



Research article

Intratympanic corticosteroid as salvage therapy in treatment of idiopathic sudden sensorineural hearing loss: A systematic review and meta-analysis



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ABSTRACT

Background: The standard treatment of idiopathic sudden sensorineural hearing loss (ISSNHL) constitutes of systemic oral corticosteroid. Although oral corticosteroid might revert the acute deafness, some patients with ISSNHL display a more treatment refractory course. For these patients, corticosteroid installed directly into the middle ear has become a more frequent treatment, due to the potential benefits of a high, local concentration compared to a systemic administration. As such, for patients being refractory to standard treatment, intratympanic injection of a high dosage of corticosteroid as salvage therapy may be beneficial.

Objectives: To evaluate the efficacy of intratympanic corticosteroid (ITC) as a salvage treatment of ISSNHL.

Methods: A systematic literature search was performed in relevant databases. Both randomized trials and observational studies were considered for inclusion. The risk of bias was evaluated using the Cochrane risk of bias tool (randomized trials) or ROBINS-I tool (observational studies). Meta-analysis was performed to investigate the improvement of PTA (dB) and number of patients displaying recovery following salvage ITC injections. Occurrence of serious side effects was investigated. Finally, the certainty of the evidence was evaluated using the GRADE approach.

Results: Eleven relevant studies were identified (4 randomized trials and 7 observational studies). Both observational and randomized trials showed that salvage ITC significantly increased the number of patients displaying recovery. No serious adverse events were identified in any of the included studies. The certainty of evidence ranged from moderate to very low, due to risk of bias, imprecision, and heterogeneity.

Conclusion: Collectively, our findings indicate that salvage ITC treatment may be a beneficial and safe treatment for patients with sudden hearing loss, who otherwise are refractory to standard treatment approaches. However, the evidence level indicates need for a cautious interpretation of especially the magnitude of effect and thus the extrapolation on how much the individual may improve from this treatment. Furthermore, it remains to be investigated whether treatment outcomes may vary across different patient groups presenting with ISSNHL. This potential variation in treatment response should be kept in mind, when counselling the patient.

Trial registration number: The protocol is registered in PROSPERO. Registration number: CRD42019130586.

1. Introduction

Hearing loss is one of the leading disabilities in the world with an tremendous impact on quality of life and need for rehabilitation (Cieza et al., 2021). Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as rapid onset of sudden hearing loss within 72 h with no identifiable cause of the hearing loss despite adequate investigation (Stachler

et al., 2012). It is characterized as more than 30 dB hearing loss in three consecutive frequencies in pure tone audiometry (PTA) (Stachler et al., 2012) and it is often accompanied by tinnitus and vestibular symptoms. ISSNHL most frequently occurs in the fourth to fifth decade of life with equal gender distribution (Rauch, 2008). Global incidence has been estimated to be 5 to 20 per 100,000 persons per year (de Cates and Winters, 2021).

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The etiology of ISSNHL is unknown and consequently a wide range of different treatment modalities has been proposed during the past 80 years, including corticosteroid, antivirals and hyperbaric oxygen therapy (Awad et al., 2012; Bayoumy and de Ru, 2019; Wilson et al., 1980). Corticosteroids are widely used as a first-line treatment option for ISSNHL worldwide. Corticosteroids may be administered orally, intravenously or as intratympanic instillations. Corticosteroid installed directly into the middle ear cavity has become a more frequently applied approach because of the potential benefits of a high, local concentration yielding a more favorable profile of adverse effects compared to systemic administration (Chandrasekhar, 2001; Parnes et al., 1999). However, a recent meta-analysis did not find intratympanic corticosteroid (ITC) to be superior to systemic corticosteroids as a first-line treatment modality in the case of moderate to severe ISSNHL (Mirian and Ovesen, 2020).

ITC is also often recommended as salvage therapy for the group of patients with inadequate hearing recovery despite initial systemic corticosteroid treatment (Chandrasekhar et al., 2019). In contrast the latest Cochrane review from 2013 concluded that the value of corticosteroids in the treatment for ISSNHL is unclear (Wei et al., 2013). All the various treatment modalities and opposing conclusions for treatment of ISSNHL generate conflicting opinions among otolaryngologists.

Several studies have evaluated the effects of ITCs as salvage treatment for ISSNHL, mainly retrospective designed studies and smaller sample sized randomized controlled studies.

In this systematic review and meta-analysis, we aim to provide an update of the current evidence for the use of ITC as salvage treatment for ISSNHL after failed initial response to systemic corticosteroids. We include all study designs, randomized as well as observational studies. The intention of including all study designs is to explore homo- and heterogeneity. Our primary objective is to examine the efficacy in mean PTA gain (dB) and if odds for recovery is different between high dose ITC salvage therapy versus non-salvage therapy for patients suffering from ISSNHL.

