The Laryngoscope

Systematic Review

Intratympanic Dexamethasone in Sudden Sensorineural Hearing Loss: A Systematic Review and Meta-Analysis

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Objective: Systemic dexamethasone has demonstrated conclusive benefits in reversing sudden sensorineural hearing loss (SSNHL) despite considerable number of potential side effects. In contrast, the intratympanic route of steroid administration averts several possible complications. This study aims to examine the literature to delineate the efficacy and side effect of intratympanic dexamethasone (ITD) injection for the treatment of SSNHL.

Data Source: Cochrane, Embase, and MEDLINE electronic databases from January 1950 to August 2014, with an update performed on November 10, 2014.

Review Methods: Systematic review and meta-analysis of randomized controlled clinical trials (RCCTs), using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram and guidelines. Quality assessment was performed using The Cochrane Collaboration Tool for Assessing Risk of Bias.

Results: Eight RCCTs on SSNHL were included Three of the eight studies had high risk of bias. Substantial heterogeneity was found. The meta-analysis failed to detect statistically significant difference between ITD and alternative treatment (odds ratio = 0.39, 95% credible intervals = 0.11–1.27). The side-effects profile was favorable for ITD. No serious adverse events were recorded.

Conclusion: There is no sufficient scientific evidence to support a difference between ITD and alternative therapy for SSNHL. We recommend larger RCCTs to determine the effectiveness of ITD compared to oral steroid therapy. We encourage a shift in study design selection toward noninferiority or superiority studies. Avoiding systemic corticotherapy, especially in vulnerable populations, should be the rationale for future research in the field.

Key Words: Intratympanic, sudden sensorineural hearing loss, middle ear, steroids, dexamethasone, injection, treatment, SSNHL, meta-analysis, systematic review.

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INTRODUCTION

The etiologies of sensorineural hearing loss (SNHL) vary widely by patient population, underlying the mechanism and propensity to be reversed by timely medical intervention. Among the pathologies widely studied during the last few decades is the idiopathic sudden sensorineural hearing loss (SSNHL). The interest in researching treatments for this disease lies in the two major defining characteristics: 1) relatively high prevalence (5–20 of 100,000 per year [1]), and 2) tendency to be reversed. Although the mechanism behind SSNHL is multifactorial and remains to be fully elucidated, there is increasing data on the involvement of immunomodulatory cells and increased concentrations of proinflammatory cytokines in the inner ear. Also, tumor necrosis factor α (TNF-α) recently has been shown to reduce cochlear blood flow via activation of vascular sphingosine-1-phosphate signaling, which could explain some cases of SSNHL being related to ischemic microvascular events triggered by TNF-α. The majority of the treatment protocols developed for this pathology are centered on glucocorticoids due to their antioxidant and antiinflammatory properties.[2–9] Although systemic glucocorticoids demonstrated conclusive benefits in reversing SSNHL,[10–14] many clinicians are reluctant to administer these medications given their potential adverse effects. These include partial inhibition of the hypothalamic-pituitary-adrenal axis in up to 40% of patients on oral prednisolone following a short course of prednisolone treatment,[15] increasing the risk for Addisonian crisis in the setting of physiological stress such as an acute illness or a surgery. Other potential adverse events include osteoporosis, hyperglycemia, hypertension, and osteonecrosis at cumulative doses of 80 to 160 mg of oral methylprednisolone.[16]

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The intratympanic (IT) route of steroid administration to the inner ear for the treatment of SSNHL is a promising technique that allows for the delivery of small amounts of steroids to the inner ear while simultaneously bypassing the adverse events of the systemic route. Intratympanic steroids exert the same antiinflammatory actions as oral steroids (OS) but allow for a higher steroid concentration in the perilymphatic fluid.[15,17,18] Based on an animal study by Parnes et al. that provided relevant information on the pharmacokinetics of different steroids, dexamethasone was found to be more efficacious. Absorption of dexamethasone into the stria vascularis was more rapid in contrast to methylprednisolone, which remained in the endolymph 4 to 6 hours longer.[19] Because corticosteroids are known to act intracellularly, the presence of high methylprednisolone concentrations in the endolymph reflected an inverse relationship with its intracellular concentration and efficacy, rendering dexamethasone a more effective steroid for IT injections. Furthermore, dexamethasone has the highest relative antiinflammatory potency and the lowest relative mineralocorticoid activity among corticosteroids, making it a very suitable candidate for IT injections. In one large multicenter randomized controlled clinical trial (RCCT) that compared oral versus IT steroids, equal hearing improvement was observed in the two groups.[20]

Although many steroid preparations, concentrations, and injection techniques have been explored,[2–9] a consensus has not been reached on the indications for IT steroids. Well-defined concentrations, dosage, and a standardized treatment protocol remain elusive. The side effects of IT steroids have never been systematically studied in the literature. Without reporting on the rates, the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS) guidelines state that IT steroids can have infrequent and transient side effects, such as infection, tympanic membrane perforation, dizziness, and pain.[21] One landmark study reported a 90% side-effects rate in the IT group, which included transient pain at the injection site and brief caloric vertigo. The authors argue those side effects were anticipated and manageable and that the majority resolved within 1 to 2 weeks, with rare persistent tympanic membrane perforations that lasted up to 6 months.[17]

We thus sought to systematically review the literature on the efficacy and side effects of IT-dexamethasone (ITD) in the treatment of SSNHL, the glucocorticoids of choice recommended by the AAO–HNS for the treatment of SSNHL.[21]

MATERIALS AND METHODS

Search Strategy

With the assistance of two medical librarians, eligible articles were identified through a comprehensive search of the Cochrane, Embase, and MEDLINE electronic databases from January 1950 to August 2014. A search update was performed on November 10, 2014. The search strategy included medical subject headings (MeSH) and subheadings. Keywords included "intratympanic," "sensorineural hearing loss," "sudden sensorineural hearing loss," "steroids," "dexamethasone," "injection," and "treatment."

