Review

Intratympanic vs systemic use of steroids as first-line treatment for sudden hearing loss: A meta-analysis of randomized, controlled trials

Ting Yang, Hui Liu, Fangyao Chen, An Li, Zhou Wang, Shuangyuan Yang, Shiyu Yang, Wen Zhang

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Abstract

Background: Sudden sensorineural hearing loss (SSNHL) is a common disease in otology, and steroids play an important role in its treatment. Steroids can be administered systemically or locally, and the efficacies of different administration routes remain controversial.

Methods: We searched the Cochrane, EMBASE, PubMed, Web of Science, CNKI, Wanfang and Weipu databases for randomized controlled trials (RCTs) on glucocorticoid treatments for SSNHL to compare the efficacy of topical and systemic steroid administration. The Review Manager 5.4 software was used for synthesis of data: the rate of reported hearing improvement and change in pure-tone audiometry (PTA).

Results: In all the included studies, when intratympanic administration was compared to systemic therapies, the risk difference (RD) using reported hearing improvement as an outcome measure was 0.08 (95% CI: 0.01–0.14, I² = 45%). Using PTA changes as an outcome measure in 4 studies, the mean difference (MD) was 10.43 dB (95% CI: 3.68–17.18, I² = 81%). Hearing improvement RD was also compared among different types of steroid, recovery criteria, follow-up times and diagnostic criteria, and showed no significant differences exception for recovery criteria (>10 dB) (RD -0.06, 95% CI: 0.14-0.2, I² = 0%).

Conclusion: As the initial treatment for SSNHL, topical steroids seem to be superior to systemic steroid administration, especially in patients with contraindications to systemic steroids usage. However, further verification based on high-quality research is needed.

Keywords:
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* Corresponding author.
E-mail addresses: 18191619266@163.com (T. Yang), liuhui1105@163.com (H. Liu), chenfy2017@hotmail.com (F. Chen), li-an0835@163.com (A. Li), ikrush@11.com (Z. Wang), 18701586796@163.com (S. Yang), yangshiyu0316@163.com (S. Yang), smuleww@foxmail.com (W. Zhang).

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1. Introduction

Disabling hearing loss affects greater than 6.8% of the world’s population and people of all ages (Neumann et al., 2019). Patients with hearing loss experience impaired quality of life, with emotional and financial burdens seriously affecting their livelihood and families. In 1944, Kleyk first described and defined sudden sensorineural hearing loss (SSNHL) as hearing loss of at least 30 dB at three or more consecutive frequencies on pure-tone audiogram in 3 days or less (Kleyk, 1994). SSNHL affects 5–27 (US) and 160–400 (Germany) per 100,000 people each year (Steth, 2016). However, the exact cause of this disease remains unclear. Infections, congenital diseases, autoimmune mechanisms, ototoxic drugs and other conditions have been reported as risk factors for the occurrence of SSNHL (Dan et al., 2016). If is not detected and treated in due time, SSNHL can lead to persistent hearing loss and significantly compromised quality of life (QOL) in patients. Therefore, early management and intervention are essential.

However, treatments and interventions for this disease remain a subject of ongoing debate. To date, many treatment methods have been reported, including various kinds of corticosteroids, vasoactive agents, hyperbaric oxygen (Dan et al., 2016) and antiviral therapies. Since the 1980s, two double-blind trials have shown the efficacy of corticosteroids, including the Wilson study. Corticosteroids have become one of the most commonly used and effective clinical treatments for SSNHL, probably due to their anti-inflammatory actions and effects on blood rheology.

Currently, there are two methods for inner ear steroids administration, namely, systemic steroid treatment (SST) and local therapy, with systemic use being the most widely accepted.

Intratympanic (IT) steroids treatment was first used on the basis of injection of streptomycin in 1956 to relieve symptoms of Meniere’s disease (Schuknacht, 1956). Bird et al. (2007) concluded that intratympanic use of dexamethasone (DEX) resulted in a 1.270-fold increase in its perilymphatic concentration along with a decrease in plasma concentrations. Since then, IT route has been used for inner ear steroids administration and become increasingly common in practice (Fig. 1), especially in patients with contraindications or resistance to systematic use of steroids. IT steroids have also often been used in rescue treatment for those who have failed regular treatments.

Given the widespread application of IT steroids therapy, we wonder if it may be used as a first-line treatment for SSNHL. The purpose of this meta-analysis was to evaluate the efficacy and safety of IT steroids therapy as the initial treatment for SSNHL using published studies in the Chinese and English literature, as it may represent a promising technology to administer small amounts of medications and to reduce systemic adverse events.

