

Research progress in refractory sudden hearing loss: steroid therapy

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Abstract

Sudden sensorineural hearing loss (SSNHL) is a common condition with a rapid onset, and its worldwide frequency is increasing each year. Importantly, a significant number of patients with SSNHL do not respond to initial treatment, which is termed refractory sudden hearing loss (RSHL), and further treatment is not standardized in terms of type, duration, administration route, and concentration of topical steroid therapy. Dexamethasone and methylprednisolone are effective in treating RSHL, and salvage treatment typically consists of 2 weeks of steroid therapy followed by 3–6 months of follow-up. Near-continual steroid perfusion appears to be more effective than intermittent steroid injection. Furthermore, several novel therapeutic regimens have shown promising results in small-scale studies. However, the optimum treatment needs to be confirmed in larger randomized controlled trials.

Keywords

Refractory sudden sensorineural hearing loss, salvage treatment, research progress, steroid therapy, pure-tone average, intratympanic

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Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as a reduction in hearing of greater than 30 dB over at least three consecutive frequencies, occurring over a period of 72 hours or less.¹ In the United States (US), SSNHL affects 5–30 in 100,000 individuals per year,² with about 4000 new cases per year. In Japan and

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Germany, there are 60.9³ and 160⁴ new cases, respectively, of SSNHL per 100,000 individuals per annum. Furthermore, based on epidemiological investigations in Japan⁵⁻⁷ and Germany,⁸ the morbidity of SSNHL is expected to increase globally.

The spontaneous recovery rate of SSNHL ranges from 32% to 65%.^{9,10} However, approximately 30%–50% of patients do not experience an acceptable therapeutic effect following treatment with oral or intravenous steroids.¹¹ Therefore, patients who do not respond, or who respond insufficiently, to systemic steroids are typically considered to have refractory sudden hearing loss (RSHL).¹² However, the standard definition of RSHL remains highly controversial. In previous trials, some researchers have defined RSHL as an improvement in the pure-tone average (PTA) of less than 10 dB,¹²⁻¹⁵ less than 15 dB,¹⁶⁻¹⁸ or less than 20 dB^{19,20} after initial treatment, while others have defined RSHL as less than 50% recovery.²¹ Regarding an international consensus, panelists at the International Federation of ORL Societies (IFOS) 2017 ENT World Congress suggested that any PTA change exceeding 10 dB could be considered as significant.²² We can therefore consider patients with a PTA increase less than 10 dB after initial treatment to have RSHL.

Multiple prognostic factors affecting sudden deafness have been reported, including patient age, absence of vertigo and tinnitus, degree of hearing loss, shape of the audiogram, and time between the onset and treatment of SSNHL.²³⁻²⁷ In China, there is presumably a large population of individuals with RSHL, although the incidence of this condition in China has not yet been reported. Although steroid therapy is generally believed to be effective in RSHL,^{12-14,28} few studies have examined the correlation between prognosis and type, duration, and administration route of steroid treatment. Therefore, an investigation of the efficacy of

steroid treatment in RSHL is highly relevant. The aim of the present review was to evaluate recent studies to investigate the relationship between the prognosis and duration of steroid treatment in patients with RSHL, including the type, durations, administration route, and concentration of topical steroids. A MEDLINE literature search was performed using a combination of low-specificity keywords including “hearing loss,” “steroid,” and “refractory,” supported by searches of PubMed, to yield all potentially relevant results. However, most of the identified studies did not meet current criteria for high-quality evidence, such as that provided by randomized controlled trials, meta-analyses, systematic reviews, and evidence reports, so the current report represents a non-systematic review. To facilitate a clear comparison of the therapeutic effects and administration routes of various types of steroids, information on the identified RSHL studies is summarized in Table 1.

Types of steroids

Steroids can be classified as short-acting, medium-acting, and long-acting according to the duration of drug effect. Short-acting steroids include cortisone (360.444) and hydrocortisone (362.47); medium-acting steroids include prednisone (400.47), prednisolone (402.4807), and methylprednisolone (372.4547); while long-acting steroids include dexamethasone (392.5) and betamethasone (392.4641). The steroids most commonly used in the treatment of RSHL are methylprednisolone and dexamethasone,^{12-16,18,19,28-31} both of which have been shown to be effective in clinical use.