Criteria for Inclusion

We included only RCCTs of adults that compared the treatment of SSNHL with ITD (treatment group) to another modality (control group), that is, OS, intravenous steroids, hyperbaric oxygen, or normal saline placebo. We included both first- and second-line ITD studies that were published in English or French. The included studies had to report a well-defined efficacy parameter of hearing improvement (expressed in pure tone average [PTA]).

Criteria for Exclusion

Studies were not eligible for inclusion if they did not state the name of the drug used, did not describe the method of ITD injection, or did not report the numbers of patients with successful outcome. Studies with simultaneous combined modalities of therapy were excluded. Editorial letters, conference proceedings, nonrandomized observational studies, cohorts, and retrospective studies were excluded.

Study Selection

Two authors (N.G.E.S. and A.B.) independently reviewed the titles and abstracts retrieved by the electronic search and removed studies not concordant with the eligibility criteria. Reasons for exclusion were recorded and crossed-checked for agreement. Disagreements were resolved by consulting the senior author. The relevant articles underwent second stage review and were examined as full texts to revalidate inclusion. To complete our search, hand searching was performed on the included articles to identify additional studies that may have been missed.

The following data were extracted: study country of origin, treatment and control group size, dosing regimen and total cumulative dose of ITD received, condition treated, mean age of participants, first-line or second-line therapy, duration of follow-up, definition of outcome measures, adverse events, and hearing outcome (reported as PTA).

Definition of Improvement

According to the AAO–HNS, complete recovery is defined as a return to within 10-dB HL of the unaffected ear and recovery of the Word Recognition Score (WRS) to 5% to 10% of the unaffected ear. Partial recovery is defined as a return of the hearing in the affected ear that was rendered nonserviceable after the SSNHL event to a serviceable state (the ear is candidate for traditional hearing amplification). For an ear with SSNHL that is still in the serviceable range, a 10-dB HL improvement or an improvement in WRS of 10% or more should be considered partial recovery. Any improvement less than 10-dB HL is considered as no recovery.[21]

Due to the variability in reporting hearing outcomes among the studies, we opted to invoke the PTA improvement criterion of the AAO–HNS clinical practice guidelines as the only outcome assessment of hearing recovery in this study.[21] The WRS was not used as a criterion in the assessment of hearing recovery because none of the included studies used it.

Quality Assessment

The methodological quality of the included RCTs was assessed using the Cochrane Collaboration tool for assessing

risk of bias.[22] Two reviewers (N.G.E.S.and M.J.S.) undertook the quality assessment of studies.

Statistical Analysis and Synthesis

Differences in study methods, patient characteristics, and practice patterns suggest that the effects of the treatment are likely to vary from study to study. We therefore used a Bayesian hierarchical (random effects) model, which accounts for between-study variations in odds ratios (ORs). At the first level of this hierarchical model, the probability (*P*) of an outcome within each group of each study varies. In particular, the logarithm of the OR for the outcome is assumed to have a normal distribution. The mean of the normal distribution of log ORs across studies represents the average effect in the studies, and the variance of the normal distribution represents the between-study variability. Low-information prior distributions were used throughout such that the study data drives the final inferences. WinBUGS software, version 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom) was used for analyses. Forest plots were produced to display the OR and 95% credible intervals (CrIs) for all major outcomes pooled in our meta-analysis. Credible intervals are the Bayesian analogue to frequentist confidence intervals.

Definition and Classification of Side Effects

Given the absence of a classification scale for IT treatment side effects, our group decided to separate them into four different groups: The first group included procedure-related, very short-term, self-resolving side effects. The second group included procedure-related short-term side effects requiring medical or surgical interventions. The third group included procedure-related long-term side effects requiring medical or surgical interventions. The fourth group included any drug-related side effect.

RESULTS

The literature searches yielded 933 articles, of which 508 (54.4%) were duplicate citations. The remaining 425 citations were screened for relevance, of which 314 (73.9%) were irrelevant and excluded, yielding 111 articles. An updated literature search added nine new articles. These 120 articles were then assessed for eligibility, of which 112 were subsequently excluded (Fig. 1), yielding a total of eight RCCTs for inclusion in our study.