2. Methods

This review was structured by the population, intervention, comparison and outcome (PICO) framework (Guyatt et al., 2011a). The

population included patients with idiopathic sudden sensorineural hearing loss (ISSNHL). Patients with identifiable causes of sensorineural hearing loss such as vestibular schwannoma, Menière's disease, and Lyme disease were excluded. The intervention consisted of salvage therapy by use of ITCs injections. Corticosteroids had to be administered exclusively and not as combination therapy. The comparator was either placebo or no treatment. Outcomes included improvement in PTA (dB), number of participants achieving recovery, and reported serious side effects. The protocol for this review was registered in PROSPERO (CRD42019130586).

2.1. Literature search and selection

We performed a systematic search for literature in February 2021 in the databases; PubMed, Embase, OvidSP, CINAHL and The Cochrane library. The following search terms were applied: "sudden deafness OR ISSNHL OR ISSHL OR SSNHL OR sudden sensorineural hearing loss OR acute hearing loss" AND "steroid OR corticosteroid OR dexamethasone OR methylprednisolone" AND "Salvage therapy OR Salvage". There were no restrictions on publication status, however, language was limited to English, Danish, Swedish, or Norwegian. Both randomized controlled trials and observational studies were considered for inclusion.

Results from the literature search was imported into the Covidence software for screening and data management. Initially, the eligibility of studies was assessed based on titles and abstracts followed by full text evaluation. The screening and evaluation of eligibility of studies was performed by two independent reviewers (LD and HEC). Any disagreements were resolved through discussion. The reviewers were not blind to journal, year of publication, study author, or institution. A flowchart was created to document the literature selection (see Figure 1).

2.2. Data extraction and risk of bias assessment

Relevant data from the identified studies were independently extracted by two reviewers (LD and HEC). Data extraction included study design, number of participants included, description of the intervention and control groups, and outcome data. The risk of bias in randomized

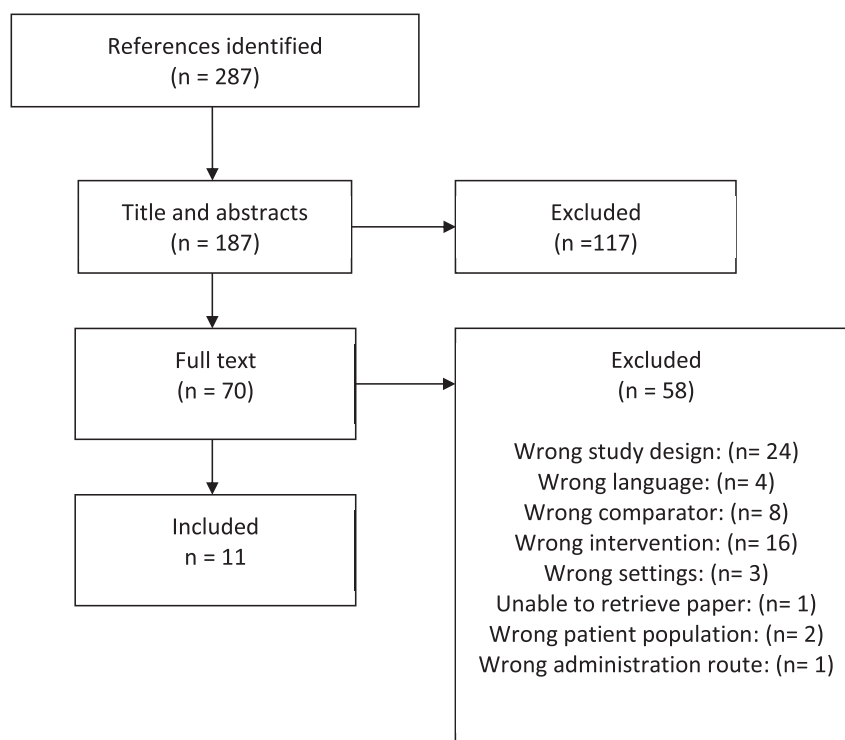


Figure 1. Flowcharts showing the inclusion and exclusion of studies.

controlled trials (RCT) was assessed using the Cochrane risk of bias tool (Higgins et al., 2011). For observational studies this was evaluated using the ROBINS-I tool (Sterne et al., 2016). Any discrepancies were resolved through discussion. The authors of the included studies were not contacted for further information. Data and risk of bias information was subsequently exported to Review Manager (version 5.2) (2014).

