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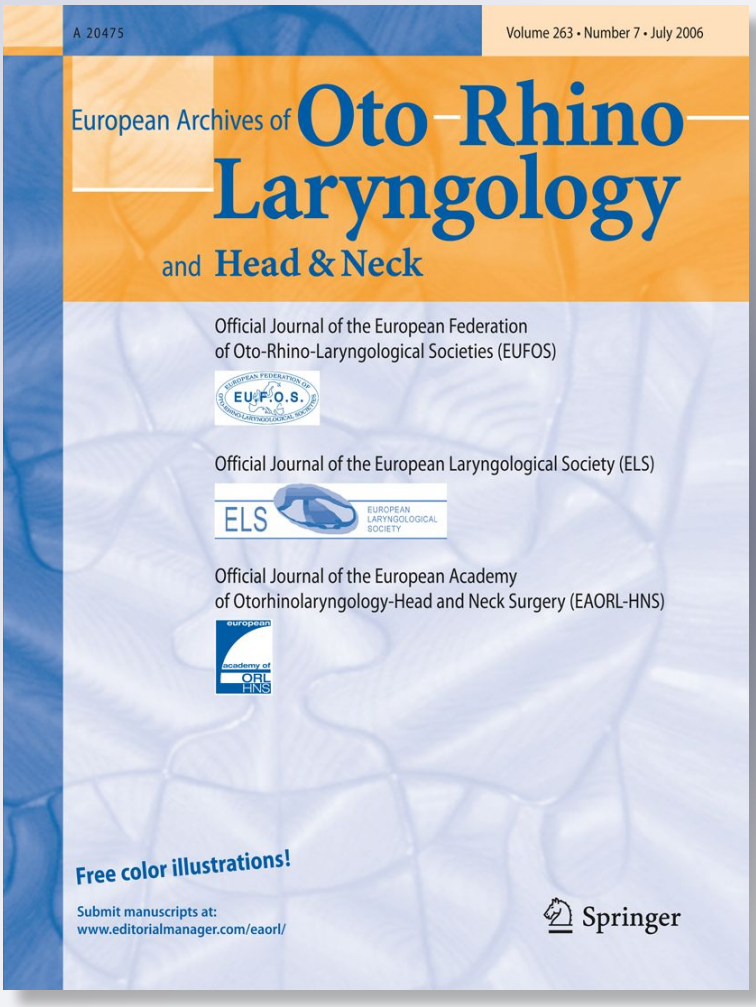

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REVIEW ARTICLE

Are intra-tympanically administered steroids effective in patients with sudden deafness? Implications for current clinical practice

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Abstract Over 60 years since its first report, sudden sensorineural hearing loss (SSNHL) still represents an ill-explained condition, with potentially devastating effects for the quality of life of previously well patients. The present study critically reviewed the available evidence regarding the efficacy of intra-tympanic steroid administration in the treatment of SSNHL. Factors affecting that efficacy were also explored. The literature was systematically reviewed in Medline and other database sources until July 2011, and analyzed through critical analysis of pooled data. The study selection included multi-center prospective randomized control trials, prospective randomized comparative, prospective comparative and prospective studies, retrospective comparative and retrospective studies. The total number of analyzed studies was 43. Intra-tympanic steroids appear to be effective as primary (strength of recommendation A), or salvage treatment (strength of recommendation B) in SSNHL. It is difficult to draw definite conclusions regarding the efficacy of combination therapy. The identification of a time window for effective treatment in the former two approaches yields a grade C strength of recommendation. Primary intra-tympanic treatment is the most effective modality in terms of complete hearing recovery (34.4% cure rate). There is not enough evidence to attribute treatment failures to impaired permeability of the round window membrane. Most complications of intra-tympanic treatment are minor, temporary, and conservatively managed. Intra-tympanic steroids can theoretically provide a more organ-specific treatment in patients with SSNHL. The observation that they seem effective both as primary and salvage treatment modalities with a very low complication rate may have serious implications for current clinical practice.

Keywords SSNHL · Steroids · Intra-tympanic · Primary · Salvage · Perfusion

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Introduction

Over 60 years since its first report by De Kleyn [1], sudden sensorineural hearing loss (SSNHL) still represents an ill-explained condition, with potentially devastating effects for the social function and quality of life of previously well patients [2]. The largely descriptive term, which is still used to illustrate an almost exclusively unilateral SNHL, of at least 30 dB in three consecutive frequencies of the pure-tone audiogram, established within 72 h, confirms the lack of knowledge about the exact etiology of this condition, and may also imply that SSNHL may not be a single

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disease, but a spectrum of pathologies that affect the inner ear [3].

Unsurprisingly, the treatment of SSNHL has been a subject of ongoing debate, complicated by the fact that spontaneous recovery is reported to occur in 30–60% of patients, typically within 2 weeks of symptom onset [4, 5]. Largely based on the work of Wilson et al. in the early 1980s, systemic steroids represent the only widely accepted treatment for SSNHL which was found effective in several quality clinical trials [6, 7]. They are, however, associated with well-known adverse effects and their administration should also be carefully considered in special categories of SSNHL sufferers (i.e. patients with diabetes mellitus, or glaucoma).

Intratympanic steroid delivery, on the other hand, seems to provide a more targeted approach in the treatment of SSNHL. Initially used by Schuknecht for the treatment of vertigo in Meniere's disease, intratympanic pharmacotherapy has gained popularity in various inner ear disorders, employing a variety of administered agents including steroids, local anesthetics, otoprotective drugs, or antibiotics [8–11]. Animal experiments suggest that intratympanic steroids produce higher perilymph concentration, compared to either intravenous or oral administration [12, 13], whilst no ototoxic effects from direct steroid application have been documented in human studies so far [3].

However, the two primary advantages of intratympanic versus systemic steroid administration for the treatment of SSNHL (i.e. the ability to achieve higher inner ear drug concentration, and the avoidance of systemic side effects) have not been fully exploited yet, probably due to the lack of proof about the superiority, or at least comparable efficacy, of the former against the latter in successfully treating this condition.

The aim of the present study was to critically review and analyze the available evidence regarding the efficacy of intratympanic steroid administration in the treatment of SSNHL. Factors which may affect that efficacy were also explored.

Materials and methods

An extensive search of the literature was performed in Medline and other available database sources until July 2011, establishing two main categories of outcomes:

a) assessment of the clinical effectiveness of intratympanic steroid administration in the treatment of SSNHL and,
b) comparison of the clinical effectiveness of intratympanic versus systemic steroid administration in the treatment of SSNHL.