2. Methods and materials

2.1. Literature retrieval

This study was designed based on the Preferred Reporting Items for Systematic Review Protocols (PRISMA-P) Statement 7 (Shamseer et al., 2015). An electronic database search was conducted to identify all available randomized controlled trials (RCTs) examining the use of corticosteroids in SSNHL. The Cochrane, EMBASE, PubMed, Web of Science, CNKI, Wanfang and Weipu electronic databases were searched for articles published before May 25, 2020. The following search terms were used: “sudden hearing loss”, “sudden deafness”, “sudden sensorineural hearing loss”, “idiopathic sensorineural hearing loss”, “idiopathic deafness”, “corticosteroids”, “dexamethasone”, “betamethasone”, “methylprednisolone”, “steroids”, “glucocorticoid”, “intratympanic”, “tympanic”, “auripuncture” and “eustachian tube”. The search was limited to the English and Chinese languages. A flow chart of this process is shown in Fig. 2.

2.2. Inclusion criteria

The research sought to compare pure-tone audiometry (PTA) improvement, recovery rate and complications between IT steroids and SST. The following inclusion criteria were used: (a) studies investigating patients with valid SSNHL diagnosis; (b) initial treatment studies; (c) while nonsteroid treatments could be combined into in therapies, steroids were the main therapy; (d) studies reporting a well-defined hearing outcome efficacy parameter; (e) studies comparing IT (via auripuncture or eustachian catheter or...
tympanotomy tube) and SST (oral or intravenous) administration; (f) not restricted by region, age, race or underlying diseases (such as hypertension and diabetes); (g) RCTs.

2.3. Exclusion criteria

Studies with following characteristics were excluded: (a) underreporting results or treatment methodologies; (b) not in English or Chinese; (c) involving patients with identifiable causes of sensorineural hearing loss, such as Menière disease; (d) involving small patient samples; (e) review articles, conference abstracts or case reports; (f) duplicate articles; and (g) a sham treatment was used as main therapy in the control group.

Fig. 1. A schematic representation of inner ear anatomy and IT drug delivery.

Fig. 2. Flow chart of articles review and inclusion.
| Study (Publication Year) | Country | Sample Size | Mean Age | Time to Onset (d) | Affected Ear (R) | Sex (F) | With Tinnitus (n) | With Vertigo (n) | Initial PTA (dB) | Diabetic population |
|--------------------------|---------|-------------|----------|------------------|-----------------|---------|-----------------|----------------|------------------|-------------------|
| [1] Chen, 2018 | China | 40 | 40 | 39.8 ± 2.5 | NA | 19 | 19 | 19 | 20 NA | 69.4 ± 14.6 | 69.5 ± 14.7 |
| [3] Hong et al., 2009 | Korea | 32 | 31 | 56.9 | 56.2 | NA | 14 | 13 | 19 | 20 NA | 77.5 ± 23.5 |
| [4] Liang et al., 2012 | China | 60 | 50 | 21 | 79 | ± 78 | 8.5 | 8.0 | 7.5 | 8.4 | 69.5 ± 16.43 |
| [5] Li Hui et al., 2013 | China | 38 | 38 | 45.3 ± 15.2 | 6.34 ± 2.3 | 5.8 ± 3.5 | NA | 22 | 24 | 29 | 30 | 66.55 ± 16.52 |
| [6] Lim, 2013 | Korea | 20 | 20 | 53.3 ± 15.3 | 51.3 ± 14.5 | 10.1 ± 8.1 | 5.4 ± 2.8 | 5.3 ± 3.5 | NA | 20 | 18 | 16 | 31 | 32 | 13 | 16 | 81.4 ± 23.5 |
| [7] LI Zhi et al., 2015 | China | 32 | 32 | 45.2 ± 11.3 | 44.1 ± 10.5 | 4.9 ± 1.9 | 5.4 ± 2.3 | 5.3 ± 1.9 | NA | 12 | 13 | 11 | 14 | 12 | 13 | 77.5 ± 23.5 |
| [8] Michael, 2018 | Greece | 34 | 35 | 53.2 ± 12.0 | 50.1 ± 11.5 | 9.5 ± 8.1 | 5.4 ± 2.8 | 5.3 ± 1.9 | NA | 12 | 13 | 11 | 14 | 12 | 13 | 77.5 ± 23.5 |
| [9] Tang et al., 2015 | China | 25 | 25 | 35.8 ± 9.0 | 34.2 ± 8.6 | 9.5 ± 8.1 | 5.4 ± 2.8 | 5.3 ± 1.9 | NA | 12 | 13 | 11 | 14 | 12 | 13 | 77.5 ± 23.5 |
| [12] Zhang et al., 2016 | China | 42 | 49 | 45.2 ± 15.3 | 45.1 ± 14.5 | 9.5 ± 8.1 | 5.4 ± 2.8 | 5.3 ± 1.9 | NA | 12 | 13 | 11 | 14 | 12 | 13 | 77.5 ± 23.5 |
| [13] Rauch, 2011 | America | 129 | 121 | 51(19 years) | 52(18 years) | 7.0(6.4 years) | 6.7(6.1 years) | 6.5(6.0 years) | NA | 12 | 13 | 11 | 14 | 12 | 13 | 77.5 ± 23.5 |
| [14] Kosyakov et al., 2011 | Tanzania | 24 | 25 | 49(35 years) | 40(32 years) | 7.0(6.1 years) | 6.7(6.0 years) | 6.5(6.0 years) | NA | 12 | 13 | 11 | 14 | 12 | 13 | 77.5 ± 23.5 |
| [15] Dispenza et al., 2011 | Italy | 25 | 21 | 39 | 59 | 3 | 10 | 20 | 18 | 16 | 31 | 32 | 13 | 16 | 81.4 ± 23.5 |