2.3. Data synthesis and meta-analysis

If the extracted data was comparable in terms of how data was reported in the individual studies, a meta-analysis was performed, using the random-effects model. Continuous outcome was analyzed using the mean difference (MD) alongside the 95% confidence interval. Dichotomous outcomes were analyzed using the relative risk (RR) and 95% confidence interval. Statistical heterogeneity was determined using I² statistics (I² >50 % indicating moderate to high heterogeneity) (Higgins and Thompson, 2002). A forest plot was created for each outcome. If applicable, subgroups were performed based on mean baseline hearing loss and time to start treatment.

2.4. Summary of findings and certainty of evidence

The estimates obtained were included into a summary of finding table, constructed in the online program MagicApp. The certainty of the evidence was evaluated using the GRADE approach, which included four possible ratings: very low, low, moderate, and high level of certainty. If needed, the certainty of estimates obtained in randomized controlled trials, was down-graded based on degree of risk of bias, inconsistency, indirectness, imprecision, and publication bias. Upgrading the certainty of estimates obtained in observational studies was possible in the following cases: effects were robust following assessment of all possible confounders; a large magnitude of effect was observed, or a clear dose-response gradient was identified (Guyatt et al., 2011b; Higgins et al., 2011).

3. Results

We identified a total of 287 references. Following exclusion of duplicates and initial title and abstract screening, we selected 70 relevant studies. These studies were obtained in full and read for final eligibility. Eleven studies were finally included, which comprised of four randomized controlled trials (Lee et al., 2011; Li et al., 2011; Wu et al., 2011; Xenellis et al., 2006) and seven observational studies (Ahn et al., 2008; Amarillo et al., 2019; Clary et al., 2011; Covelli et al., 2018; Erdur et al., 2014; Moon et al., 2011; Morita et al., 2016). A flowchart showing the selection of studies can be seen in Figure 1 and an overview of the included studies is found in Table 1. An overview of excluded studies is found in the supplementary information.

3.1. Improvement in pure tone audiometry (PTA)

3.1.1. Observational studies

The average improvement in PTA (dB) was investigated within a timeframe ranging from one month to 12 months after end of treatment. Data was based on 675 patients in five observational studies. Patients receiving salvage corticosteroid treatment displayed an improvement in PTA as compared to the control group (MD 8.38 higher (95% CI 3.64–13.13), I² = 71%, p = 0.0005) (Figure 2). The certainty of evidence was rated as very low due to inconsistency.

3.1.2. Randomised studies

The average improvement in PTA (dB) was investigated within a timeframe ranging from six weeks to six months after end of treatment. Data was based on 182 patients in four randomized controlled studies. Results showed no improvement following salvage corticosteroid treatment PTA as compared to the control group (MD 5.89 (95% CI -1.75

-13.53), I² = 58%, p = 0.13) (see Figure 3). The certainty of evidence was rated as very low due to risk of bias, inconsistency, and imprecision.

3.2. Proportion of patients displaying recovery

3.2.1. Observational studies

Patients displaying a tendency towards recovery were investigated in 704 patients in six observational studies. The definition of recovery was based on a defined change in PTA, which ranged across studies from a PTA improvement of >10 dB to >20dB. The timeframe ranged from one month to 12 months after end of treatment. Results showed that salvage corticosteroid treatment increased the number of patients who experienced recovery following treatment as compared to the control group (RR 2.45 (CI 95% 1.18–5.1), I² = 84%, p = 0.02) (see Figure 4). When measured as absolute effect estimates, this is equivalent to a difference of 631 more patients pr. 1000 reaching recovery in the salvage group (CI 95% 78 more – 1784 more). The certainty of evidence was rated as very low due to inconsistency.

3.2.2. Randomised studies

Patients displaying a tendency towards recovery were investigated in 182 patients in five randomized controlled studies. The definition of recovery was based on a defined change in PTA, which ranged across studies from a PTA improvement of >10 dB to >30dB. The timeframe ranged from 6 weeks to 6 months after end of treatment. Results showed that salvage corticosteroid treatment increased the number of patients displaying recovery as compared to control group (RR 4.19 (CI 95% 2.39–7.36), I² = 0%, p < 0.00001) (see Figure 5). When measured as an absolute effect estimate, this is equivalent to a difference of 351 more patients pr. 1000 displaying recovery in the salvage group (CI 95% 153 more to 700 more). The certainty of evidence was rated as moderate due to risk of bias.

3.3. Reported side effects

No serious adverse events was reported in any of the included studies.

3.4. Subgroup analysis

The data reported in the individual studies, did not allow for further subgroup analysis.

3.5. Certainty of estimates

Risk of bias was evaluated for each of the included studies. The risk of bias in the included randomized trials ranged from low risk to unclear due to a general inadequate description of random sequence generation, allocation concealment and blinding (the risk of bias assessment can be seen in conjunction with the respective meta-analysis). Evaluation of the included observational studies identified a moderate to serious level of bias. The ROBINS-I evaluation is found in the supplementary information. The risk of bias assessment was subsequently used in the collective evaluation of the certainty of estimates, presented in the summary of findings table (see Table 2). Overall, the certainty of evidence for the assessed outcomes ranged from moderate to very low. The summary of finding table is seen in Table 2.