Using this framework of results, the retrieved studies were critically appraised, according to evidence-based guidelines for the categorisation of medical studies (Tables 1, 2) [14]. In addition, two secondary end-points were also analysed: (a) the timing of the intratympanic administration (vs. the systemic, when applicable), as a determinant of this treatment modality, (b) the factors which may significantly influence the absorption of intratympanic steroids by the inner ear.

During the search, the keywords "sudden sensorineural hearing loss", "steroids", "inner ear", "systemic", and "intratympanic" were utilized. The keywords "sudden sensorineural hearing loss" and "steroids" were considered primary, and were either combined to each of the other keywords individually, or used in groups of three. In addition, reference lists from the retrieved articles were manually searched. Language restrictions limited the search to English-language articles only.

Table 1 Levels of evidence regarding the primary research question in studies that investigate the results of a treatment (http://www.cebm.net/index.aspx?o=1025)

Category of evidence	Study design
Level I	• High quality randomized trial with statistically significant difference, or no statistically significant difference but narrow confidence intervals
	• Systematic review of Level I randomized control trials (and study results were homogenous)
Level II	• Lesser quality randomized control trial (e.g. <80% follow up, no blinding, or improper randomization)
	• Prospective comparative study
	• Systematic review of Level II studies or Level 1 studies with inconsistent results
Level III	• Case control study
	• Retrospective comparative study
	• Systematic review of Level III studies
Level IV	• Case series
Level V	• Expert opinion

Table 2 Strength of recommendation by category of evidence for guideline development [14]

Strength of recommendation	Category of evidence
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Results

Forty-five studies met the defined criteria and were initially included in study selection. Among these studies, one pilot study included results which were partially incorporated at a later study by the same principle author, and was not included in the analysis of pooled data. Another study had used intra-tympanic steroids both as primary, and salvage treatment, and the study population did not exclusively comprise patients with idiopathic SSNHL. In the absence of clear-cut data about the efficacy of local administration as primary versus salvage therapy, and its clinical effectiveness in patients with exclusively idiopathic SSNHL, this study was also not used in the analysis of pooled data.

Overall, three multi-center prospective randomized control trials, six prospective randomized comparative, 14 prospective comparative, and eight prospective studies, four retrospective comparative, and eight retrospective studies, which utilized intra-tympanic steroids as part of their treatment protocol for SSNHL, were systematically analyzed (Tables 3, 4, 5, 6).

Fourteen studies used intra-tympanic steroids as a single treatment modality. Two studies were excluded from further analysis due to the limitations previously mentioned. Among the remaining nine studies, five were prospective and four retrospective. Three studies represented Level I, four studies Level II, and five studies level III evidence. The total number of treated patients was 522. Detailed audiometric data of treatment outcome were not reported in 252 patients. All researchers concluded that intra-tympanic steroids appear to be effective as a primary treatment modality in SSNHL. Complete hearing recovery was reported in 34.4% of patients. Four researchers reported that the time-interval between the onset of hearing loss, and the initiation of treatment negatively influenced the clinical effectiveness of the intra-tympanic administration. Finally, two Level I studies showed that intra-tympanic steroid administration is at least not inferior to systemic therapy, and two Level II studies suggested that it gives better hearing results than systemic therapy, if used as an initial treatment.

Nearly half of the analyzed studies ($n = 21$) used intra-tympanic steroid administration as a salvage therapy for SSNHL, after the failure of systemic steroids. One of them had used intra-tympanic steroids both as primary, and salvage treatment, but the study population did not solely include patients with idiopathic SSNHL. This study was, therefore, excluded from further analysis. Among the remaining 20 studies, 13 were prospective and seven retrospective. One study represented Level I, 12 studies Level II, and seven studies level III evidence. Overall, 525 patients received this treatment modality. Detailed audiometric data of treatment outcome were not reported in 227 patients. All studies concluded that intra-tympanic steroid administration is effective as salvage therapy in patients with SSNHL. Complete hearing recovery was, however, only reported in 13.4% of patients. With regard to the timeline for effective treatment, six studies identified a time-window of 1–4 weeks from the onset of hearing loss as clinically significant.

The present analysis also identified six additional studies, which used direct round window membrane perfusion as salvage therapy for SSNHL. These studies were analyzed separately, because the employed surgical intervention may not be so easily applicable in everyday clinical practice. Five of these studies were prospective and one retrospective. One study represented Level I, four studies Level II, and one study level III evidence. The total number of treated patients was 87. Detailed audiometric data of treatment outcome were not reported in 26 patients. There was agreement among researchers that round window membrane steroid perfusion induced hearing recovery in a significant proportion of patients, who had failed conventional therapy for SSNHL. Return to baseline hearing was achieved in 21.3% of patients. In addition, four research groups reported that the time-interval between the onset of hearing loss and the initiation of treatment negatively influenced the clinical effectiveness of the steroid perfusion.

Finally, the present analysis identified six studies which used combination therapy protocols as the treatment modality for SSNHL. All studies were prospective; three studies represented Level I, and three Level II evidence. The total number of treated patients was 221. The majority of researchers suggested that the combination of intra-tympanic steroid administration and systemic steroid therapy did not yield additional benefits compared to systemic steroids alone in the treatment of patients with SSNHL. Complete hearing recovery was reported in 21.3% of patients. With regard to the time-window for effective treatment, a trend for improved hearing results, if the intra-

Table 3 Study characteristics of intra-tympanic steroid administration as a primary treatment modality for SSNHL