Condition

The medical condition in the eight studies was SSNHL

Control Groups

Five of the studies used OS and/or combination therapy in their control groups,[23–27] and two used IT normal saline as placebo.[28,29] In one study, the authors used their institution's standard treatment modality as control, consisting of a vasodilator, benzodiazepine, and vitamin B complex.[30]

Treatment Protocols

The concentrations of ITD varied among the studies and ranged from 4 mg/mL[23,28–30] to 12 mg/mL.[27] The mode concentration was 4 mg/mL and was used in four studies,[23,28–30] followed by 5 mg/mL in three studies.[24–26]

The dosing regimens of ITD also varied among the studies, and none of the authors justified the choice of ITD dosage, which seemed arbitrary. The most condensed dosing regimen consisted of one ITD injection/day for 8 consecutive days.[24] Other regimens varied from weekly ITD injections for 3[27,30] or 4 [23] weeks to twice a week for 2 weeks[25] and three times a week for 2 weeks.[26] In one study, the mode of administration was a continuous infusion through a round-window catheter applied for 14 days.[28] In contrast to the dosing regimens, the delivery technique to the middle ear cavity was more consistent and homogenous among the different RCCTs. In all studies, patients were put in the otologic position (one side down, affected ear up for 15–30 minutes[21]), and applied topical anaesthesia to the external acoustic canal and the tympanic membrane (TM). In five studies, a single myringotomy was performed using spinal needles between 22- and 27-gauge in size. One study used an implanted round window catheter for continuous infusion[28]; another performed two myringotomies on the TMs (one for ventilation and the other for injection)[25]; and a third performed laser-assisted tympanostomy.[27] The volume of ITD injected into the middle ear varied between 0.3 and 0.7 mL. The myringotomies were performed in the anterior superior quadrant in three studies.[23–25] One study described a myringotomy in the anterior inferior quadrant,[30] another at the junction of the superior and inferior quadrants posteriorly,[29] and one in the posterior inferior quadrant.[27]

Follow-up

Seven studies discussed their follow-up on patients after the completion of treatment. The follow-up period varied from 2 weeks[28] to 6 months.[30]

Patient Characteristics

The total number of participants across the studies was 416 with 192 patients (46.0%) in the treatment groups and 224 (55.0%) in the control groups. There were 171 men (47.4%) and 190 women (52.6%) who participated in seven studies, but one study did not report the participant gender ratio.[26] The mean age of participants ranged between 47 and 60 years.

Quality Assessment

We used the Cochrane Collaboration tool for assessing risk of bias[22] and added one criterion that we judged important for the assessment bias risk: the Intention to Treat Analysis. The results are presented in Table I.

Efficacy

Wu et al. reported the highest efficacy rate (89%) for ITD as a second-line treatment for refractory SSNHL after first-line treatment failure.[27] The lowest efficacy rate observed was 50% in the study by Plontke et al.[28] Overall, hearing improvement was seen in 72% of all the patients randomized into the ITD treatment arms in the

