BL2014002), the Six-Talent Projects of Jiangsu Province, China (W She, grant number WSN-009), and an International Joint Research grant from the Science and Technology Department of Nanjing Jiangsu Province, China (W She, grant number 2012 sd311038).

### References

1 Schreiber BE, Agrup C, Haskard DO, Luxon LM. Sudden sensorineural hearing loss. *Lancet* 2010;**375**:1203–11
2 Wilson WR, Byl FM, Laird N. The efficacy of steroids in the treatment of idiopathic sudden hearing loss. *A double-blind clinical study.* Arch Otolaryngol 1980;**106**:772–6
3 Schuknecht HF. Ablation therapy for the relief of Meniere's disease. *Laryngoscope* 1956;**66**:859–70
4 Chandrasekhar SS, Rubinstein RY, Kwartler JA, Gatz M, Connelly PE, Huang E *et al*. Dexamethasone pharmacokinetics in the inner ear: comparison of route of administration and use of facilitating agents. *Otolaryngol Head Neck Surg* 2000;**122**:521–8
5 Parnes LS, Sun AH, Freeman DJ. Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. *Laryngoscope* 1999;**109**:1–17

https://doi.org/10.1017/S0022215117000548 Published online by Cambridge University Press

6 Tsai HT, Hsueh N, Huang CM, Lin HC. Intratympanic steroid injection as a first-line therapy in uremia patients with sudden sensorineural hearing loss. *Acta Otolaryngol* 2015; **135**:786–90
7 Filipo R, Covelli E, Balsamo G, Attanasio G. Intratympanic prednisolone therapy for sudden sensorineural hearing loss: a new protocol. *Acta Otolaryngol* 2010;**130**:1209–13
8 Battaglia A, Burchette R, Cueva R. Combination therapy (intratympanic dexamethasone + high-dose prednisone taper) for the treatment of idiopathic sudden sensorineural hearing loss. *Otol Neurotol* 2008;**29**:453–60
9 Ahn JH, Yoo MH, Yoon TH, Chung JW. Can intratympanic dexamethasone added to systemic steroids improve hearing outcome in patients with sudden deafness? *Laryngoscope* 2008;**118**:279–82
10 Ho GM, Lin HG, Shu MT. Effectiveness of intratympanic dexamethasone injection in sudden deafness patients as salvage treatment. *Laryngoscope* 2004;**114**:1184–9
11 Belhassen S, Saliba I. Intratympanic steroid injection as a salvage treatment for sudden sensorineural hearing loss. *J Laryngol Otol* 2014;**128**:1044–9
12 Plaza G, Herraiz C. Intratympanic steroids for treatment of sudden hearing loss after failure of intravenous therapy. *Otolaryngol Head Neck Surg* 2007;**137**:74–8
13 Moon IS, Lee JD, Kim J, Hong SJ, Lee WS. Intratympanic dexamethasone is an effective method as a salvage treatment in refractory sudden hearing loss. *Otol Neurotol* 2011;**32**:1432–6
14 She W, Dai Y, Du X, Yu C, Chen F, Wang J *et al*. Hearing evaluation of intratympanic methylprednisolone perfusion for refractory sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg* 2010;**142**:266–71
15 Trune DR, Kempton JB. Aldosterone and prednisolone control of cochlear function in MRL/MpJ-Fas(lpr) autoimmune mice. *Hear Res* 2001;**155**:9–20
16 Mathers C, Smith A, Concha M. Global burden of hearing loss in the year 2000. In: www.who.int/healthinfo/statistics/bod_hearingloss.pdf [24 December 2016]
17 Chinese Sudden Hearing Loss Multi-Center Clinical Study Group. Prospective clinical multi-center study on the treatment of sudden deafness with different typings in China [in Chinese]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2013;**48**:355–61
18 Edizer DT, Çelebi Ö, Hamit B, Baki A, Yiğit Ö. Recovery of idiopathic sudden sensorineural hearing loss. *J Int Adv Otol* 2015;**11**:122–6
19 Hou J, She W, Du X, Dai Y, Xie L, Zhou Q. Histone deacetylase 2 in sudden sensorineural hearing loss patients in response to intratympanic methylprednisolone perfusion. *Otolaryngol Head Neck Surg* 2016;**154**:164–70
20 Michel O, Deutsche Gesellschaftfür Hals-Nasen-Ohren-Heilkunde, Kopf-und Hals-Chirurgie. The revised version of the German guidelines 'sudden idiopathic sensorineural hearing loss'. *Laryngorhinootologie* 2011;**90**:290–93
21 Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM *et al*. Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg* 2012;**146**: S1–35
22 Banerjee A, Parnes LS. Intratympanic corticosteroids for sudden idiopathic sensorineural hearing loss. *Otol Neurotol* 2005;**26**: 878–81
23 Ito S, Fuse T, Yokota M, Watanabe T, Inamura K, Gon S *et al*. Prognosis is predicted by early hearing improvement in patients with idiopathic sudden sensorineural hearing loss. *Clin Otolaryngol Allied Sci* 2002;**27**:501–4
24 Plaza G, Herráiz C. Intratympanic steroids for treatment of sudden hearing loss after failure of intravenous therapy. *Otolaryngol Head Neck Surg* 2007;**137**:74–8
25 Rauch SD. Intratympanic steroids for sensorineural hearing loss. *Otolaryngol Clin North Am* 2004;**37**:1061–74
26 Mattox DE, Simmons FB. Natural history of sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 1977;**86**:463–80
27 Piccirillo JF. Steroids for idiopathic sudden sensorineural hearing loss: some questions answered, others remain. *JAMA* 2011;**305**:2114–15
28 Rauch SD. Clinical practice. Idiopathic sudden sensorineural hearing loss. *N Engl J Med* 2008;**359**:833–40
29 Shirwany NA, Seidman MD, Tang W. Effect of transtympanic injection of steroids on cochlear blood flow, auditory sensitivity, and histology in the guinea pig. *Am J Otol* 1998;**19**:230–5
30 Fukushima M, Kitahara T, Uno Y, Fuse Y, Doi K, Kubo T. Effects of intratympanic injection of steroids on changes in rat inner ear aquaporin expression. *Acta Otolaryngol* 2002;**122**: 600–6
31 Plontke SK, Biegner T, Kammerer B, Delabar U, Salt AN. Dexamethasone concentration gradients along scala tympani after application to the round window membrane. *Otol Neurotol* 2008;**29**:401–6
32 Sha SH, Taylor R, Forge A, Schacht J. Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals. *Hear Res* 2001;**155**:1–8
33 Billett TE, Thorne PR, Gavin JB. The nature and progression of injury in the organ of Corti during ischemia. *Hear Res* 1989;**41**: 189–97
34 Alzamil KS, Linthicum FH Jr. Extraneous round window membranes and plugs: possible effect on intratympanic therapy. *Ann Otol Rhinol Laryngol* 2000;**109**:30–2

Address for correspondence:
Prof. W She,
Department of Otolaryngology – Head and Neck Surgery,
Nanjing Drum Tower Hospital,
Clinical College of Nanjing Medical University,
321 Zhongshan Road,
Nanjing, 210008,
People's Republic of China

Fax: +86 25 8331 7016
E-mail: shewandong@163.com

Prof. W She takes responsibility for the integrity of the content of the paper
Competing interests: None declared