References	Study type	Evidence level	Number of subjects	Administration method	Administered steroid	Outcome measure	Complete recovery	Remarks
Rauch et al. [15]	Multicenter prospective randomized comparative	I	129	Bi-weekly IT injections for 2 weeks	Methyl, 40 mg/ml	10 dB non-inferiority versus systemic steroids/HT change in the 2 month follow up	32/129	a) IT Methyl was not shown inferior to systemic steroids for the restoration of hearing in patients with SSNHL b) Baseline HTs >90 dB, and patients with dizziness show a trend for better treatment outcomes following systemic steroid administration
Dispenza et al. [16]	Prospective randomized comparative	I	25	Weekly IT injection for 4 weeks	Dex, 4 mg/ml	PTA improvement ≥10 dB	n.r.	a) IT Dex can result in hearing improvement in 80% of patients b) IT administration can be a first line treatment for SSNHL, as the results are similar to systemic therapy, and better than the expected results of spontaneous hearing recovery
Tsai et al. [17]	Retrospective	III	128	Bi-weekly IT injections for 2 weeks	Dex, 5 mg/ml	PTA improvement ≥10 dB	n.r.	a) The response rate after IT treatment is 68.8% b) Patients treated sooner than 7 days from symptom onset show significantly better response to treatment c) Mid and low frequency HL are more responsive to IT treatment
Fillipo et al. [18]	Prospective	II	34	Daily IT injection for 3 days	Prednisolone 62.5 mg/ml	Criteria Furuhashi et al. [19]	16/34	a) IT Pednisolone is more efficacious than any other treatment described in the literature b) The time-interval between symptom onset and initiation of therapy was inversely proportional to the improvement in HT c) Daily administration, and high concentration may be crucial determinants of treatment success
Kara et al. [20]	Prospective comparative	II	29	Daily IT injection for 5 days	Dex, 4 mg/ml	Difference to contra-lateral ≤10 dB/HT <15 dB	14/29	a) IT steroids give better hearing results that systemic steroids, with no side-effects b) Some patients achieve additional hearing benefit 10 days after the injections, possibly due to Dex pharmacokinetics, and anti-inflammatory effect to IHCs
Kakehata et al. [21]	Retrospective	III	19	Daily IT injection for 8 days	Dex, 4 mg/ml	Criteria Acute Severe Hearing Loss Study Group [22]	12/19	a) The response and cure rates of daily short-term IT Dex alone as initial treatment reached 95 and 63%, respectively b) Daily injections are more effective than weekly injections, and comparable to combination therapy
Hong et al. [23]	Prospective randomized comparative	I	32	Daily IT injection for 8 days	Dex, 5 mg/ml	Siegel's Criteria [24]	10/32	a) The restoration of HCs and their response to steroids do not depend only on the concentration gradients passing through the RWM b) Daily IT Dex administration as a primary treatment modality is effective for the management of SSNHL c) IT steroids tend to improve more the lower frequencies

Table 3 contiuned

References	Study type	Evidence level	Number of subjects	Administration method	Administered steroid	Outcome measure	Complete recovery	Remarks
Zernotti et al. [25]	Retrospective	III	18	Weekly IT injection for 3 weeks	Dex, 4 mg/ml	PTA improvement ≥25 dB	n.r	IT Dex is effective in the treatment of SSNHL, and represents a viable option for patients who cannot be treated with systemic steroids
Han et al.[a] [26]	Prospective comparative	II	34	Bi-weekly IT injections for 2 weeks	Dex, 5 mg/ml	PTA improvement ≥15 dB	n.r.	a) Even low concentration of steroids in the inner ear ay be enough to work efficiently b) IT steroids as initial treatment is as effective as systemic in patients with diabetes, and therefore more useful in the presence of peripheral vascular complications, or poor glycemic control
Fitzgerald and McGuire [27]	Retrospective	III	21	Weekly IT injection for 3 weeks	Methyl, 62.5 mg/ml	PTA improvement ≥10 dB/word discrimination score improvement ≥15%	n.r	a) Locally administered steroids appear to be an effective treatment for SSNHL, especially if given within 2/52 after symptom onset b) Prompt treatment is the only variable significantly affecting the outcomes at the 95% confidence interval
Kakehata et al.[a] [28]	Prospective comparative	II	10	Daily IT injection for 8 days	Dex, 4 mg/ml	PTA improvement ≥30 dB	4/10	a) Response rate of more than 10 dB improvement is significantly better in IT compared to systemic steroids b) IT Dex is at least as effective as IV Dex treatment in diabetic patients, and does not require daily blood glucose measurements and insulin therapy
Banerjee and Parnes [29]	Retrospective	III	26	Bi-weekly IT injections p.r.n.[b]	Methyl, 40 mg/ml	SRT <50 dB/speech discrimination >50%	n.r.	a) Patients treated within 10 days of onset showed statistically significant improvement in SRT and PTA in affected frequencies compared with those who started their treatment after 10 days b) There is no difference between IT steroid-treated patients with initial severe HL, and those with smaller losses
Chandrasekhar [30]	Prospective	II	3	One or more IT injections, according to PTA	Dex, 4 mg/ml	Not defined	n.a.	a) IT Dex results in significantly higher perilymph steroid levels than when administered systematically b) IT Dex in SSNHL has distinct advantages in improved inner ear absorption, 73–80% improvement rates, and absence of systematic side-effects c) Patients with long intervals between HL onset and IT treatment, and those with downward slopping HL do no recover hearing

Table 3 continued

References	Study type	Evidence level	Number of subjects	Administration method	Administered steroid	Outcome measure	Complete recovery	Remarks
Parnes et al. [13]	Prospective	II	13	Bi-weekly IT injections for 3 weeks	Dex, 25 mg/ml/ Methyl, 62.5 mg/ml	Not defined	n.a.	a) Dex, hydrocortisone, and Methyl penetrate the blood-labyrinthine barrier after systemic administration b)The IT route results in significantly higher inner ear levels compared with the systemic routes at all sampling times c) IT Methyl achieves the highest concentration for longest duration in both endolymph and perilymph d) 50% of patients showed significant improvement in auditory thresholds

Methyl methylprednisolone, *Dex* dexamethasone, *IT* intra-tympanic, *HT* hearing thresholds, *IHCs* inner hair cells, *SSNHL* sudden sensorineural hearing loss, *HL* hearing loss, *PTA* pure tone audiometry, *RWM* round window membrane, *SRT* Speech Reception Threshold, *n.r.* not reported, *n.a.* not analysed

[a] Study involves diabetic patients

[b] Patients received injections until they reached a plateau in hearing improvement. A minimum of 2 injections were administered

tympanic steroid is added to systemic therapy within approximately 10–11 days of hearing loss onset, was reported in two studies, but not proven statistically significant in the end.

Discussion

Among the wide variety of agents which have been used in the treatment of SSNHL, systemic steroid administration has been the only widely accepted method of treatment. Wilson et al. [7] reported that 78% of SSNHL sufferers improved following systemic steroid administration (excluding patients with profound hearing loss, or mid-frequency hearing loss with a tendency of spontaneous resolution), in a double-blinded placebo-controlled study. Their results were further supported by the findings of Moskowitz et al., [6] who reported even more significant improvement (89%) in the steroid group in an unblinded prospective randomized trial, but questioned by other contemporary researchers [4]. In addition, recent systematic reviews have failed to identify the exact merit of systemic steroids in the treatment of SSNHL [60], and provided no evidence of superior outcomes over placebo [61], thus questioning their value as a gold standard [62]. The high rate of spontaneous recovery in patients with SSNHL (30–65%) [5], however, may be at least partially responsible for the controversy in the aforementioned clinical outcomes.