2.4. Data extraction and collection

All qualified studies were independently read by two reviewers (Yang and Li), including titles and abstracts, to exclude irrelevant publications. Data were summarized and analyzed according to treatment modalities: i.e. intratympanic (treatment group) and SST (control group) administration. From full text review of all eligible articles, information regarding country of origin, authorship, sample size, mean age, time to onset, side affected, sex, initial pure-tone audiometry and accompanying symptoms (such as tinnitus and vertigo) was extracted (summarized in Table 1), as well as details of treatments (e.g. type of drugs used, mode of administration and treatment time) (Table 2) and treatment efficacy (including PTA changes and adverse reactions) (Table 3). Data extraction was performed by one reviewer (Chen), and verified by another reviewer (Liu).

2.5. Evaluation of studies quality

The Cochrane Collaboration Group tool was used to evaluate methodological quality of RCTs to assess the risk of bias by two reviewers (Zhou and Yang) using the Cochrane Handbook 5.4 software. In particular, the following domains were considered: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. We judged each domain as having either a low, unclear or high risk of bias.

2.6. Statistical methods

The RevMan 5.4 and Stata 15.1 software was used for data analysis. We pooled the data and used the risk difference (RD) with 95% CI to process dichotomous results: i.e. hearing recovery, and the mean difference (MD) with 95% CI for continuous measures: i.e. PTA changes in dB. Tests of heterogeneity were conducted using the chi-square test as an X^2 variable.

Heterogeneity between studies was evaluated using the I^2 value to represent the chance that variability between different effect estimates exceeded expectations, which was categorized as following using the Nordic Cochrane Centre (2011) reference we considered the following:

I^2 = 0–40%, no important heterogeneity; I^2 = 30–60%, moderate heterogeneity; I^2 = 50–90%, substantial heterogeneity; I^2 = 75–100%, considerable heterogeneity.

2.7. Subgroup variable analysis

The following potential subgroup variables were also analyzed: type of steroids (methylprednisolone [MP] or dexamethasone [DEX]), recovery criteria (>10 dB or 15 dB), follow-up time (<3 or ≥3 months), mode of drug administration and diagnostic criteria (20 dB hearing loss involving 2 or 3 consecutive frequencies).