Based on extensive research into the treatment of RSHL,^{12-16,19,29} the cure rate of RSHL following intratympanic low-dose dexamethasone therapy ranges from 30.6%¹⁶ to 48.5%.¹⁵ Approximately 0%^{12,32} to 16.9%¹⁵ of patients who do not receive

Table 1. Summary of studies of trans-tympanic steroid use for the treatment of refractory sudden hearing loss

Study/No.	Inclusion criteria	Salvage therapy method / dose / duration of injection	Outcome measures	Outcomes
Wu et al. ¹⁹ 2011, n = 55	Improvement in PTA <20 dB	IT, dexamethasone 4 mg/mL, 0.5 mL 4 times within a 2-week period (n = 27) vs. IT, normal saline 0.5 mL, four times within a 2-week period (n = 28)	Improvement in PTA >10 dB	Study group: 44.4% (12/27) Control group: 10.7% (3/28)
Lee et al. ¹³ 2011, n = 46	Improvement in PTA <10 dB	IT, dexamethasone 5 mg/mL; 0.3–0.4 mL (n = 21) four times within a 2-week period vs. no further steroid treatment (n = 25)	Improvement in PTA >10 dB	Study group: 47.6% (10/21) Control group: 16% (4/25)
Erdur et al. ²⁰ 2014, n = 51	Improvement in PTA <20 dB within 14 days	Insert dexamethasone through a ventilation tube, five drops four times per day for 2 weeks (n = 21) vs. no further treatment (n = 30)	Improvement in PTA >20 dB	Study group: 47.6% (10/21) Control group: 10% (3/30)
Hunchaisri et al. ¹² 2010, n = 21	Improvement in PTA <10 dB or <15% in SDS	IT, dexamethasone 4 mg/mL, 0.3–0.4 mL once per week for a maximum of three sessions (n = 14) vs. no further treatment (n = 7)	Improvement in PTA >10 dB or SDS >15%	Study group: 43% (6/14) Control group: 0% (0/7)
Ahn et al. ¹⁶ 2008, n = 99	Improvement in PTA <15 dB	IT, dexamethasone 5 mg/mL, 0.3–0.4 mL twice weekly for 2 consecutive weeks (n = 49) vs. no further treatment (n = 50)	Improvement in PTA >15 dB	Study group: 30.6% (15/49) Control group: 16.0% (8/50)
Choung et al. ¹⁴ 2006, n = 66	Improvement in PTA <10 dB	IT, dexamethasone 5 mg/mL, 0.3–0.4 mL twice per week for 2 consecutive weeks (n = 33) vs. no further treatment (n = 33)	Improvement in PTA >10 dB or SDS >15%	Study group: 38.2% (13/34) Control group: 6.1% (2/33)
Moon et al. ¹⁵ 2011, n = 151	Improvement in PTA <10 dB	IT, dexamethasone 5 mg/mL, 0.4–0.5 mL every other day for five treatments (n = 66) vs. systemic reapplication group	Improvement in PTA >15 dB	IT group: 48.5% (32/66) Systemic reapplication group: 15.4% (4/26) Control group: 16.9% (10/59)

(continued)

Table 1. Continued.

Study/No.	Inclusion criteria	Salvage therapy method / dose / duration of injection	Outcome measures	Outcomes
Ferri et al. ²¹ 2012, n = 55	Improvement in PTA < 50%	(n = 26) vs. control group, no further treatment (n = 59) IT, methylprednisolone 40 mg/mL, 0.4–0.5 mL once every 2–3 days for seven treatments	Improvement in PTA > 15 dB	52.7% (29/55)
She et al. ¹⁷ 2010, n = 49	Improvement in PTA < 15 dB	Methylprednisolone through a micro-catheter 40 mg/mL, 0.5 mL/d for 10 days (n = 26) vs. placebo (n = 23)	Improvement in PTA > 15 dB	Study group: 50% (13/26) Control group: 21.7% (5/23)
Berjts et al. ¹⁸ 2016, n = 50	Improvement in PTA < 15 dB	IT, methylprednisolone 40 mg/mL, 0.5 mL three times, once every 3 days (n = 25) vs. dexamethasone 4 mg/mL, 0.5 mL, three times, once every 3 days (n = 25)	Improvement in PTA > 15 dB	Methylprednisolone group: 84% (21/25) Dexamethasone group: 64% (16/25)

IT: intratympanic therapy; PTA: pure-tone average; SDS: speech discrimination score

further treatment can expect a further hearing improvement of 10 dB or 15 dB 2–3 months after the initial steroid treatment. Furthermore, Wu et al.¹⁹ conducted a double-blind controlled trial of the effect of intratympanic dexamethasone (ITD) in patients with RSHL. The study group consisted of 27 people who received 4 injections of 0.5 mL of dexamethasone (4 mg/mL) within a 2-week period and a control group included 28 people who received the same volume of normal saline. After treatment, 44.4% and 10.7% of subjects improved by 10 dB or more in the study group and the control group, respectively.