The mechanism of action of steroids in the inner ear is not fully understood. Both local and systemic effects have been proposed, even though controversy over the precise mode of action still exists. The former may be mediated by the presence and distribution of glucocorticoid receptors in the inner ear [63], and include regulation of ion homeostasis, antioxidant action, inhibition of apoptosis, down-regulation of local pro-inflammatory cytokines, and promotion of cochlear blood flow [53, 64–67]. Although several factors seem to define the responsiveness of the inner ear to steroids [68], local dexamethasone treatment was shown to protect hair cells against TNFα apoptosis in vitro by increasing the nuclear transport of NF-kappaB [69, 70], and up-regulating the expression of Bcl-2, and Bcl-xl [71] (anti-apoptotic properties). In addition, the inner ear mineralocorticoid receptor is a significant target of glucocorticoids, and a factor that should be considered in the regulation of the micro-homeostasis in the inner ear [72]. Systemic effects, on the other hand, may result from systemic immunosuppression, which can decrease the number of circulating blood leukocytes, and/or inhibit inflammatory mediators [73].

Unfortunately, the systemic administration of steroids is not without risks, whereas certain groups of patients (e.g.

Table 4 Study characteristics of intra-tympanic steroid administration as salvage therapy in SSNHL

References	Study type	Evidence level	Number of subjects	Administration method	Administered steroid	Outcome measure	Complete recovery	Remarks
Lee et al. [31]	Prospective comparative	II	21	Bi-weekly IT injections for 2 weeks	Dex, 5 mg/ml	PTA improvement ≥10 dB	2/21	a) Salvage IT treatment results in significant hearing improvement, especially in the lower frequencies, or patients with HT ≥70 dB b) Sequential IT administration after initial systemic therapy may be more effective than systemic therapy alone for hearing improvement in patients with SSNHL c) Early IT administration tends to yield better results
Zhou et al. [32]	Prospective comparative	II	37	4 IT injections on alternate days	Methyl, 40 mg/ml	PTA improvement ≥15 dB/ speech discrimination score improvement ≥15%	n.r.	a) 46% of patients with poor prognostic factors experience statistically significant improvement in their HTs, and 43% in their speech discrimination following salvage IT steroid treatment b) Patients with poor prognosis may have better treatment outcome, if IT steroids are administered earlier
Hunchaisri et al. [33]	Prospective comparative	II	14	Weekly IT injection for 3 weeks max according to PTA	Dex, 4 mg/ml	PTA improvement ≥10 dB/ speech discrimination score improvement ≥15%	n.r.	a) Hearing improvement occurred in 43% of patients that received IT Dex b) There was no difference in treatment outcome if IT treatment started within, or after 2 weeks of symptom onset
Chen et al. [34]	Retrospective	III	38	IT injection every 48 h up to a max of 4 injections	Methyl, 40 mg/ml	Criteria of the Otolaryngology-Head and Neck Surgery Subcommittee of the Chinese Medical Association for hearing recovery in SSNHL	8/38	a) IT treatment may be considered instead of systemic administration in patients with refractory HL b) There is a trend for improved hearing results if IT injection is performed within 23 days of symptom onset c) 1 IT injection cannot ensure effective drug delivery d) The use of an endoscope is helpful for ensuring effective drug delivery
Raymundo et al. [35]	Prospective	II	14	IT injection every 48 h for 4 days	Methyl, 40 mg/ml	PTA improvement ≥20 dB/ speech discrimination score improvement ≥20%	6/14	The recovery rate in IT-treated patients is 71.4%

Table 4 continued

References	Study type	Evidence level	Number of subjects	Administration method	Administered steroid	Outcome measure	Complete recovery	Remarks
Kakehata et al.[a] [21]	Retrospective	III	24	Daily IT injection for 8 days	Dex, 4 mg/ml	Criteria Acute Severe Hearing Loss Study Group [22]	2/24	a) Salvage treatment results in 58% response rate, 29% successful treatment, and 8% cure rate b) Salvage treatment onset later than 19 days does not yield successful outcomes
Dallan et al. [36]	Retrospective	III	27	Single IT injection	Methyl, 40 mg/ml	Relative Gain	n.r.	IT steroids can be useful in patients with refractory SSNHL, as more than 50% of them improve their relative gain
Lee et al. [37]	Retrospective comparative	III	34	IT injection every 48 h for 2 weeks	Dex, 5 mg/ml	Siegel's Criteria [24]	4/34	a) IT Dex as salvage treatment for patients with profound SSNHL has very poor prognosis b) The recovery rate of severe SSNHL is significantly better than the respective rate of profound HL (37.5 vs. 5.5%)
Ahn et al. [38]	Retrospective comparative	III	49	Bi-weekly IT injections for 2 weeks	Dex, 5 mg/ml	PTA improvement ≥15 dB	n.r	a) The rate of hearing improvement is associated with the timing of IT Dex; patients treated 1.5 months after onset are less likely to improve b) Hearing improvement is more definite in low & middle frequencies
Kilic et al. [39]	Prospective comparative	II	19	Bi-weekly IT injections for 2 weeks	Methyl, 62.5 mg/ml	PTA improvement ≥10 dB	n.r.	a) 76.8% of patients who failed high-dose systemic steroids respond to IT injection b) IT injection can be performed as first line of approach
Plaza and Herraiz [40]	Prospective comparative	II	9	Weekly IT injection for 3 weeks	Methyl, 20 mg/ml	PTA improvement ≥15 dB/ speech discrimination score improvement ≥15%	n.r.	a) IT methyl significantly improves the outcome of SSNHL after failure of IV steroid treatment b) Onset-to-therapy of more than a week is related to less hearing improvement
Choung et al. [41]	Prospective comparative	II	33	Bi-weekly IT injections for 2 weeks	Dex, 5 mg/ml	PTA improvement ≥10 dB/ speech discrimination score improvement ≥15%	3/33	a) IT Dex can be performed in refractory SSNHL regardless of the response to initial systemic steroids b) IT Dex may be more effective in low frequency SSNHL c) Treated patients show much more hearing gain and improvement in subjective symptoms than can be merely attributed to the natural course of the disease