4. Discussion

The objective of this systematic review was to provide an overview and quality assessment of the current evidence regarding ITC as salvage treatment for ISSNHL. Following a systematic search for literature, we identified four randomized controlled trials (Lee et al., 2011; Li et al., 2011; Wu et al., 2011; Xenellis et al., 2006) and seven observational studies (Ahn et al., 2008; Amarillo et al., 2019; Covelli et al., 2018; Erdur et al., 2014; Clary et al., 2011; Moon et al., 2011; Morita et al., 2016) that matched our inclusion criteria. The meta-analysis of both the randomized

Table 1. Study description of the included studies.

Included studies	Study design	No. Participants (Male)	Comparison (Age)	Treatment group (Age)	Application details and timing of treatment	Outcomes included (Underlined>: as defined in this review)	Follow-up
Moon et al., 2011	Observational study design	151	No further treatment (Mean years± SD: 51.19 ± 15.64)	Salvage intratympanic dexamethasone (Mean years ±SD: 50.30 ± 17.52)	Initial systemic treatment: - 60 mg of dexamethasone orally for 5 days and tapered down to 10 mg on day 10. - Intravenous 750 mg of acyclovir for 5 days. Salvage treatment: - Undiluted dexamethasone (5 mg/ml). - Initiated 2 weeks after initial systemic treatment, applied every other day for a total of 5 treatments	Gain in PTA, (Mean average of the 500, 1000, 2000 & 3000 Hz): - Relative hearing gain as difference between presalvage and final pure-tone threshold Patients achieving recovery: - No. of patients displaying hearing improvement based on Siegel's criteria	After 2 months of salvage treatment
Amarillo et al., 2019	Observational study design	109 (42)	No further treatment (Mean years± SD: 47.97 ± 3.15)	Salvage intratympanic methylprednisolone (Mean years± SD: 48.95 ± 1.67)	Initial systemic treatment: - Oral corticosteroids, prednisone at 1 mg/kg per day or deflazacort at the corresponding dose of tapered for 30 days of treatment or - Intravenous corticosteroids, methylprednisolone at 1 mg/kg per day and methylprednisolone boluses of 500 mg per day, both for 7 days, followed by a tapering until completing 30 days of treatment. Salvage treatment: - Methylprednisolone of 40 mg - Applied 7 days after initial treatment, once a week for 3 weeks	Gain in PTA (Mean average of 250, 500, 1000, 2000, 4000 & 8000 Hz) - Mean improvement in decibel	6 months after salvage treatment
Ahn et al., 2008	Observational study design	99 (61)	No further treatment (Mean years± SD: 45.6 ± 18.9)	Salvage intratympanic dexamethasone (ITD) (Mean years± SD: Early-ITD 43.2 ± 13.6; Mid-ITD 43.4 ± 18.8; Late-ITD 40.2 ± 14.2)	Initial systemic treatment: - 48 mg methylprednisolone for 9 days, followed by tapering for 5 days - Vitamins and lipo-PGE1 Salvage treatment: - 5 mg/ml dexamethasone - Timing varied: - Early-ITD group: within 2 weeks - Mid-ITD group: between 2 weeks and 1 month - Late-ITD group: between 1 and 2 months	Patients achieving recovery: - Total no. of patients experiencing hearing improvement - Defined as >15dB decrease in PTA (Mean average at 500, 1000, 2000 and 3000 Hz)	3 months after outbreak of sudden hearing loss
Morita et al., 2016	Observational study design	51 (16)	No further treatment (Median years 50.5, range 30–61)	Salvage intratympanic dexamethasone (Median years 46.0, range 13–60)	Initial systemic treatment: - Oral dexamethasone tapered from 40–60 mg/day for 14–16 days. The procedure was done once weekly. - Isosorbide (70%, 90 ml), vitamin B 12 and adenosine triphosphate disodium. Salvage treatment: - Dexamethasone disodium phosphate 0.5 ml (8 mg/2 ml) - 14–16 days after initial systemic treatment	Patients obtaining recovery: - No. of patients with hearing loss recovery - Defined as hearing levels at three low frequencies (125, 250 and 500 Hz) returned within 20 dB of normal	1 year after salvage treatment
Clary et al., 2011	Observational study design (poster)	39	No further treatment (No information on age)	Salvage intratympanic corticosteroid (No information on age)	Initial systemic treatment: - 60 mg of oral prednisone daily for 10–14 days Salvage treatment: - Not described	Patients achieving recovery: - Improvement in the affected ear of 20 dB or more in PTA (frequencies ?) or 20 % improvement in Speech Discrimination score	Not described
Erdur et al., 2014	Observational study design	51 (28)	No further treatment (Mean years± SD: 44.47 ± 15.16)	Salvage intratympanic dexamethasone (Mean years± SD: 42.71 ± 17.89)	Initial systemic treatment: - Methylprednisolone intravenously (250 mg) at the first day and followed by orally (1 mg/kg) tapering for 14 days Salvage treatment: - Dexamethasone (Onadron 1 mg/mL) Had placed a ventilation tube. Self-administration of five drops in the external auditory canal four times a day for 2 weeks. - 14 days after initial treatment	Gain in PTA: (Mean average of 500, 1000, 2000, 4000 Hz) - Pure tone average improvement in dB Patients achieving recovery: - No. of patients who displayed hearing improvement of 20 dB or more	2 months after completion of initial treatment