To investigate the effect of intratympanic methylprednisolone therapy on RSHL, Xenellis et al.³² carried out a study in 37 patients with RSHL, of which 19 patients received approximately 0.5 mL of methylprednisolone (40 mg/mL) while the other 18 patients received no further treatment. The cure rate was 47.3% in the methylprednisolone treatment group while no patient in the no further treatment group had an increase in PTA greater than 10 dB.

From these previous studies, we cannot infer whether methylprednisolone is superior to dexamethasone for the treatment of RSHL. Following tympanic injection with methylprednisolone, some of the drug can flow into the mouth through the eustachian tube.³³ Therefore, Berjis et al.¹⁸ compared the effects of intratympanic dexamethasone and methylprednisolone injections in patients with RSHL and found that prednisolone (84%; 21/25) was significantly more effective than dexamethasone (64%; 16/25). This outcome may be related to the fact that methylprednisolone is active for longer and at higher concentrations than dexamethasone.³⁴ Furthermore, methylprednisolone has been shown to regulate sodium transport and/or reabsorption in the cochlea.³⁵ However, further studies in larger populations are needed to determine

the optimal steroid therapy for patients with RSHL.

Duration of steroid therapy

According to US guidelines, early treatment within 2 weeks to 3 months (i.e., from the onset of symptoms to the start of treatment) is more beneficial than later treatment.¹ The maximum spontaneous improvement or treatment-related improvement in hearing frequently occurs during the first 2 weeks, with little benefit typically seen after 4–6 weeks.^{36,37} Where hearing loss persists over 2 to 3 months, it may develop into permanent deafness.³⁸ However, Wang et al.³⁹ found that there was a therapeutic value in administering steroids to patients with an SSNHL duration of onset greater than 3 months, especially in those with mild or moderate hearing loss. Similarly, a recent study⁴⁰ showed a hearing improvement in patients with SSNHL after 3 months from symptom onset. Additionally, after a 10-day course of systemic steroid therapy and a long-term follow-up of more than 3 months, Yeo et al.⁴¹ found that 35.54%, 8.26%, and 1.65% of patients with SSNHL recovered within 1 month, 1–3 months, and >3 months, respectively, while a previous case report described a complete spontaneous recovery of hearing at approximately 9 months after the onset of SSNHL.⁴² Plontke et al.⁴³ found that hearing gain and final hearing thresholds appeared to be independent of the start of secondary therapy. Therefore, further studies are needed to determine of the duration of time after which the initiation of treatment for SSNHL is ineffective.

Although there is no consensus on the duration of steroid treatment as salvage therapy, most salvage treatment comprises 2 weeks of treatment and 3–6 months of follow-up. As shown in Table 1, the number of intratympanic steroid treatments ranges from three¹⁸ to seven,²¹ although in

most studies steroids are applied twice per week for 2 consecutive weeks.^{14,16,19,32} However, if patients receive steroids via a ventilation tube, they may receive steroid treatment once per day for 10 days¹⁷ or four times per day for 2 weeks.²⁰ Because the $t_{1/2}$ of a steroid is directly related to its frequency of use, it is necessary to consider the $t_{1/2}$ of commonly used steroids such as prednisone, methylprednisolone, and dexamethasone. The serum $t_{1/2}$ for prednisone is 2 hours, and tissue $t_{1/2}$ is 12–36 hours; serum $t_{1/2}$ of methylprednisolone is 2.3 hours, and tissue $t_{1/2}$ is 12–36 hours; and serum $t_{1/2}$ of dexamethasone is 3.5 hours, and tissue $t_{1/2}$ is 36–54 hours.⁴⁴ To date, no randomized controlled trial has examined the duration of steroid therapy. Further research is therefore needed to determine how often steroids should be administered in this patient population.