3. Results

3.1. Search results and the characteristics of included studies

We obtained 2628 articles, of which 1513 were duplicate results and therefore discarded. Title and abstract review of the remaining 1115 studies yielded 183 full-text candidates. After excluding animal experiments, case reports, review articles,
| Study (Publication Year) | SSNHL Definition | Drug Mode of administration | Duration of Treatment | Dose and Frequency adjuvant therapy |
|-------------------------|------------------|-----------------------------|-----------------------|-----------------------------------|
| [1] Chen, 2018          | At least 20 dB hearing loss in 2 CFs occurring within 3 days | MP auripuncture injection IV | 10d NA | 40 g/L: 8mg/(kg.d) reduced and stopped gradually after 6 days. All patients received vasodilators and neurotrophic agents. |
| [2] Gülce et al., 2017  | At least 20 dB hearing loss in 3 CFs occurring within 3 days | DEX auripuncture injection oral | 6d NA | 8mg/2 mL, 0.5–0.7 cc, 3 times every other day. 1 mg/kg (maximum 80 mg) and tapering 10 mg every 3 days. All patients received the standard treatment protocol of our institution for SSHL; intravenous low molecular weight dextran (5 cc/kg for 5–10 days), an oral diuretic agent (acetazolamide) for a month, an oral antiviral agent (acyclovir) for 5 days, an oral vasodilator agent (betahistine), and an oral cytoprotective agent (trimetazidine) for 3 months. |
| [3] Hong et al., 2009    | At least 20 dB hearing loss in 3 CFs occurring within 3 days | DEX auripuncture injection oral | 8d 8d | 5 mg/mL, 0.3–0.4 cc once a day. 60 mg for 4 days followed by 40 mg for 2 days and 20 mg for 2 days. IV:10 mg/d DX for 7 days and followed by oral P 30 mg/d, reduce 5 mg every 7 days. IV:triamterene injection 20 mL/d and Vinpocetine 30 mg/d; intramuscular injection: Vitamin1 0.1 g/d and Vitamin12 0.5 mg/d for 2 weeks |
| [4] Liang et al., 2012   | At least 20 dB hearing loss in 2 CFs occurring within 3 days | DEX auripuncture injection IV/oral | 10d 37d | 5 mg/mL every other day for 5 times. IV:triamterene injection 20 mL/d and Vinpocetine 30 mg/d; intramuscular injection: Vitamin1 0.1 g/d and Vitamin12 0.5 mg/d for 2 weeks |
| [5] Li Hui et al., 2013  | At least 20 dB hearing loss in 2 CFs occurring within 3 days | DEX auripuncture injection IV | 10d 14d | 5 mg/mL, 1 mL/d once a day. 60 mg/d for 5 days, 40 mg/d for 2 days, 20 mg/d for 2 days, and 10 mg/d for 1 day. IV:shuxuening injection 20 mL/d and Vinpocetine 30 mg/d; intramuscular injection: Vitamin1 0.1 g/d and Vitamin12 0.5 mg/d for 2 weeks |
| [6] Lim, 2013            | At least 20 dB hearing loss in 3 CFs occurring within 3 days | DEX auripuncture injection IV | 14d 10d | 5 mg/mL, 0.3–0.4 mL, twice a week for 2 weeks, for a total of 4 times. 60 mg/d for 5 days, 40 mg/d for 2 days, 20 mg/d for 2 days, and 10 mg/d for 1 day. IV:shuxuening injection 20 mL/d and Vinpocetine 30 mg/d; intramuscular injection: Vitamin1 0.1 g/d and Vitamin12 0.5 mg/d for 2 weeks |
| [7] Li Zhi et al., 2015  | At least 20 dB hearing loss in 2 CFs occurring within 3 days | Steroids auripuncture injection oral | 10d 10d | 5 mg/mL, every other day for 5 times. 1mg/(kg.d) all patients received vasodilators and neurotrophic agents |
| [8] Michael, 2018       | At least 20 dB hearing loss in 3 CFs occurring within 3 days | MP auripuncture injection IV/oral | 10d 17d | 62.5 mg/mL, 0.4–0.6 mL every day for 1, 3, 5, 10 days after presentation (total of 4 times). IV: P 1 mg/(kg.d) for 7 days followed by 0.5mg/(kg.d) for another 3 days; then oral MP: 32 mg/d for 4 days followed by oral MP 16 mg/d for another 3 days. IV: piroxicam 20 mg/d for 5 days, 10 mg/d for another 3 days. IV:low molecular weight dextran 500 mL, buflomedil 0.2 g, intramuscular injection: Vitamin D 0.1 g/d and Vitamin12 0.5 mg/d for 10d or 20d |
| [9] Peng et al., 2008    | At least 20 dB hearing loss in 2 CFs occurring within 3 days | DEX auripuncture injection oral | 10d 10d | 5 mg/d, once a day for 10 times. 0.75mg × 3/d for 7 days and 0.75 × 2 for another 2 days. 10 mg for 4 days and halve the dosage for another 6 days. 80 mg/d for 4 days and reduced to 40 mg/d for another 3 days. all patients received vasodilators and neurotrophic agents |
| [10] Qu et al., 2015     | NA MP auripuncture injection IV | 10d 7d | 40 mg/d every other day for 10 days. 80 mg/d for 4 days and reduced to 40 mg/d for another 3 days. all patients received vasodilators and neurotrophic agents |
| [11] Tang et al., 2015   | NA DEX auripuncture injection IV | 12d 6d | 5 mg/d every 3 day for 4 times. 5 mg/d every 3 days. all patients received vasodilators and neurotrophic agents |

(continued on next page)
3.3.2. Side-effects

In the 15 included studies, DEX, MP and prednisolone were used in intratympanic therapies through auripuncture or eustachian tubes, and administered orally or intravenously. The data from these 15 studies were pooled for meta-analysis.

3.3.2.1. Treatment outcome analysis

Based on descriptions in each study, we extracted complete or partial recovery rates to provide a recovery rate for evaluation. The treatment status and prognostic information are listed in Tables 2 and 3.

Dosage of orally or intravenously administered corticosteroids (prednisone, DEX and MP) was 10–60 mg/d for 6–14 days, while that administered intratympanically was 0.3–40 mg/injection once a day or once every 2 days for 6 days to 4 weeks. The dosage of intratympanic steroid treatment was significantly lower than that of systemic administration but typically required a longer course of treatment.

Forest plots were created to depict results of individual studies along with summarized results derived from meta-analysis, showing significantly improved hearing in patients receiving IT steroids compared with patients receiving SST.