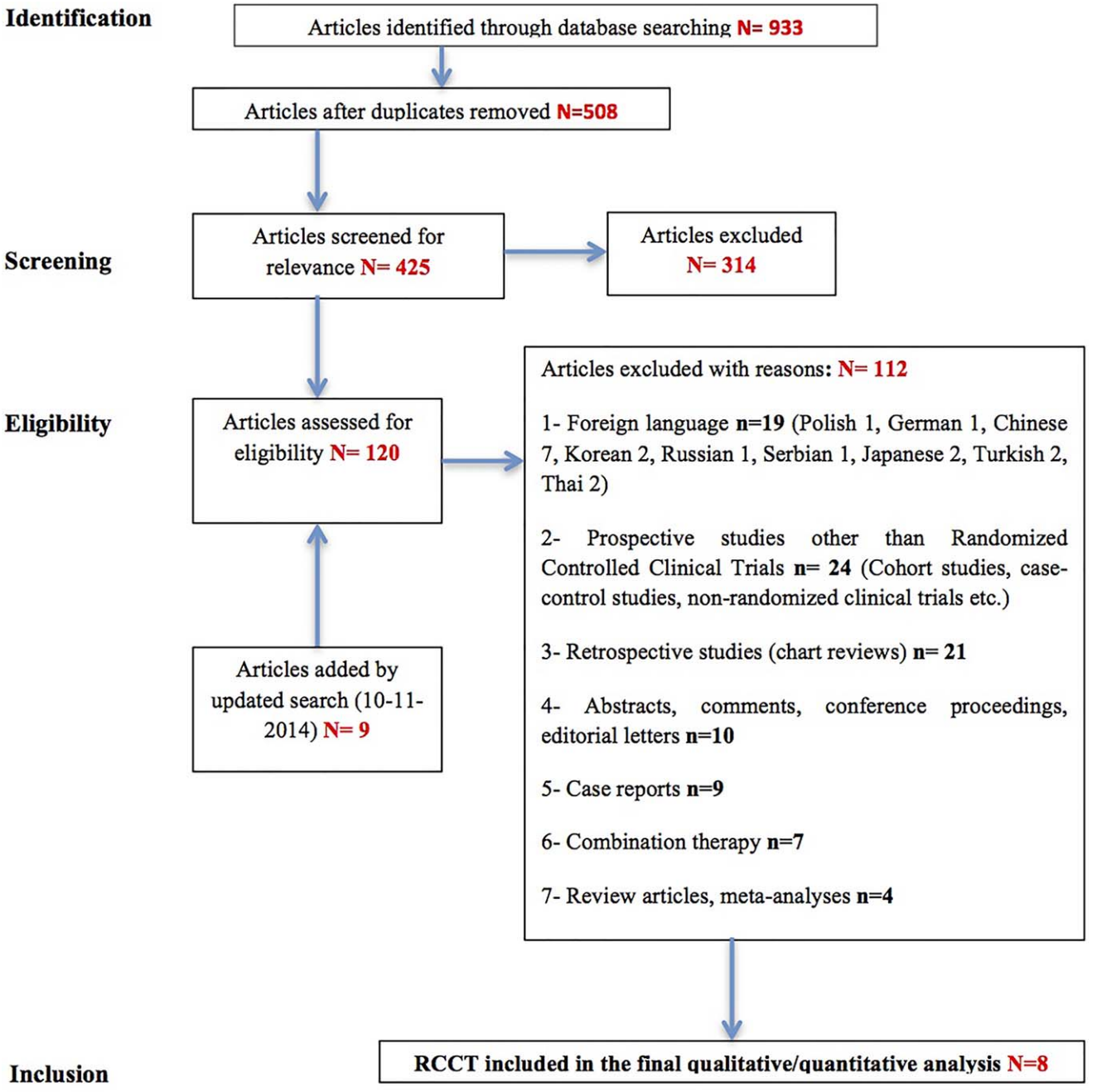

Fig. 1. Study Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. Search strategy for published randomized clinical trials on the treatment of sensorineural hearing loss with intratympanic dexamethasone injections. Data sources used were MEDLINE, Embase, and Cochrane (through November, 2014). RCCT = randomized controlled clinical trial. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

eight studies. Complete hearing recovery was achieved in 20% of patients in the ITD treatment groups, with 52% achieving partial hearing improvement and 28% showing no improvement. The efficacy rates by study are described in Table II.

Meta-Analyses

We performed a meta-analysis on the eight selected studies and compared the treatment groups (ITD) to the control groups (alternative treatment). Given the very small number of studies included, this was the only statistically reasonable comparison parameter. This meta-analysis did not reach statistical significance (OR = 0.39, CrI = 0.11–1.27). A large heterogeneity was noted among these studies. The results are described in the forest plot (Fig. 2). Given the very small number of RCCTs included, subgroup analyses based on first versus second-line treatment, treatment regimens, and control groups were proposed but deemed statistically not feasible.

TABLE I.
Assessment of Risk of Bias for RCTs That Compared ITD to Any Other Treatment for SSNHL.*

Study	How Was Allocation Sequence Generated?	How Was Allocation Sequence Concealed?	What Measures Were Taken to Blind Participants and Personnel?	What Measures Were Taken to Blind Outcome Assessors?	Is the Outcome Data Complete? Did the Authors Report Exclusion and Attritions and Give Reasons for These?	Is There the Possibility of Selective Outcome Reporting?	Are There Any Other Potential Sources of Bias?	Summary Assessment of Risk of Bias?	Was the Intention-To-Treat Analysis Conducted?
Dispenza (2011)	Unclear Authors mentioned randomization but did not specify the methods used.	Unclear Not described	Unclear Study did not address.	Unclear Not described	Low Authors describe 3 patients lost to follow-up and 2 diagnosed with vestibular schwannoma by magnetic resonance imaging.	Low All endpoints are reported.	Low None	Low	Yes
Guan-Min (2004)	Unclear Authors mentioned randomization but did not specify the methods used.	Unclear Not described	High It is understood from the methods section that participants were not blinded.	High It is understood from the methods section that assessors were not blinded.	Low The outcome data is complete. There were no exclusions and no attritions.	Low All endpoints are reported.	Low None	High	Yes
Hong (2009)	Unclear Authors mentioned randomization but did not specify the methods used.	Low Alternate sequence allocation mentioned.	High It is clear from the description that the patients knew whether they were taking ITD or conventional therapy.	Low Authors explicitly mentioned blinding of assessors but did not provide description of how the blinding was achieved.	Low Authors identify the patients that were excluded from the study or lost to follow-up. The numbers are evenly distributed between the two arms of the study.	Low All endpoints are reported.	Low None	High	No
Lim (2013)	Low Authors clearly mention sequence generation procedure.	Unclear Not described	High It is understood from the methods section that participants were not blinded.	High It is understood from the methods section that assessors were not blinded.	Low Authors identify in a flow diagram the patients that were excluded from the study or lost to follow-up. The numbers are evenly distributed between the two arms of the study.	Low All endpoints are reported.	Low None	High	Yes
Park (2011)	Low Authors clearly mention sequence generation procedure (SPSS).	Unclear Not described	Unclear Study did not address.	Low Authors explicitly mentioned blinding of assessors (audiologists).	Low Authors identify in a flow diagram the patients that were excluded from the study or lost to follow-up. The numbers are evenly distributed between the two arms of the study.	Low All endpoints are reported.	Low None	Low	No

TABLE I.
(*Continued*)

Study	How Was Allocation Sequence Generated?	How Was Allocation Sequence Concealed?	What Measures Were Taken to Blind Participants and Personnel?	What Measures Were Taken to Blind Outcome Assessors?	Is the Outcome Data Complete? Did the Authors Report Exclusion and Attritions and Give Reasons for These?	Is There the Possibility of Selective Outcome Reporting?	Are There Any Other Potential Sources of Bias?	Summary Assessment of Risk of Bias?	Was the Intention-To-Treat Analysis Conducted?
Plontke (2009)	Low Authors clearly mention sequence generation procedure.	Unclear Not described	Low Study design implies that participants were adequately blinded because both arms received the same intervention.	Unclear Not described	Low Authors identify in a flow diagram the patients that were excluded from the study or lost to follow-up. The numbers are evenly distributed between the two arms of the study.	Low All endpoints are reported.	High The nomenclature of simultaneous and subsequent implies all patients received standard therapy within the window of ITD treatment, which limits the homogeneity between the study arms	Low	Yes
Wu (2011)	Unclear Authors mentioned randomization but did not specify the methods used.	Unclear Not described	Unclear Study did not address.	Unclear Not described	Low Authors identify in a flow diagram the patients that were excluded from the study or lost to follow-up. The numbers are evenly distributed between the two arms of the study.	Low All endpoints are reported.	Low None	Low	No
Battaglia (2008)	Unclear Authors mentioned randomization but did not specify the methods used.	Unclear Not described	Low Study design implies that participants were adequately blinded because both arms received the same intervention.	Unclear Not described	Low Authors clearly identify the patients excluded or lost to follow-up. The numbers are evenly distributed between the 3 arms of the study.	Low All endpoints are reported.	Low None	Low	Yes