Steroid administration routes

Although evidence supporting the efficacy of steroid treatment in SSNHL may be considered insufficient, steroid is therapy is used as standard for first-line treatment of SSNHL, including as primary therapy and salvage therapy.¹ Systemic steroid administration can be considered the current standard of primary therapy of SSNHL.²² Research has shown that high doses of steroids are required to achieve an adequate perilymphatic concentration.⁴⁵ Because an initial dose of 1 mg/kg is generally needed for systemic steroids,⁴⁵ many physicians are hesitant to initiate a second round of treatment in patients who fail to respond to initial treatment.¹⁶ New methods of steroid administration for RSHL, such as topical application, are therefore of increasing clinical interest. Steroids used to treat RSHL can be applied topically using methods such as a transtympanic needle, tympanostomy tube, microcatheter, postauricular steroid injection, and round window niche

drilling combined with intratympanic steroids.^{20,28,31,34,46,47}

Erdur et al.²⁰ reported a 47.6% improvement in PTA in subjects who received dexamethasone through a ventilation tube. Similar studies by Ferri et al.²¹ and She et al.¹⁷ showed that 52.7% and 50% of RSHL patients, respectively, achieved an improvement in PTA of more than 15 dB.

Although postauricular steroid injection is widely used as an initial treatment in China,^{30,48} there are relatively few reports on its use in RSHL. Jing et al. has suggested that postauricular methylprednisolone injection is an effective therapy for RSHL, especially in patients with low-frequency involvement.⁴⁹

To explore the effects of different delivery methods, Li et al.³³ performed a prospective randomized clinical study in patients with RSHL and found that the effective rate in a perfusion group treated via round window microcatheter with an electronic pump was 40.6%, which was significantly higher than that achieved using ITD at the same dosage or no further treatment (20.6% and 7.7%, respectively). Similarly, Chou et al.⁵⁰ showed the superiority of applying near-continual transtympanic steroid perfusion compared with intermittent intratympanic steroid injection (53.3% vs 43.3%). However, in these studies, patients in the perfusion group reported events such as a fibrous plug covering the round window, bleeding incisions, microcatheter extrusion from the middle ear, and mild otalgia; while patients in the injection group reported vertigo and perforation of the tympanic membrane.^{33,50}

Si et al.³⁴ reported that round window niche drilling combined with daily intratympanic methylprednisolone was a safe and effective therapy in patients with RSHL, with up to 90% efficacy observed (9/10). In this study, the width of the round window membrane ranged from 1.97 to 2.50 mm, which may have increased

the contact area and time of methylprednisolone. However, drilling of the round window niche was associated with complications of total hearing loss.

Recently, several novel routes of administration have been used for the topical application of steroids to treat SSNHL.^{51,52} Lundy et al.⁵¹ reported that the application of intratympanic dexamethasone using saturated Gelfoam prolonged the contact time of steroids with the round window membrane, thus improving the hearing of patients with severe SSNHL. Furthermore, Shimoji et al.⁵² found that the magnetic injection of prednisolone into the rat cochlea is a safe and effective strategy for the treatment of SSNHL. However, further trials are needed to determine whether these treatments are also effective in RSHL.

Concentration of topical steroids

The concentration of steroids used for treatment is one of the most important factors affecting recovery in patients with RSHL. A 40.7% improvement was reported in a study in which patients with RSHL received high-dose (24 mg/mL) ITD as salvage therapy.⁵³ However, multiple trials have shown that the use of low-dose (4 mg/mL) ITD as salvage therapy might be more effective in this patient group.^{12,14,19} However, there are insufficient data at present from randomized controlled trials to evaluate the correlation between prognosis and steroid concentration.

Conclusions

Previous studies have shown that both dexamethasone and methylprednisolone are effective for the treatment of RSHL, and that methylprednisolone is more effective than dexamethasone for this indication. Salvage treatment generally consists of 2 weeks of treatment and 3–6 months of

follow-up. Furthermore, research has demonstrated that near-continual steroid perfusion is more effective than intermittent steroid injection, although a number of innovative treatment approaches are under development. However, these novel strategies have to date been shown to be effective in limited numbers of study subjects; therefore, randomized controlled trials are needed to confirm their efficacy.


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The authors declare that there is no conflict of interest.

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