(continued on next page)

Table 1 (continued)

Included studies	Study design	No. Participants (Male)	Comparison (Age)	Treatment group (Age)	Application details and timing of treatment	Outcomes included (Underlined: as defined in this review)	Follow-up
Covelli et al., 2018	Observational study design	339 (206)	No further treatment (Mean age 50.9)	Salvage intratympanic dexamethasone (Mean age 50.3)	Initial systemic treatment: - Intravenous Dexamethasone at 1 mg/kg/d for 7-days Salvage treatment: - Dexamethasone of 4 mg/mL - 3 injections within 10 days.	Gain in PTA: (Mean average of 500, 1000, 2000, 4000 Hz) - Average hearing improvement in PTA Patients achieving recovery: - Hearing improvement above 15dB after 30 days	1 months after treatment
Wu et al., 2011	Randomized study	55 (18)	Intratympanic saline injection (Mean years± SD: 47.4 ± 15.7)	Salvage intratympanic dexamethasone (Mean years± SD: 49.1 ± 14.2)	Initial systemic treatment: - Intravenous steroid therapy for 5 days during hospitalization and were tapered off with oral prednisolone for 5 days after discharge Salvage treatment: - 1 week after initial treatment - 4 injections of 0.5 ml of dexamethasone (8 mg/2 ml) within a 2-week period (4 d apart)	Gain in PTA: (Mean average of four frequencies) - Average hearing improvement in dB Patients achieving recovery: - No. of patients with PTA improvement above 10 dB	1 month after injection therapy
Lee et al., 2011	Randomized study	46 (18)	No further treatment (Mean years± SD: 45.3 ± 13.5)	Salvage intratympanic dexamethasone (Mean years± SD: 44.0 ± 16.2)	Initial systemic treatment: - Oral steroids (60 mg/day for 5 days, followed by tapering for 5 days) - Ginkgo biloba extracts for 10 days Salvage treatment: - Dexamethasone 5 mg/ml - 2 weeks after initial treatment	Gain in PTA (Mean average of 500, 1000, 2000, 3000 Hz) - Hearing improvement in PTA Patients achieving recovery - Total no. of patients with 10 dB or more decrease in PTA of the four frequencies at 0.5, 1, 2 and 3kHz)	6 weeks after initial systemic treatment
Xenellis et al., (2006)	Randomized study	37 (17)	No further treatment (Mean age 50.3)	Salvage intratympanic methylprednisolone (Mean age 50.9)	Initial systemic treatment: - Prednisolone IV, 1 mg/kg per day for 10 days, gradually tapered for 5 days. - Acyclovir, 4 g/day for 5 days. - Buflomedil hydrochloride, 300 mg, divided in 3 doses, for 10 days. - Ranitidine during steroid treatment Salvage treatment: - 4 injections of methylprednisolone acetate in a concentration of 80 mg/2 mL within 15 days.	Gain in PTA (Mean average of 500, 1000, 2000, 4000 Hz) - Difference in PTA after salvage treatment compared to initial treatment Patients achieving recovery - Hearing improvement of 10dB or more	2 months after initial treatment
Li et al., (2011)	Randomized study	44 (16)	No further treatment (Mean years 55.1, range 22–73)	Salvage intratympanic methylprednisolone (Mean years 53.5, range 18–72 years)	Initial systemic treatment: - Prednisolone (1 mg/kg) for 5 days, and gradually tapered for 9 days Salvage treatment: - 1 ml of 40 mg/ml methylprednisolone - Performed 4 times (once every 3 days) within a 15-day period	Gain in PTA (Mean average of 500, 1000, 2000, 4000 Hz) - Difference in average PTA after salvage treatment compared to initial treatment Patients achieving recovery: - Hearing improvement of 10dB or more	1.5 months after salvage treatment