*Adapted from the Cochrane Collaboration tool for Assessment of risk of bias.
ITD = intratympanic dexamethasone.

TABLE II.
Efficacy of Studies on ITD for SSNHL.

Study	% Improvement ITD Arm	% Improvement Control Arm	Treatment
Dispenza (4 mg/mL)	80%	81%	1st line
Guan-Min* (4 mg/mL)	73%	7%	2nd line
Hong (5 mg/mL)	79%	75%	1st line
Lim (5 mg/mL)	55%	60%	1st line
Park (5 mg/mL)	77%	84%	1st line
Plontke (4 mg/mL)	50%	27%	2nd line
Wu* (4 mg/mL)	89%	11%	2nd line
Battaglia (12 mg/mL)	58%	61%	1st line

*Statistically significant at $P < 0.05$

ITD = intratympanic dexamethasone; SSNHL = sudden sensorineural hearing loss.

Side Effects

Of the eight included studies, six reported side effects. We separated the side effects into the four groups based on the clinical criteria of time of onset and severity, as described in the Methods section. The first group included 54 side-effect events, such as otalgia, ear fullness, headache, short-lived vertigo, and dizziness, representing 81% of all side effects across six studies and affecting 13% of the study population. The second group counted five side-effect events: three severe dizziness events and two perforations of the TM after injection, which resolved spontaneously at 1 month follow-up. These represented 7.7% of all reported side effects and affected 1.2% of the study population. The third group included three events: one case of otorrhea requiring topical and oral antibiotic treatment,[25] one case of TM perforation requiring surgical repair by myringoplasty,[25] and one case of ear canal skin defect.[28] These represented 4.6% of all side effects and affected 0.7% of the total study population. The fourth group (dexamethasone-related side effects) included one case of acne—s reported by Guan-Min et al.[29]—and sporadic single cases of acne, gastroenteritis, hypokalemia, and increased liver function tests—as reported by Plontke et al.—who concluded that they were neither related to the intervention nor to dexamethasone.[28] In total, 65 out of 416 patients (15.6%) experienced adverse effects, more than 87% of which were mild and self-resolving. There were no serious or life-threatening side effects reported.

DISCUSSION

Intratympanic Dexamethasone for SSNHL

Although the meta-analysis showed no statistically significant difference between the ITD and the control groups, the absence of evidence is not the evidence of absence. The wide confidence intervals and the lack of statistical difference are in part due to the heterogeneity of these studies. This heterogeneity manifested at every level of the study design. In this Bayesian hierarchical (random effects), the standard deviation (SD) parameter directly measures the study-to-study variability in outcome and is the SD of the means from each study, as measured on the log scale. In this case, the measure of heterogeneity for these eight studies is an SD of 1.6 with a CrI (0.8957–1.98). This means there is very high variability from study to study (i.e., very large heterogeneity). On the log scale, a SD of 1.6 represents a range of approximately 6.4, covering a large part of the possible range. The 95% Crl indicates that the true values lie between 0.86 and 1.98, with 95% probability. Thus, it is safe to say that the SD is at least near 1, possibly as large as 2, which indicates a high degree of heterogeneity between the studies.

However, the dosing regimens, injection techniques, dosages of ITD, and follow-up windows rarely complied with the AAO-HNS guidelines. The variability in the nature of the control groups was the main contributing factor to the overall heterogeneity and made the overall assessment of efficacy more challenging and the results less generalizable. As shown in Table III, the control groups of the eight RCTs did not receive the same intervention. With the current mounting evidence supporting a role for proinflammatory cytokines and mediators in the underlying pathophysiology of SSNHL,[31] it is best that future randomized clinical trials abandon the use of normal saline, placebos, and other agents that have no proven benefits in order to bring forth an adequate estimate of the protective effects of antiinflammatory agents, namely corticosteroids. Despite their obvious heterogeneity, the rationale behind including all these studies was predominantly the scarcity of RCCTs on ITD for SSNHL, as well as our objective, as a first study to look at such a complex area of otology, to be inclusive and account for every RCCT that compared ITD to any other modality. Secondly, our secondary objective to assess the side-effect profile of ITD necessitated the inclusion of all the above studies.

We homogenized the outcomes among studies by translating the reported outcomes into the AAO–HNS 2012 guidelines. The PTA improvement criterion was the cornerstone of this standardization of results. The WRS criterion was absent from all the studies and thus was not part of our hearing outcome standardization. The incorporation of the WRS into future trials can improve the homogenization of results reporting and interpretation.