Table 4 continued

References	Study type	Evidence level	Number of subjects	Administration method	Administered steroid	Outcome measure	Complete recovery	Remarks
Roebuck and Chang [42]	Retrospective comparative	III	31	Single IT injection[b]	Dex, 24 mg/ml	PTA improvement ≥10 dB/ speech discrimination score improvement ≥15%	n.r.	There is a good indication that IT steroids provide more benefit compared to oral steroids in patients who have already failed initial oral steroid therapy
Haynes et al. [43]	Retrospective comparative	III	40	Single IT injection	Dex, 24 mg/ml	PTA improvement ≥20 dB/ speech discrimination score improvement ≥20%	1/40	a) 39% of IT-treated patients improved, compared to 9.1% of controls, provided that they were treated within 6 weeks of symptom onset b) There is a trend towards efficacy of steroid perfusion in patients who have failed systemic steroid therapy
Xenellis et al. [3]	Prospective comparative	II	19	Bi-weekly IT injections for 2 weeks	Methyl, 40 mg/ml	PTA improvement ≥10 dB	2/19	a) IT steroid administration is effective in patients with SSNHL b) 47.4% who had not responded to IV steroid therapy showed significant hearing improvement with IT Methyl
Slattery et al. [44]	Prospective	II	20	Bi-weekly IT injections for 2 weeks	Methyl, 62.5 mg/ml	Improvement compared to contra-lateral ≥50%/PTA improvement ≥10 dB/ speech discrimination score improvement ≥12%	1/20	a) A significant proportion of subjects (55%) experienced clinically significant improvement in PTA/speech discrimination; only 5% experienced full recovery b) IT treatment affects more than hearing; tinnitus and dizziness also tend to improve c) The greatest improvement appears between 2,000–4,000 Hz d) Patients who begin oral steroid treatment within 10 days of symptom onset, and IT injections within 1 month have better chances for improvement
Selivanova et al. [45]	Prospective	II	18	IT injection every 48 h for up to 2 weeks	Dex, 8 mg/ ml + hyaluronic acid 0.2 mg/ml	PTA improvement ≥10 dB	n.r	Treatment results for patients with low frequency SSNHL as a rescue therapy after failure of IV treatment are promising (77% improvement rate)

Table 4 continued

References	Study type	Evidence level	Number of subjects	Administration method	Administered steroid	Outcome measure	Complete recovery	Remarks
Guan-Min et al. [46]	Prospective randomized comparative	I	15	Weekly IT injection for 3 weeks	Dex, 4 mg/ml	Criteria Furuhashi et al. [16]	4/15	a) Patients with severe HL tend to respond more favourably to IT Dex than profound SSNHL sufferers (recovery rate 44.4 versus 9.5%, respectively) b) IT-DEX injection effectively improves hearing in patients with severe or profound SSNHL, after treatment failure of conventional therapy c) Hearing gain is not likely to take place, if there is no notable improvement with the first 2 injections
Gouveris et al. [47]	Prospective	II	40	IT injection every 48 h for up to 2 weeks[c]	Dex, 8 mg/ml + hyaluronic acid 0.2 mg/ml	PTA improvement ≥10 dB	7/40	a) IT Dex + hyaluronic acid resulted in significant global improvement in hearing in patients with pantonal SSNHL, who were refractory to treatment with IV steroids and vaso-active therapy b) IT Dex + hyaluronic acid improved the frequencies of 1.5 & 3 kHz in patients with high-frequency SSNHL, and 0.5, 0.75 and 1 kHz in patients with profound SSNHL (or sudden deafness)
Gianoli and Li [48]	Prospective	II	23	Bi-weekly IT injections for 2 weeks	Dex, 25 mg/ml/methyl, 62.5 mg/ml	PTA improvement ≥10 dB/speech discrimination score improvement ≥10%	n.r.	a) Salvage IT injection results in 44% response rate in patients with SSNHL who had failed systemic steroids, irrespective of the onset of the condition b) younger patients, males, and Methyl-treated show a trend for better results

Dex dexamethasone, *Methyl* methylprednisolone, *IT* intra-tympanic, *IV* intravenous, *SSNHL* sudden sensorineural hearing loss, *HL* hearing loss, *PTA* pure tone audiometry, *n.r.* not reported

[a] See also Table 3

[b] 5 patients received more than 1 injection

[c] 6 patients received 1 injection, 13 patients received 2 injections, 11 patients received 3 injections, 8 patients received 4 injections, 1 patient received 5 injections, 1 patient received 7 injections

Table 5 Round window membrane perfusion as salvage therapy in SSNHL

References	Study type	Evidence level	Number of subjects	Administration method	Administered steroid	Outcome measure	Complete recovery	Remarks
She et al. [49]	Prospective comparative	II	26	RWM daily perfusion (micro-catheter) for 10 days	Methyl, 40 mg/ml	PTA improvement ≥15 dB	n.r	a) RWM daily perfusion is an effective treatment for refractory SSNHL, mainly in patients whose onset-to-perfusion period is less than 2 months b) RWM perfusion has a better effect on lower than higher frequencies
Plontke et al. [50]	Multi-center prospective double-blind randomized placebo-controlled	I	21	RWM continuous infusion (micro-catheter) for 2–4 weeks[a]	Dex, 4 mg/ml	Criteria Furuhashi et al. [19]/ improvement compared to contra-lateral ≥50%/PTA	5/21	a) The observed differences in the time-course of improvement between the 2 groups suggests that hearing recovery was associated with the RWM infusion therapy b) There is a tendency towards better hearing improvement in the treatment group c) There is a tendency for better improvement in those patients with an earlier onset and longer duration of continuous RWM infusion
Van Wijck et al. [51]	Prospective comparative	II	12	RWM daily perfusion (micro-wick) for 3 weeks	Methyl, 62.5 mg/ml	PTA improvement ≥10 dB	5/12	a) Steroid perfusion results in improvement in 66% of patients b) No further gain is obtained after 2–3 weeks of perfusion
Herr and Marzo [2]	Retrospective	III	17	RWM daily perfusion (micro-wick) for 7 days/RWM continuous infusion (micro-catheter) for 10–13 days[b]	Dex, 10 mg/ml/Methyl, 62.5 mg/ml	PTA improvement ≥ 10 dB/speech discrimination score improvement ≥20%	2/17	a) There is a 53% rate of improvement in patients with SSNHL refractory to conventional systemic steroids, following this treatment modality b) The authors do not recommend IT therapy as a primary treatment option
Lefebvre and Staecker [52]	Prospective comparative	II	6	RWM continuous infusion (micro-catheter) for 10 days	Methyl, 62.5 mg/ml	Not defined	0/6	RWM perfusion of Methyl resulted in significant recovery of hearing function (primarily speech discrimination) in all treated patients, after the failure of standard SSNHL treatment
Kopke et al. [53]	Prospective	II	5	RWM continuous infusion (micro-catheter) for 2 weeks	Methyl, 62.5 mg/ml	PTA improvement ≥10 dB/word identification score improvement ≥15%	1/5	a) RWM perfusion earlier than 6 weeks from symptom onset resulted in PTA improvement in all patients b) Patients showing no change after 48–96 h of micro-catheter placement, and those treated later than 6 weeks from symptom onset show less, or no improvement c) RWM continuous infusion should only be used in patients with severe to profound HL, in whom more conservative therapy has failed