Fig. 4a compares the overall efficacy represented by the recovery rate between IT steroids and SST. With $I^2 = 35\% < 40\%$ and $P = 0.08 < 0.10$, indicating minimal heterogeneity and reasonable random-effects model, the summarized hearing recovery RD at 0.08 (95% CI: 0.01–0.14, $P = 0.02$) indicated better total effective rate with IT steroids than with SST.

When comparing PTA changes (pre/post treatment differences) between the IT and SST groups in 4 studies after excluding studies with high heterogeneity (Fig. 4b), the random-effects model used due to high heterogeneity and justification ($P = 0.0003$, $I^2 = 81\%$). The pooled PTA MD was 10.43 dB (95% CI: 3.68–17.18 dB), again indicating better PTA improvement with IT steroids than with SST.

3.3.2.2. Side-effects

Ten of the 15 studies reported adverse reactions (473 in the IT group and 475 in the control group), including 1 study [10] that reported absence of side effects in either group (Fig. 5).
| Study (Publication Year) | Criterion for hearing recovery | Outcome (Recovery Rate [%]) | PTA Before Treatment (dB) | PTA Differences (dB) | Frequency for PTA (kHz) | Follow-up Period | Results |
|--------------------------|--------------------------------|-----------------------------|---------------------------|---------------------|-------------------------|-----------------|---------|
| [1] Chen, 2018           | >15 dB improvement in PTA    | 67.5                        | 37.5                      | 69.4 ± 14.6         | 69.5 ± 14.7            | NA              | NA      |
| [2] Gülce et al., 2017   | >10 dB improvement in PTA    | 87.5                        | 84.2                      | NA                  | NA                      | 0.5, 1.0, and 2.0 | 3M      |
| [3] Hong et al., 2009    | >15 dB improvement in PTA    | 75                          | 72                        | 77.5 ± 27.6         | 79.9 ± 23.5            | NA              | NA      |
| [4] Liang et al., 2012   | >15 dB improvement in PTA    | 91.7                        | 80                        | 66.55 ± 16.52       | 66.2 ± 16.43           | NA              | NA      |
| [5] Li Hui et al., 2013  | >15 dB improvement in PTA    | 84.2                        | 60.5                      | 68.3 ± 23.5         | 63.2 ± 21.7            | NA              | 0.5, 1, 2 and 4 | 1M      |
| [6] Lim, 2013            | >10 dB improvement in PTA    | 55                          | 60                        | 58.9 ± 31.2         | 57.8 ± 28.5            | 12.1 ± 14.6     | 12.8 ± 15.4 | 3W      |
| [7] Li Zhi et al., 2015  | >15 dB improvement in PTA    | 81.3                        | 75                        | 64.5 ± 20.1         | 65.8 ± 18.7            | 13.9 ± 17.16    | 14.8 ± 16.5 | NA      |
| [8] Michael, 2018       | >15 dB improvement in PTA    | 70.6                        | 77.1                      | 81.4 ± 23.3         | 81.1 ± 28.8            | 27              | 29      |
| [9] Peng et al., 2008    | >15 dB improvement in PTA    | 80.95                       | 61.9                      | 72.0 ± 18.6         | 69.0 ± 16.5            | 43.2 ± 21.5     | 21.3 ± 16.6 | 90d     |
| [10] Qu et al., 2015     | >15 dB improvement in PTA    | 80.7                        | 78.26                     | 71.0 ± 18.67        | 70.0 ± 17.6            | 48.1 ± 15.2     | 27.5 ± 14.5 | 1W      |
| [11] Tang et al., 2015   | NA                            | 84                          | 68                        | 85.4 ± 5.6          | 84.8 ± 5.6             | 53.7 ± 5.17     | 53.6 ± 5.28 | 15d     |
| [12] Zhang et al., 2016  | NA                            | 84.1                        | 73.7                      | 76.95 ± 15.49       | 78.08 ± 15.90          | 25.88 ± 14.46   | 22.85 ± 12.37 | 8W      |
| [13] Rauch, 2011         | >10 dB improvement in PTA    | 76.7                        | 84.3                      | 86.4(82.8–90.0)     | 86.7(82.9–90.6)        | NA              | NA      |
| [14] Kosyakov et al., 2011| >15 dB improvement in PTA   | 88                          | 56                        | 41.0 ± 12.87        | 39.1 ± 16.97           | 24.8 ± 5.83     | 14.0 ± 3.58 | 6M      |
| [15] Dispenza et al., 2011| >10 dB improvement in PTA    | 80                          | 81                        | 65                  | 51                      | 0.5, 1, 2 and 4 | 6M      |

T, Treatment group; C, control group; PTA, pure tone average; NA, not available.
The main adverse effects reported in the SST group were sleep loss (n = 69), and fluctuations in blood glucose and blood pressure (n = 36). Other side effects included mood swings, appetite changes, increased thirst or dry mouth and gastrointestinal distress. After discontinuing steroids, most of these symptoms gradually disappeared, although some patients needed drug intervention. For example, the 34 patients with blood glucose and pressure fluctuations reported by Tang [11], Li [5], and Zhang [12] needed drug intervention, especially for those with diabetes and hypertension. The 5 patients with gastrointestinal symptoms reported by Tang [11] needed antacid therapy. Rauch [13] reported a serious complication in 2011 as a mild deterioration of preexisting renal insufficiency in a patient with type 2 diabetes.