The nature of the intervention (1st line vs. 2nd line) was another factor intrinsic to the study design that likely exacerbated the heterogeneity effect. A subgroup analysis on first- versus second-line treatments was not feasible due to the very small number of studies. It would be interesting to see more clinical trials designed to compare ITD to OS as a first-line treatment for SSNHL.

Nevertheless, some remarkable efficacy results were noticed. The Wu et al. and Guan-Min et al. studies were the only two to show statistically significant results.[27,29] Guan-Min et al. compared ITD to conventional therapy as second-line treatment, after failure of conventional therapy (OS, vasodilators, vitamin-B complex, and benzodiazepine).[29] Their results showed 73% improvement in the ITD arm compared to 7% in the control arm. Wu et al.'s study compared ITD to IT normal

TABLE III.
Randomized Controlled Clinical Trials on the Treatment of Sensorineural Hearing Loss with Intratympanic Dexamethasone in Adults.

Author	Country	Intervention	Treatment and Control Groups	Average Age	Condition	ITD Concentration	Follow-up	Side Effects (n)	Definition of Outcome Measures (study's own criteria)	Hearing Outcome (AAO–HNS PTA improvement criterion)	Conclusion
Dispenza (2011)	Italy	4 injections (1/week)	ITD: 25 OS 21	47	SSNHL (1st line)	4 mg/mL	6 months	N/M	> 10 dbB improvement in PTA	Improvement: 20 (80%)	Equal results between systemic therapy and ITD: consider ITD as a first-line treatment
Guan-Min (2004)	Taiwan	3 injections (1/week)	ITD: 15 Standard therapy: 14	N/M	SSNHL (salvage)	4 mg/mL	2.6 months	Vertigo (1) Acne (1)	No recovery: PTA improvement < 10 dB Slight: PTA improvement > 10 dB and < 30 dB Moderate: PTA Improvement > 30 dB Complete: PTA < 25 dB	Complete: 4 (26.6%) Moderate: 4 (26.6%) Slight: 3 (20%) Total: 11 (73.3%) No recovery: 4 (26.6%) Mean hearing improvement: 28.4 dB	ITD effectively improves hearing in patients with severe or profound SSNHL
Hong (2009)	Korea	8 injections (1/day)	ITD: 32 OS 31	56.9	SSHNL (1st line)	5 mg/mL	N/M	None (0%)	Siegel criteria (no, slight, partial, complete)	Complete: 10 (32%) Moderate: 7 (22%) Slight: 8 (25%) No recovery: 7 (22%) Mean hearing improvement: 27 dB	Daily ITD as primary treatment modality is effective for the management of idiopathic SSNHL (as effective as OS)
Lim (2013)	Korea	4 injections (2/week)	ITD: 20 ITD + OS 20 OS 20	53.3	SSNHL (1st line)	5 mg/mL	3 weeks	N/M	AAO–HNS 2012	Recovery: 11 (55%) Complete: 3 (15%) Partial: 8 (40%)	Systemic and/or local steroid therapy can be suggested as an initial treatment in idiopathic SSNHL.

TABLE III.
(*Continued*)

Author	Country	Intervention	Treatment and Control Groups	Average Age	Condition	ITD Concentration	Follow-up	Side Effects (n)	Definition of Outcome Measures (study's own criteria)	Hearing Outcome (AAO–HNS PTA improvement criterion)	Conclusion
Park (2011)	Korea	6 injections (over 2 weeks)	ITD: 44 Simultaneous IVS/OS + ITD: 44	48.05	SSNHL (1st line)	5 mg/mL	3 months	Otalgia (11), transient dizziness (9), ear fullness (8), headache (5), TM perforation (2), otorrhea (4)	Siegel criteria	Complete: 17 (38.6%) Partial: 8 (18.2%) Slight: 9 (20.5%) No recovery: 10 (22.7%) Mean hearing improvement: 32.59 dB	No difference between simultaneous and subsequent ITD therapy
Plontke (2009)	Germany	Round window catheter Total dose: 0.58 mg	ITD: 12 ITNS: 11	56	SSNHL (salvage)	4 mg/mL	2 weeks	Otalgia (2), headache (1). Ear canal skin defect (1), vertigo (1)	Ho Classification[29] and changes in PTA and Speech Discrimination Score	ITD: 6/12 (50%) improved >10dB Mean hearing improvement: 13.9 dB	No statistically significant hearing improvement. Encourages further investigation of this treatment
Wu (2011)	Taiwan	4 injections (over 2 weeks)	ITD: 27 ITNS: 28	49.1	SSNHL (salvage)	4 mg/mL	1 month	Dizziness (18), TM perforation (1)	Any PTA improvement	> 20 dbB: 4 (14.8%) > 15 dB: 8 (29.6%) > 10 dB: 12 (44.4%) Mean hearing improvement: 9.8dB	ITD is audiologically beneficial for SSHL after the failure of initial systemic steroid therapy.
Battaglia (2008)	United States	3 injections (1/week)	ITD: 17 OS 18 Conventional therapy: 16	60	SSNHL (1st line)	12 mg/mL	3 months	None (0%)	Complete: PTA within 5 dB of the contralateral ear Partial: decrease of 15 dB	Partial: 5 (29%) Complete: 5 (29%) Mean hearing improvement: 30 dB	CT > ITD alone

AAO–HNS = American Academy of Otolaryngology–Head and Neck Surgery; CT = computed tomography; ITD = intratympanic dexamethasone; ITG = intratympanic gentamycin; ITNS = intratympanic normal saline; IVS = intravenous steroids; N/M = not mentioned; OS = oral steroids; PTA = pure tone average; SSNHL = sudden sensorineural hearing loss.