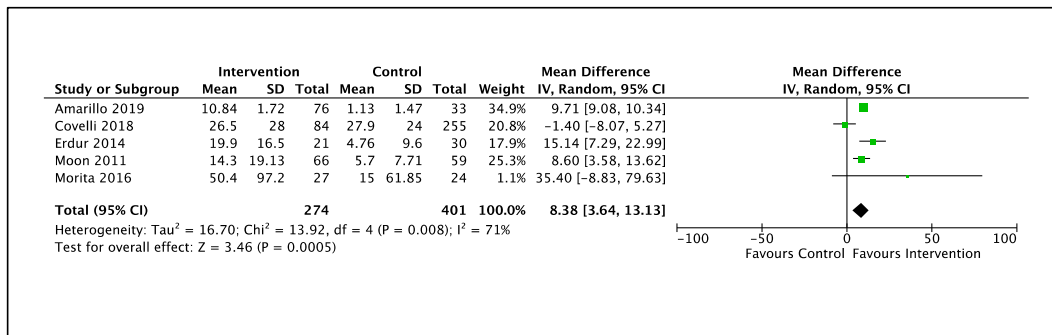


Figure 2. Observational studies. Gain in PTA (dB) (Follow-up 1 to 12 months after treatment).

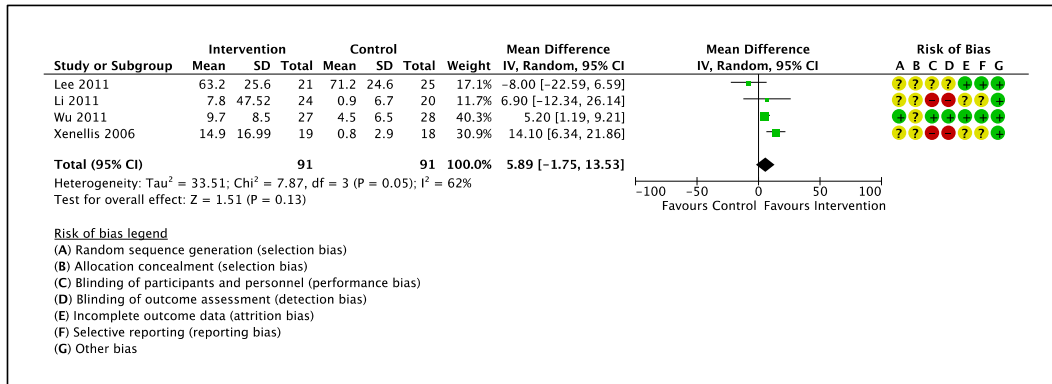


Figure 3. RCT studies. Gain in PTA (dB) (Follow-up 6 weeks to 6 months after treatment). RCT-studies.

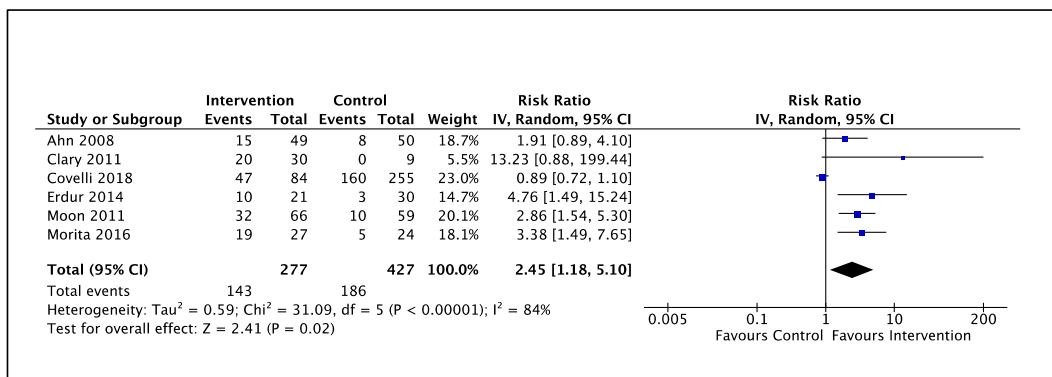


Figure 4. Observational studies. Patients achieving recovery.

controlled trials and observational studies showed a statistically significant increase in the number of patients obtaining recovery in favor of ITC as salvage treatment for patients with ISSNHL. ITC treatment for Meniere's disease, autoimmune inner ear disease, and ISSNHL was pioneered over 25 years ago (Silverstein et al., 1996). ITC is presumed to pass the blood-labyrinth barrier and reach the perilymph via the membrane of the round window, and to a smaller extent through the oval window membrane and the lacunar mesh surrounding the labyrinth (Phillips and Westerberg, 2011). The perilymphatic concentration of corticosteroid following intratympanic installation has been estimated up to 260 times higher compared to oral administration (Bird et al., 2011). The local application of corticosteroids is also favorably in order to avoid unwanted side effects of systemically administered corticosteroids. No serious adverse events were reported in the included studies, indicating that the intervention is generally well tolerated and safe to apply.