Dex dexamethasone, *Methyl* methylprednisolone, *IT* intra-tympanic, *SSNHL* sudden sensorineural hearing loss, *PTA* pure tone audiometry, *RWM* round window membrane, *n.r.* not reported

[a] 4 weeks treatment group, 2 weeks placebo group

[b] in patients also refractory to microwick perfusion

Table 6 Study characteristics of combination therapy in the treatment of SSNHL

References	Study type	Evidence level	Number of subjects	Administration method	Administered steroid	Outcome measure	Complete recovery	Remarks
Arslan et al. [54]	Randomized prospective comparative	I	85	5 IT injections on alternate days	Methyl, 125 mg/ml	PTA improvement ≥10 dB	n.r.	a) Adding IT Methyl to systemic therapy increases the probability of hearing recovery in patients with SSNHL b) Combination therapy leads to hearing improvement in 70% of patients
Fu et al. [55]	Prospective comparative	II	22	IT injection every 48 h for 8 days	Dex, 5 mg/ml	Criteria Sudden Deafness Research Committee of the Japanese Ministry of Health and Welfare	0/22	a) Higher IT Dex concentration resulted in higher accumulation, and longer duration in the tissues, compared to the standard dose; hence, Dex concentration plays a role in pharmacokinetics b) Lower frequencies were found to have better recoveries, compared to higher ones
Battaglia et al. [56]	Multi-center prospective double-blind randomized placebo-controlled	I	33[a]	Weekly IT injection for 3 weeks	Dex, 12 mg/ml	Difference to contra-lateral ≤5% + difference between groups ≥15%	10/16[a]	a) Combination therapy leads to significant improvements in speech discrimination compared to HDPT alone, with no additional complications b) Combination therapy has significantly better odds of partial or complete hearing recovery, when compared with HDPT alone, or IT Dex alone; this recovery is also quicker c) Treatment should be initiated as quickly as possible, and ideally within 10 days (or less) of onset
Ahn et al. [57]	Randomized prospective comparative	I	60	IT injections on days 1, 3, 5	Dex, 5 mg/ml	Siegel's Criteria [24]	15/60	a) The combination of IT Dex and systemic steroids did not have additional benefits compared with systemic steroids alone in the treatment of patients with SSNHL b) The addition of IT Dex was associated with clinically significant hearing improvement in the frequency of 250 Hz
Lautermann et al. [58]	Prospective comparative	II	13	Daily IT injection for 5 days	Methyl, 32 mg/ml	Not defined	2/13	Additional IT therapy with local steroids does not result in improved recovery, compared to the standard therapy with systemic steroids and rheologic infusion
Battista [59]	Prospective	II	25	Bi-weekly IT injections for 2 weeks	Dex, 25 mg/ml	Difference to contra-lateral ≤10 dB/improvement ≥50%/PTA	2/25	a) There is no significant hearing recovery using IT Dex in conjunction with oral steroids for profound SSNHL b) There is a possible trend for improved hearing results if IT treatment is performed within 11 days of HL onset

Dex dexamethasone, *Methyl* methylprednisolone, *IT* intra-tympanic, *HT* hearing thresholds, *HDPT* high dose prednisone taper, *SSNHL* sudden sensorineural hearing loss, *PTA* pure tone audiometry, *HL* hearing loss

[a] 17 patients received intra-tympanic injections with placebo HDPT, with a complete recovery rate of 5/17

patients with diabetes, or glaucoma) may require even closer monitoring. In addition, not only the optimal dose of steroids, and the duration of treatment are largely unknown, and therefore often empirical, but also their limited ability to penetrate the blood–perilymph barrier may result in a suboptimal therapeutic effect (at least in non-toxic doses).

By contrast, the intra-tympanic route of administration can provide organ-specific treatment, with two theoretical advantages; the potential of direct steroid uptake through the round window membrane, resulting in higher perilymph levels [74–76], and a lesser or none systemic steroid absorption and toxicity.

Although intra-tympanic corticosteroids were shown to increase cochlear blood flow, prevent aminoglycoside toxicity, and improve ionic homeostasis, without having any adverse effects against cochlear function [65, 67, 77–79], their main disadvantage, when set against systemic administration, is still the reservations regarding their efficacy. Reviews of published data exist in the literature, however, they tend to be rather descriptive, and mostly report the existing heterogeneity in treatment protocols and outcome measures [80], whereas recommendations about the clinical effectiveness of intra-tympanic steroids, according to the principles of evidence-based medicine have not been published so far.

From the 12 studies that used intra-tympanic steroids as a single treatment modality and were included in the study selection, two studies had included exclusively diabetic patients, and were analyzed separately.

Despite the heterogeneity in the utilized steroid and the treatment regimens, inclusion and exclusion criteria were clearly defined in all studies, and appeared quite homogenous. There was some further heterogeneity regarding outcome measures among studies, however, most authors considered a 25–30 dB improvement in the hearing thresholds of the affected ear as clinically significant. Four authors considered a 10 dB hearing improvement as significant, with one author admitting that his criteria were adapted from the evaluation of therapy in patients with Meniere's disease.

Based on the quality of studies, which supported intra-tympanic steroids as an effective primary treatment modality in SSNHL, the strength of this recommendation can be graded as A. The fact that two Level I studies showed intra-tympanic steroid administration to be at least not inferior to systemic therapy, and two Level II studies suggested that it actually gives better hearing results than systemic therapy, further support the previous conclusion. However, since only two (out of 12) studies found intra-tympanic steroids superior to systemic therapy, these results need to be adopted with caution, until superiority and not non-inferiority are reproduced in Level I studies. Finally, a rate C recommendation can be adopted for the conclusion that the time-interval between the onset of hearing loss and the initiation of treatment influences the clinical effectiveness of the intra-tympanic administration in a negative way.