The IT group experienced typical side effects of topical treatments, with transient earache being the most common [13]. Short-term caloric vertigo and ear infections were also reported. However, most of these side effects were surgery related and short term. Eardrum perforation was reported in 6 cases [12,13], and persisted after 6 months in 1 case [12]. However, no other serious or life-threatening side effects were reported.

In short, besides a risk of local side effects, such as earache and transient vertigo, fewer complications were noted in the IT group as compared with the SST group.

3.4. Subgroup variable analysis

Analysis of subgroup variables such as types of steroids used, criteria of recovery, follow-up time, medication use and diagnostic criteria showed mixed effect sizes (Fig. 6).

3.4.1. Types of steroids used

As shown in Fig. 6a, studies using MP exhibited substantial heterogeneity ($I^2 = 79\%, P = 0.03$), while those using DEX exhibited no significant heterogeneity ($I^2 = 0\%, P = 0.91$). There were no obvious differences in treatment outcomes noted between the two types of steroids in IT vs SST comparison (MP, RD = 0.15, 95% CI = 0.12–0.42; DEX, RD = 0.22, 95% CI = 0.12–0.33), suggesting that IT steroids might be a superior treatment modality for SSNHL, regardless of the type of steroid.

3.4.2. Criteria of recovery

The studies were divided into two groups based on their criteria (definition) for hearing recovery: i.e. >10 dB or >15 dB. IT vs SST hearing recovery RD was −0.06 (95% CI = −0.14–0.02, $I^2 = 0\%$) for studies using the >10 dB criterion and 0.10 (95% CI = 0.04–0.17, $I^2 = 22\%$) for those using the >15 dB criterion (Fig. 6b), although spontaneous recovery would be more difficult to be excluded for
Fig. 4. Meta-analysis forest map comparing the rate of hearing recovery and mean PTA gain (in dB) between IT steroids and SST.

### a

| Study or Subgroup   | IT       | Total | SST      | Total | Weight | M-H, Random, 95% CI | Risk Difference |
|---------------------|----------|-------|----------|-------|--------|---------------------|----------------|
| Chen 2018           | 27       | 40    | 15       | 40    | 5.9%   | 0.30 [0.09, 0.51]    |                |
| Dispenza 2011       | 20       | 25    | 17       | 21    | 5.3%   | -0.01 [-0.24, 0.22]  |                |
| Gulce 2017          | 16       | 19    | 14       | 16    | 5.2%   | -0.03 [-0.26, 0.20]  |                |
| Hong 2009           | 24       | 32    | 22       | 31    | 5.6%   | 0.04 [-0.18, 0.26]   |                |
| Kosyakov 2011       | 21       | 24    | 14       | 25    | 5.1%   | 0.31 [0.08, 0.55]    |                |
| Li hui 2013         | 32       | 38    | 23       | 38    | 6.5%   | 0.24 [0.04, 0.43]    |                |
| Li zhi 2015         | 26       | 32    | 24       | 32    | 6.2%   | 0.06 [-0.14, 0.26]   |                |
| Liang 2012          | 55       | 60    | 40       | 50    | 9.4%   | 0.12 [-0.01, 0.25]   |                |
| Lim 2012            | 11       | 20    | 12       | 20    | 3.5%   | -0.05 [-0.36, 0.26]  |                |
| Michea 2017         | 24       | 34    | 27       | 35    | 6.0%   | -0.07 [-0.27, 0.14]  |                |
| Peng-a 2008         | 17       | 21    | 13       | 21    | 4.3%   | 0.19 [-0.08, 0.46]   |                |
| Peng-b 2008         | 18       | 21    | 14       | 21    | 4.7%   | 0.19 [-0.06, 0.44]   |                |
| Qu 2015             | 46       | 57    | 54       | 67    | 8.9%   | 0.00 [-0.14, 0.14]   |                |
| Raunch 2011         | 99       | 129   | 102      | 121   | 11.2%  | -0.08 [-0.17, 0.02]  |                |
| Tang 2015           | 21       | 25    | 17       | 25    | 5.2%   | 0.16 [-0.07, 0.39]   |                |
| Zhang 2016          | 32       | 42    | 36       | 49    | 7.1%   | 0.03 [-0.15, 0.21]   |                |