Our results showed that PTA improved with an average of 8.38 dB in the meta-analysis of observational studies. However, no significant improvement in PTA was found from the data obtained in the

randomized studies. As such, due to these discrepancies caution should be made when it comes to interpreting the findings, including the magnitude of effect.

Spontaneous recovery rates of ISSNHL are reported in the literature in up to 65% of cases but only a small number of patients are reported to restore hearing to functional levels (Ahmadzai et al., 2019). One must especially bear this in mind when looking at the results of the observational studies. The certainty of the evidence, as assessed by the GRADE approach, show that the confidence in the obtained estimates ranges from moderate to very low. This is mainly due to the presence of heterogeneity, risk of bias, and imprecision. Apart from one outcome (patients obtaining recovery assessed in RCTs), the statistically heterogeneity ranges from 62-84% for the remaining outcomes, which is considered to be substantial. Indeed, a difference in effect sizes is seen between studies, which is reflected in the high level of statistically heterogeneity as well as in the wide confidence intervals found in the meta-analysis. As such, although the majority of studies all point towards favorable outcomes following salvage treatment, the final magnitude of

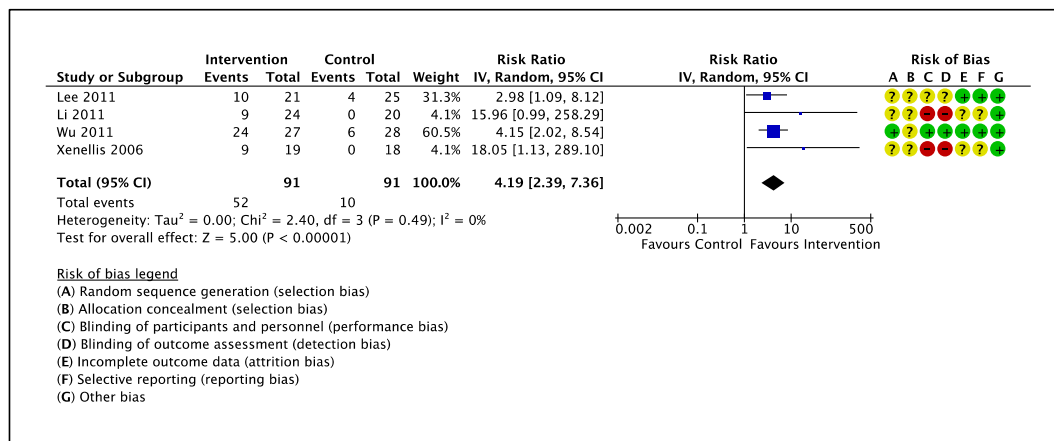


Figure 5. RCT studies. Patients achieving recovery.

effect and whether this essentially may be considered clinically relevant for the individual, still needs further assessment.

Furthermore, results are based on studies that irrespective of the study design display a certain degree of risk of bias. Observational studies are by default prone to risk of bias due to the inherent problems of such study designs. In contrast, RCTs are considered state of the art. Nevertheless, the included RCTs in this review still hold methodological limitations. Across studies, there is a general inadequacy in providing information on how the randomization sequence was generated despite that a proper randomization process holds the very foundation of a well-performed RCT. Blinding is furthermore generally inadequately described. Providing sufficient blinding of especially participants and personnel is difficult due to the nature of the intervention. However,

sufficient blinding of outcome assessors involved in data processing, would be possible. Collectively, the presence of risk of bias decreases the enthusiasm towards the included studies, and points towards a careful interpretation of the estimates obtained.

Our results showed an increase in the number of patients recovering from hearing loss. However, following merging of data, it became evident, that the definition of “recovery” varies substantially across trials, ranging from an improvement in >10dB to >30dB. The lack of a proper definition of recovery is a well-known problem among studies investigating ISSHL (Inoue et al., 2012). This is a limitation that hinders the interpretation and comparison of treatments used for ISSHL, including the effect of ITC as salvage treatment. Thus, the results concerning recovery in this review may generally reflect an increase in the number of

Table 2. Summary of findings – Corticosteroid.