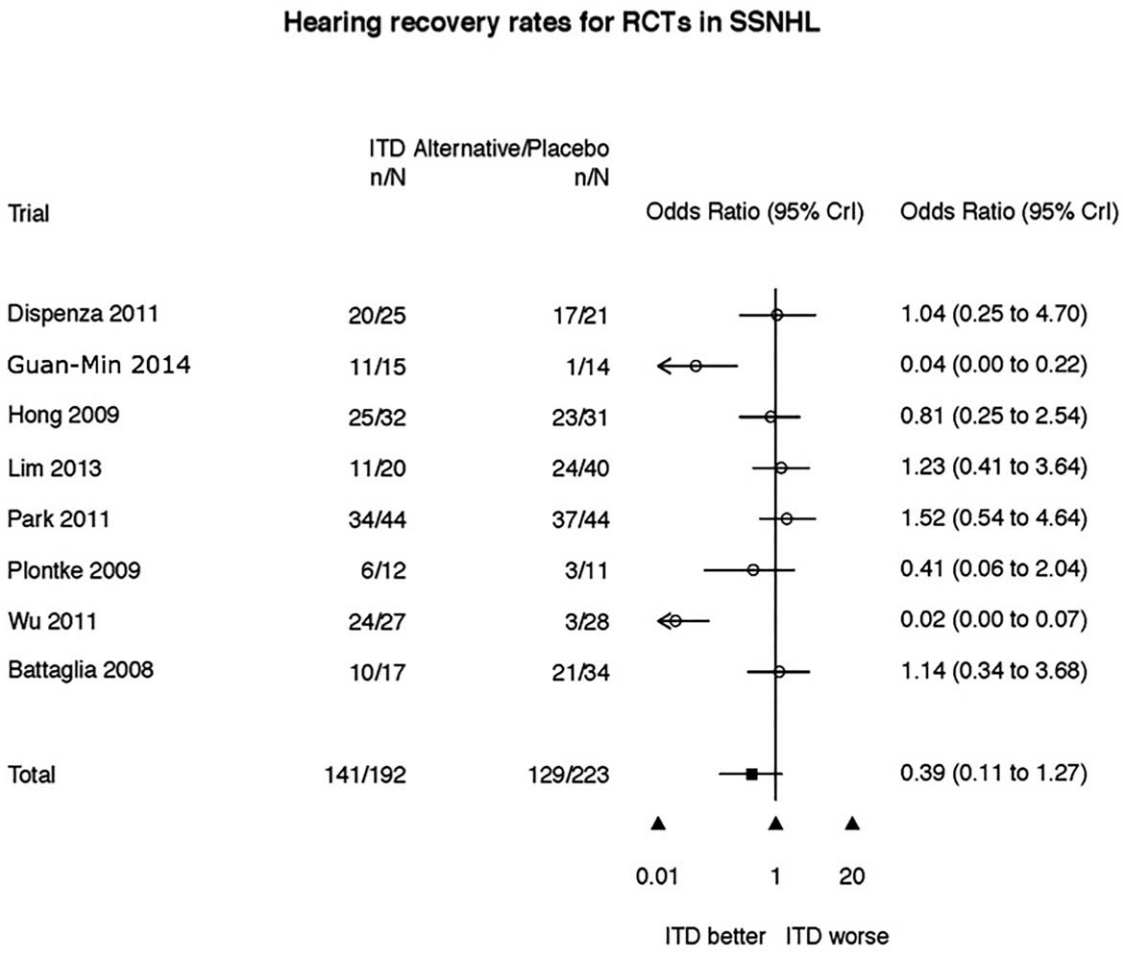

Fig. 2. Hearing recovery rates for RCTs in SSNHL.
Forest plot of RCTs on ITD versus alternative treatment or placebo for treatment of SSNHL.
CrI = credibility interval; IDT = intratympanic dexamethasone; n = number of successes; N = sample size; RCT = randomized controlled clinical trials; SSNHL = sudden sensorineural hearing loss.

saline as a second-line treatment after failure of primary OS therapy.[27] Their results described 89% improvement in the ITD arm compared to 11% in the control arm. Interestingly, these two studies shared some similarities such as 1) the use of ITD as a second-line treatment, 2) concentration of 4 mg/ml, and 3) close adherence to the regimen proposed by the AAO–HNS guidelines. Designing equally strong studies with ITD as first-line treatment could prove essential in establishing not only the efficacy of ITD as an initial treatment modality but also as a potential substitute for oral corticotherapy.

Quality Assessment

We used the Cochrane Collaboration tool for assessing risk of bias[22] as the measure of quality and added one criterion: the intention to treat (ITT) analysis. In general, this systematic review revealed a relatively low overall risk of bias. Five studies were found to have a low bias risk, as described in Table I, and five out of eight studies were found to have ITT (although these were not the same 5 studies). Three studies were high on risk of bias.[23,24,29] The most common source of bias was the performance bias: the absence of blinding of participants, personnel, and assessors. Blinding of participants and personnel was absent in three studies.[23,24,29] Two studies failed to blind the assessors.[24,29] None of studies had incomplete outcome data or had failed to report exclusions, attritions, or give reasons for these. To allow for a larger sample size and large attrition rates, collaboration among referral centers is recommended, as is following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. In addition, several studies did not clearly describe their blinding strategy, which casts doubts on the nature and efficacy of the blinding process. Furthermore, we believe that an emphasis on adequate study methodology and design is necessary to confer stronger internal validity to the results. The higher the internal validity of future RCTs is, the stronger the projected strength of association will be between treatment and response.