**Total (95% CI)**

| IT       | Total | SST      | Total | Weight | M-H, Random, 95% CI | Risk Difference |
|----------|-------|----------|-------|--------|---------------------|----------------|
| 619      | 612   | 100.0%   | 0.08  | [0.01, 0.14]        |                  |

**Total events**

| IT       | Total | SST      | Total | Weight | M-H, Random, 95% CI | Risk Difference |
|----------|-------|----------|-------|--------|---------------------|----------------|
| 489      | 444   |          |       |        |                     |                |

**Heterogeneity:**

\( \tau^2 = 0.01 \); \( \chi^2 = 27.36, \text{df}=15 (P = 0.03); I^2 = 45\%

**Test for overall effect:** \( Z = 2.31 (P = 0.02) \)

### b

| Study or Subgroup   | IT Treatment | SD | Total | Systemic Treatment | SD | Total | Mean Difference | IV, Random, 95% CI | Mean Difference | IV, Random, 95% CI |
|---------------------|--------------|----|-------|-------------------|----|-------|-----------------|-------------------|----------------|-------------------|
| Kosyakov 2011       | 24.8         | 5.83| 24    | 14                | 3.58| 25    | 25.9%           | 10.80 [8.08, 13.52] |                |
| Lim 2012            | 12.1         | 14.6| 20    | 12.8              | 15.4| 20    | 17.9%           | -0.70 [-10.00, 8.60] |                |
| Peng 2008-a         | 43.2         | 21.5| 21    | 21.3              | 16.6| 21    | 15.0%           | 21.90 [10.28, 33.52] |                |
| Peng 2008-b         | 48.1         | 15.2| 21    | 27.5              | 14.5| 21    | 18.3%           | 20.60 [11.62, 29.58] |                |
| Zhang 2016          | 25.88        | 14.46| 42    | 22.85             | 12.37| 49    | 22.9%           | 3.03 [-2.55, 8.61]   |                |

**Total (95% CI)**

| IT Treatment | Systemic Treatment | Mean Difference | IV, Random, 95% CI | Mean Difference | IV, Random, 95% CI |
|--------------|--------------------|-----------------|--------------------|----------------|--------------------|
| 128          | 136                | 100.0%          | 10.43 [3.68, 17.18]|                |                    |

**Heterogeneity:**

\( \tau^2 = 43.80; \chi^2 = 20.78, \text{df}=4 (P = 0.0003); I^2 = 81\%

**Test for overall effect:** \( Z = 3.03 (P = 0.002) \)
studies using the >10 dB criterion, as some researchers have reported spontaneously recovery independent of medical treatment in some patients (Mattox and Simmons, 1977).

3.4.3. Follow-up time
When comparing studies with follow-up time <3 months to those with follow up time ≥3 months, the IT vs SST hearing recovery RD was 0.09 (95% CI: 0.01-0.18, $I^2 = 52\%$) for those with short follow up times vs 0.05 (95% CI: 0.09-0.18, $I^2 = 41\%$) for those with longer follow up times (Fig. 6c), showing no significant differences.

3.4.4. Modality of steroids administration
Comparison of steroid administration modalities showed: (a) hearing recovery RD was 0.11 (95% CI: 0.02-0.24, $I^2 = 74\%$) when the auripuncture route was compared to intravenous administration; (b) the RD was 0.08 (95% CI: 0.01-0.16, $I^2 = 0\%$) when auripuncture injection was compared to oral administration; and (c) the RD was 0.13 (95% CI: 0.02-0.25, $I^2 = 0\%$) when injection via eustachian tube was compared to intravenous administration, indicating that different routes of steroid administration are not a source of heterogeneity (Fig. 6d).

3.4.5. Diagnostic criteria
The IT vs SST hearing recovery RD was 0.12 (95% CI = 0.03–0.20, $I^2 = 33\%$) when 20 dB hearing loss at 2 continuous frequencies (CFs) within 3 days was used as the diagnostic criteria and 0.06 (95% CI: 0.07-0.19, $I^2 = 34\%$) when 20 dB hearing loss at 3 CFs within 3 days was used, showing that this factor did not completely negate the study.

3.5. Sensitivity analysis
When each study was sequentially excluded based on the rule of omission to assess stability of final results, we found that no individual study alone significantly affected the pooled risk estimate (Fig. 7a).

3.6. Publication bias
Potential meta-analysis biases were evaluated by funnel plots, as shown in Fig. 7b. The essentially symmetrically distributed dots indicated no obvious publication bias in our results.

4. Discussion
Etiologies and pathophysiological mechanisms of SSNHL have not been completely elucidated. Nonetheless, steroid therapy has been the recommended first-line treatment for this disease (Seth
et al., 2019), with long records of safety and efficacy. When SST fails, IT steroids has commonly been used as a rescue treatment, although in recent years, an increasing number of clinicians have started to use it as an initial treatment, with its efficacy still being controversial.