As mentioned earlier, intra-tympanic steroid administration was also performed as initial treatment in diabetic patients with SSNHL. Diabetes mellitus is not uncommon in patients with SSNHL, as it has been reported to exist in 5.7–12.5% of cases. Systemic steroid administration may induce a severe hyperglycemic state in these patients, which may not be possible to be controlled even by insulin injections, and may warrant cessation of treatment. This was indeed observed in approximately 15% of patients in one study [26]. In addition, long-standing diabetes may cause micro-angiopathy and impaired micro-circulation in the inner ear, thus hindering systemic steroids from efficiently reaching the cochlear fluids [81, 82].

Both studies that assessed the clinical efficacy of intra-tympanic steroids in diabetic patients with SSNHL were Level II studies. Although there was some heterogeneity in the treatment protocols, and the definition of improvement, both research teams considered intra-tympanic steroids to be at least as effective as systemic therapy in these patients, while demonstrating the advantage that close monitoring of blood glucose levels, and insulin therapy are not necessary during treatment.

The largest volume of clinical research, which has used intra-tympanic steroid administration in the treatment of SSNHL, employed this modality as a salvage therapy, after the failure of systemic steroids. Despite some heterogeneity in the utilized steroid and the treatment regimens, inclusion criteria were clearly defined and appeared fairly homogenous in most studies, with the exception of two studies which had recruited patients with a 24-h onset of SNHL (instead of the most commonly considered 3-day interval) and two studies, that had set a 20 dB hearing loss in three consecutive frequencies of the pure tone audiogram as their cut-off inclusion criterion (instead of the most commonly used 30 dB hearing loss). Exclusion criteria were quite homogenous across studies; however, they were not reported at all in eight of them. Heterogeneity was observed between studies, with regard to the definition of a successful outcome. The majority of authors ($n = 11$) considered a 10 dB improvement in the hearing thresholds of the affected ear (or alternatively a 10–15% improvement in speech discrimination) as clinically significant. Five research groups considered 15–20 dB improvement as being clinically significant, whereas even stricter criteria of more than 30 dB improvement were adopted in only four studies. It is quite possible that the 10 dB criterion was adopted by researchers on the basis of the previous experience of Otology Groups, with regard to successful

therapy in patients with Meniere's disease [27], or was incorporated in study designs based on the preliminary results of the pilot study by Silverstein et al. [77].

Based on the quality of studies that endorsed intra-tympanic steroid administration as effective salvage therapy in patients with SSNHL, the strength of this recommendation can be graded as B. It is conceivable that the improvement in the hearing thresholds after intra-tympanic therapy may not always result in serviceable hearing (e.g. speech reception threshold lower than 50 dB, or speech discrimination better then 50%). Due to the heterogeneity in the original definition of a clinically significant outcome (as mentioned above), no clear conclusion can be drawn on the proportion of patients that improves after failing the initial conventional treatment. Indeed, the related response rates range between 30.6 and 77.7% (Fig. 1).

The identification of a time-window for effective treatment 1–4 weeks from the onset of hearing loss in six studies should be weighed against three research groups that reported successful results, irrespective of the onset-to-treatment interval. Hence, the strength of this recommendation can only be rated as C.

Finally, intra-tympanic steroid administration seems to be more promising in low and middle frequency hearing losses. This result is reported in four Level II studies, and one Level III study.

It should be noted that most studies focus on the success rate of the intra-tympanic steroid administration, whereas less attention is given to the potential etiology of treatment failure. Obviously, the fact that the exact etiology of SSNHL remains elusive, affects the clinical effectiveness of all therapeutic agents employed in the so-called "shotgun" regimens, including intra-tympanic steroids. Indeed, it is conceivable for instance that local steroid treatment may be incapable of preventing a system-wide immune response from affecting the inner ear, or have access to the more central portions of the auditory pathway [27]. In addition, the permeability of the round-window membrane, and the affinity of the utilized steroid to the glucocorticoid receptors

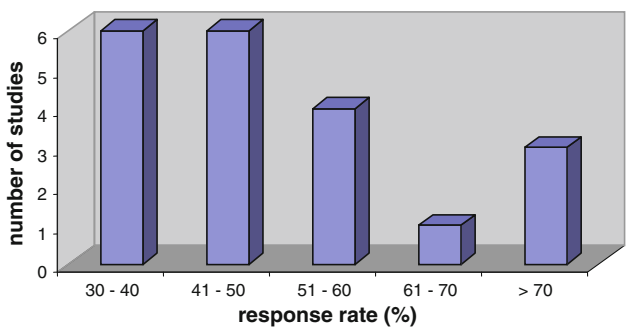

Fig. 1 Efficacy of salvage intra-tympanic steroid administration

of the inner ear may also affect the therapeutic efficacy of the intra-tympanic route of steroid administration.

Indeed, Yoshioka et al. administered gadolinium intra-tympanically, and monitored its inner ear fluid kinetics using 3-Tesla magnetic resonance imaging with a 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) protocol. They reported that round window permeability was poor in 13%, and totally absent in 5% of ears, thus either essentially precluding intra-tympanic drug therapy, or at least resulting in suboptimal candidacy. In addition, the gadolinium movement into the inner ear was more faintly observed in 8% of ears that had shown round window absorption [83]. Furthermore, Silverstein et al. [84] have also reported that the round window membrane macroscopically appears partially or completely obstructed in 12, and 17% of examined middle ears in the native state (e.g. before round window membrane perfusion for inner ear disorders). The addition of facilitating substances in the form of hyaluronic, or histamine-based hydrogels to the intra-tympanically delivered steroid may provide a more steady release mechanism, or improve their absorption through the round window membrane [30, 46, 85, 86]. The use of endoscopes to ascertain that the area of the round window niche is free from adhesions [28, 48, 51], and/or the intra-tympanic injection of Gadolinium with subsequent high magnetic field MRI scanning [83] may also be tried in patients not responding to intra-tympanic treatment.