Outcome	Results	Absolute effect estimates		Certainty of evidence	Narrative
		No salvage corticosteroid	Salvage corticosteroid		
Time frame					
Observational studies					
Patients displaying recovery Follow-up 1–12 months after treatment	Relative risk: 2.45 (CI 95% 1.18–5.1) Based on data from 704 patients in 6 studies ¹	435 per 1.000 Difference: 631 more per 1.000 (CI 95% 78 more - 1784 more)	1066 per 1.000	Very low Due to serious inconsistency ²	Salvage corticosteroid may increase the number of patients displaying recovery
Improvement in PTA (dB) Follow-up 1–12 months after treatment	Based on data from 675 patients in 5 studies ³	Difference: MD 8.38 higher (CI 95% 3.64 higher - 13.13 higher)		Very low Due to serious inconsistency ⁴	Salvage corticosteroid may improve the gain in PTA (dB)
Randomized studies					
Patients displaying recovery Follow-up 6 weeks to 6 months after treatment	Relative risk: 4.38 (CI 95% 2.56–7.52) Based on data from 211 patients in 5 studies ⁵	105 per 1.000 Difference: 355 more per 1.000 (CI 95% 164 more - 685 more)	460 per 1.000	Moderate Due to serious risk of bias ⁶	Salvage corticosteroid may increase the number of patients displaying recovery
Improvement in PTA (dB) Follow-up 6 weeks to 6 months after treatment	Based on data from 211 patients in 5 studies ⁷	Difference: MD 7.39 higher (CI 95% 0.55 higher - 14.22 higher)		Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision ⁸	Salvage corticosteroid may improve the gain in PTA (dB)

¹ Ahn 2008, Clary 2011, Covelli 2018, Erdur 2014, Moon 2011, Morita 2016.

² Inconsistency: Serious. The magnitude of statistical heterogeneity was high, with I2: 84%.

³ Amarillo 2019, Covelli 2018, Erdur 2014, Moon 2011, Morita 2016.

⁴ Inconsistency: Serious. The magnitude of statistical heterogeneity was high, with I2: 71%.

⁵ Ho 2004, Lee 2011, Wu 2011, Li 2011, Xenellis 2006.

⁶ Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias.

⁷ Wu 2011, Ho 2004, Lee 2011, Xenellis 2006, Li 2011.

⁸ Risk of bias: Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I2: 58%; **Imprecision: Serious.** Wide confidence intervals.

patients experiencing improvement in hearing abilities, yet whether this may be defined as recovery per se remains to be determined. There is a general lack in reported baseline data, including the initial level of hearing loss. As this data is unavailable, it remains unknown, whether the difference in the definition of recovery used across studies, may be linked to a difference in the baseline properties of the patients. Other reviews (Crane et al., 2015; El Sabbagh et al., 2017; Garavello et al., 2012; Li et al., 2015; Liebau et al., 2018; Ng et al., 2015) have also investigated the effect of intratympanic steroid as salvage treatment for patients with sudden hearing loss. These reviews in large include the same studies as our review, and not surprisingly, also find that patients may respond positively towards salvage treatment. However, a common concern in all reviews, as also shared by us, is the inadequate quality of the few included studies, the heterogeneity between studies and the lack of a streamlined protocol of therapy. Indeed, there is a large variety in the study protocols both in term of initial treatment, ITC treatment and calculation of audiometric outcome (as evident in Table 1). None of the included studies demonstrate when it is most beneficial to offer ITC treatment and following our literature search, it became evident that no novel studies on the matter have been published since the mentioned reviews. Other parameters are also warranted in future studies, in order to get a better understanding of the treatment as a whole. The current studies do not allow for subgroup investigations of the effect on baseline hearing loss and whether the time to initiate treatment affects treatment outcomes. It remains unknown whether the observed variation in the magnitude of effect found in this review, may reflect differences in such baseline parameters. In addition, given that these are critical factors when it comes to accessing which patient group may show the largest benefit, future studies on the matter are encouraged to include such baseline data including interaural data.

Thus, despite the promising results, we are left with reservations and questions. Further research should be undertaken to investigate more outcomes than merely changes in PTA of a pure tone audiogram. Prospective studies ought to include outcomes as speech audiometry parameters, interaural data, knowledge of the effects on concomitant symptoms as tinnitus and vertigo and possibly also patient-reported outcome measurements (PROMs). More knowledge is needed to optimize the guidance and advice to patients with inadequate hearing recovery despite initial systemic corticosteroid treatment.

5. Conclusion

Results show that salvage ITC is a safe and a potential beneficial treatment leading to improvement in the number of patients experiencing recovery. Yet, given the current level of evidence, the magnitude of effect still needs further assessment, including whether results essentially may be considered clinically relevant for the individual. Furthermore, it remains to be determined which subgroups presenting with ISSNHL potentially may achieve the largest benefit of treatment. This potential variation in treatment responses should be kept in mind, when counselling the patient.

Declarations

Author contribution statement

Henriette Edemann Callesen and Louise Devantier: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Therese Ovesen, Christian Mirian, and Lasse Rehné Jensen: Conceived and designed the experiments; Analyzed and interpreted the data.

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Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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