4.1. Condition of existing studies

A number of systematic reviews and meta-analyses studies on steroid treatment of SSNHL exist, of which 7 compared effects of IT steroids with SST as the initial treatment (Mirian and Ovesen, 2020; Garavello et al., 2015; Han et al., 2017; Lai et al., 2017; Qiang et al., 2017; Ding et al., 2013; Chen et al., 2015). Mirian and Ovesen (2020), Garavello et al. (2015) and Han et al. (2017) concluded that there were no statistically significant differences between the two treatment modalities, while 3 other studies (Han et al., 2017; Lai et al., 2017; Chen et al., 2015) showed better outcomes with IT steroids, similar to the current study. Chen et al. found a significant difference in the effective rate between IT and intravenous steroid therapies (RR = 1.17, 95% CI: 1.02–1.34, P < 0.05), but not between IT and oral steroid administration (RR = 1.15, 95% CI: 0.92–1.42, P > 0.05). Ding et al. reported no significantly different rates of recovery between patients receiving systemic and IT steroids (RR = 1.11 95% CI: 0.96–1.28, P = 0.15), although a difference was noticed between intraperitoneal and systemic steroids in diabetic patients (RR = 1.24, 95% CI = 1.02–1.50, P = 0.03).

4.2. Strengths and weaknesses of the study

The current meta-analysis study included RCTs in English and Chinese literatures for the first time and analyzed subgroup variables such as type of drugs, recovery criteria, follow-up time, steroid administration routes and diagnostic criteria. Literature search was comprehensive involving 8 large databases with a systematic review following PRISMA guidelines, including systematic evaluation of quality and treatment outcomes in all studies published to date. Given emergence of new evidence regarding IT steroids for SSNHL, we believe that this route is more effective than SST.

However, the following limitations regarding this study need to be considered. First, the research included in this article exhibits a risk of bias. Most articles did not explain their specific methods of randomization and concealment. Second, we could not adjust for the heterogeneity implied by the use of different assessment schemes nor could we adjust for differences at baseline, including (a) age, (b) dosage and duration of treatment, (c) time to treatment start, and (d) audiometric pattern/severity. We were unable to analyze these factors due to the small sample size and lack of detailed classification in the original literature. Third, the possibility of spontaneous recovery unrelated to treatment cannot be excluded. Fourth, some of the studies combined non-steroid therapies as part of the treatment regimen, including vasodilators and vasoactive substances. The effects of these substances on SSNHL has not been proven, but they may potentially affect the outcomes and accuracy of analysis to some extent. The medications are all listed in Table 2. Given the variations in dosage, types of drug, course of treatment and administration routes across the studies, it was difficult to determine how they could affect outcomes or was a source of heterogeneity. Finally, few high-quality studies on IT steroids as the initial treatment for patients with diabetes or hypertension are available, making analyzing these subgroups variables impossible.

4.3. Future practice and research

From our study, we suggest that future studies need to focus on (a) recording hearing recovery based on classifications of audiometric pattern/severity (b) taking age and underlying conditions (e.g. diabetes and hypertension); into consideration when grouping subjects, with corresponding standard treatment protocols; (c) quantifying adverse side effects using appropriate scales for comprehensive and complete assessment; (d) establishing standardized follow-up criteria in large sample studies to evaluate short- and long-term treatment impact and safety; (e) standardizing and improving recovery criteria to allow comparability between trials; and (f) comparing various techniques of inner ear steroids delivery through the tympanic cavity. The traditional auripuncture injection has been reported to be associated with loss of drug solution through the eustachian tube, shortening inner ear exposure time. Moreover, this approach is invasive and requires surgical skills. New techniques and tools allowing direct steroids delivery to the round window membrane and taking advantage of the eustachian tube route are therefore being studied. As more data become available, new IT steroids delivery techniques will allow clinicians to apply local drug delivery systems designed for specific groups of patients for improved tissue targeting and drug delivery efficacy.

5. Conclusion

In summary, this meta-analysis review evaluated the correlation between different steroids administration routes in initial SSNHL treatment involving 1233 patients and showed better efficacy with IT steroids than with SST, regardless of type of steroids, diagnostic criteria, follow-up time and mode of administration. Nonetheless,
further prospective, randomized and multicenter studies are needed to confirm these findings.

In practice, patients receiving oral drug treatment need only one visit for evaluation and prescription, while patients receiving IT steroids require multiple visits and remaining in a lying down position for 30 min after each injection (Rauch, 2011). Due to the cost of surgery and transportation, intratympanic steroid therapy is more expensive than oral steroids. Therefore, clinicians should fully explain the advantages and disadvantages of both methods and carefully choose the appropriate approach according to the patient’s wishes.

Declarations of competing interests

All authors have no conflicts of interest relevant to this paper.

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