Side Effects

This systematic review is the first to assess side effects of IT steroids in adults. Adverse events often

dictate the treatment modality and limit the implementation of new clinical trials in vulnerable populations. We believe that an IT steroids side-effects scale, like the one we proposed in this study, can be helpful in quantifying IT steroid-related side effects and divide them according to time of onset, severity, and underlying mechanism (procedure- or drug-related) to help steer further research and unfold the full potential of IT steroids, especially in the pediatric and other vulnerable populations. According to a prospective study from Switzerland, IT corticosteroids did not interfere with either endogenous cortisol secretion or bone metabolism, two highly glucocorticoid-sensitive endogenous systems that can detect minor interferences from exogenous steroid sources.[31] Therefore, the incidence of systemic side effects was expected to be negligible, which is concordant with the results that we derived out of our side-effect assessment.

The side effects were not systematically examined in all studies. None of the studies reported local outer-, middle-, or inner-ear side effects, whether related to external acoustic canal skin changes, middle-ear ossicular disruption or thinning, or inner ear toxicity. Dexamethasone-related side effects were virtually absent. The remaining three categories of side effects are technique-related. Despite affecting 15.6% of the overall study population, the majority of these events were technique-related, very short-term and self-resolving. They included ear fullness, slight otalgia during injection, and transient dizziness/vertigo postinjection, all of which can be attributed to the immediate injection technique and the preinjection local anesthesia. Given their resolution in just a few minutes, we believe the transient vertigo attacks are the manifestation of the physiological vestibular caloric test that is due to the introduction of warm or cold liquids into the external ear canal. A minority of side effects recorded required closer medical or surgical attention (second and third group). Two cases of persistent TM perforations were reported, to which patch repair was warranted 1 month after the procedure. Another case of TM perforation resolved spontaneously at the next follow-up visit. The very small number of serious, locally aggressive adverse events indicates that the injection techniques used are mostly appropriate, and that the posttreatment follow-up and care are adequate in detecting these adverse events and promptly addressing them. We suggest the design and implementation of a standard IT steroid side-effect scale that is inspired by the criteria we used in this study. More so, such a scale could be modified and adapted to assess the side-effect profiles of various other intratympapnic drug preparations, facilitating horizontal comparison across the literature.

In their study, Plontke et al.[28] dismissed the relationship of these adverse events to the ITD therapy and the very unlikely systemic absorption of the drug. Thus, we can affirm, according to the retrospective and prospective studies examined, that ITD has not been shown to be systemically absorbed at a clinically significant level and has not been shown to lead to systemic and severe cortisol-related adverse events. It is therefore suitable to suggest that ITD therapy is a safe and reasonable procedure, and that dexamethasone injected intratympanically is not absorbed systemically and does not carry risks of cortisol-related metabolic or endocrine side effects. Furthermore, the slightly different techniques of ITD delivery described in the AAO–HNS 2012 guidelines are efficient in dispensing dexamethasone into the middle ear cavity. They remain however, surgeon-dependant.

Implication for Practice

As expected, the quality of reporting of the clinical trials was not of the highest quality. Most importantly, ITT (an integral concept of therapeutic RCT, in which all randomized patient data should be analyzed at the end of the study) was only conducted in five of the eight studies. We believe that in order to produce RCTs of higher quality, academic clinicians should pursue continuing medical education in epidemiology and implement the highest standards of research to include consideration of involving clinical epidemiologists in study design, data collection, and interpretation

CONCLUSION

This systematic review is the first to examine the efficacy and safety of ITD for SSNHL. In part, the inconclusiveness of the meta-analysis is due to the small number of RCTs conducted to date and to the heterogeneity among studies. To address these issues in the future, we suggest collaboration among otolaryngology groups to implement a large multi-center clinical trial to compare routes of administration of dexamethasone (ITD vs. oral) as first-line treatment, and their respective side-effects profiles. Similar to what we did in this study, it could be helpful to the field to develop a side-effect classification or scale of intratympanic injections based on procedure- versus drug-related, time of onset, and severity. Furthermore, this is an excellent opportunity to design a study that reports on the side-effect profiles in comparison to other treatment modalities.

We advise future researchers to develop and assess various preparations of ITD, especially those that remain longer in the middle ear cavity and allow for a longer exposure time of the inner ear to dexamethasone, because research is beginning to show that exposure time has a much greater impact than concentration in achieving higher inner ear dexamethasone permeability.[32] Finally, we believe it is important to establish that IT-dexamethasone is noninferior to systemic steroids as first-line treatment of SSNHL. If such noninferiority is established, we can shift the treatment approach in favor of the less harmful IT route, especially if the side-effect profile is favorable. Finally, the reporting on side effects in this study can be of particular importance for the efforts aimed at designing RCTs on ITD for chemotherapy-induced hearing loss in vulnerable populations, especially the pediatric cancer patients. To date, efforts to establish such RCTs have been halted by IRBs due to the absence of safety and side-effects data from adult trials. The thorough description of side effects in this study can help propel such areas of research that could benefit millions of children worldwide.

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