The therapeutic efficacy of steroids is also largely related to their tissue-binding affinity. Hargunani et al. [87] demonstrated that intra-tympanically injected dexamethasone is binding to the glucocorticoid receptors of the inner ear, but is not detected 24 h after administration. Parnes et al. [13] reported that methylprednisolone shows higher concentration and longer duration in the perilymph and endolymph than dexamethasone. Taken together, these data may imply that dexamethasone may have more avid receptor uptake than methylprednisolone, and may result in improved treatment efficacy. However, taking the higher concentration and longer duration of prednisolone in the inner ear fluids into account, the opposite theory may stand as well. Hence, studies demonstrating the binding affinity of methylprednisolone to the inner ear receptors are necessary before final conclusions can be drawn in this respect. In addition, intra-tympanically administered dexamethasone may have little impact in the inner ear tissue after 24 h, thus making continuous infusion, or at least daily injections, more superior therapeutic regimens than single or weekly administrations.

Drawing on the effect of the round window permeability to the success of intra-tympanically-based steroid treatment for SSNHL, the present analysis identified six studies that used direct round window membrane perfusion. There was agreement among researchers that this method of

management induced hearing recovery in a significant proportion of patients, who had failed conventional therapy for SSNHL (strength of recommendation B). However, this treatment modality may not be so easily applicable in everyday clinical practice, as it can be associated with a higher rate of complications, thus requiring the presence of an experienced otologist.

It should be noted that the results from this group of studies did not seem dramatically different than the ones from studies utilizing intra-tympanic injections. In addition, the successful treatment of Meniere's disease by local administration of gentamycin into the middle ear indicates that pseudo-membranes in the round window niche cannot completely block the diffusion of drugs into the human inner ear. Hence, there is not enough evidence to suggest that the permeability of the round window membrane is the primary reason of treatment failure after local steroid administration for SSNHL.

In an effort to by-pass the aforementioned shortcomings, a third approach was added to primary or salvage intra-tympanic therapy for SSNHL; combination therapy utilizes high-dose systemic steroids with the concomitant administration of intra-tympanic steroids. Despite some heterogeneity in the utilized steroid and the treatment regimens, inclusion criteria were clearly defined and appeared fairly homogenous among studies, with the exception of one study, which had recruited patients with a 24-h onset of SNHL (instead of the most commonly considered 3-day interval), and one study, that had set a 20 dB hearing loss in three consecutive frequencies of the pure tone audiogram as the cut-off inclusion criterion (instead of the most commonly used 30 dB hearing loss). Exclusion criteria were not reported in one study, but appeared quite homogenous among the rest. Strict and clearly defined outcomes of successful treatment, demonstrating satisfying homogeneity were adopted by most researchers using this treatment modality, with the exception of one study, which had not specifically stated which outcomes were considered as clinically significant, and one study which had adopted the 10 dB criterion of post-treatment improvement.

Although most of the researchers (four vs. two) suggested that the combination of intra-tympanic steroid administration and systemic steroid therapy did not yield additional benefits compared to systemic steroids alone in the treatment of patients with SSNHL, the fact that two out of the three Level I studies, including the highest quality study within this group of studies, explicitly stated that combination therapy has significantly better odds of partial or complete recovery compared to high-dose systemic therapy (or intra-tympanic administration as a single treatment modality), precludes us from drawing definite conclusions regarding the strength of the respective recommendations. Nevertheless, the addition of intra-tympanic steroids to systemic steroid therapy seems to be associated with clinically significant hearing improvement in the lower frequencies.

By contrast, the suggestion of a time-window of approximately 10–11 days for the addition of intra-tympanic steroids to the systemically administered ones, to maximize the chances of effective treatment was not proven statistically significant, and cannot, therefore, be given any strength of recommendation.

When making recommendations about the efficacy of intra-tympanic steroid administration for the treatment of SSNHL, there needs to be a clear view on what the definition of success is. From a clinical standpoint, some patients who experience success, defined as a 10 dB improvement in their pure tone thresholds, or 10% improvement in speech discrimination, may not notice a subjective improvement in their hearing, especially if the contralateral ear is normal, and in fact it would be entirely possible that a patient could meet a criterion of success and not have serviceable hearing, or even be unaidable. Hence, in terms of complete hearing recovery, the intra-tympanic administration of steroids as a primary treatment seems to be the most effective modality, with over one-third of the treated patients (34.4%) returning to baseline hearing (Fig. 2). However, this percentage should be interpreted with caution, as clear audiometric data regarding complete hearing recovery were not reported in a number of studies. Therefore, there is an urgent need for a consensus in defining hearing outcomes and success of treatment in patients with SSNHL.

In addition to the expected efficacy of intra-tympanically administered steroids as primary, salvage, or combination therapy, appropriate preoperative informed consent requires that the patient is aware of the potential risks which can be associated with this specific intervention (Table 7). However, the intra-tympanic route of steroid administration is overall considered as a relatively safe procedure. Most complications reported in the literature are minor, temporary, and conservatively managed. Vertigo or temporary disequilibrium during treatment is reported in most studies, and can be largely attributed to a caloric effect from the injected steroid solution. Nausea and vomiting can also

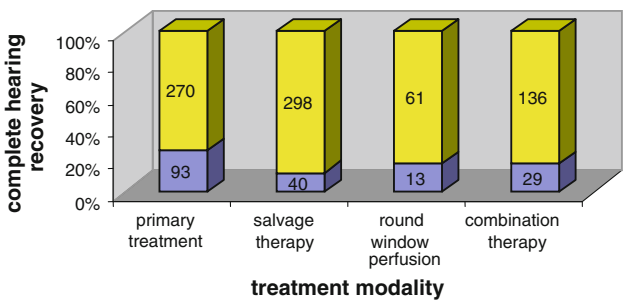

Fig. 2 Complete hearing recovery by mode of intra-tympanic steroid treatment

Table 7 Complications of intra-tympanic steroid administration for the treatment of SSNHL

Severity of complications	Type of management
Minor	
Vertigo/disequilibrium	Spontaneous resolution
Nausea/vomiting	Conservative
Hearing deterioration	Spontaneous resolution
Acute otitis media	Conservative
Otorrhea	Conservative
Earache	Conservative
Headache	Conservative
Tongue paresthesia	Spontaneous resolution
Dysgeusia	Spontaneous resolution
Acne	Conservative
Major	
Persistent tympanic membrane perforation	Surgical[a]
	Conservative[b]
Chronic otitis media	Surgical
Ear canal skin defect	None reported
Device dislocation	Surgical

[a] $n = 7$

[b] $n = 50$

occur, if the stimulation is stronger. These complications may be prevented, if the solution is warmed to body temperature before administration. Pain or burning sensation during treatment is mostly associated with methylprednisolone administration, and can be minimized by adding 0.1 ml lignocaine 2% solution to the injected steroid. Acute otitis media, otorrhea, hearing deterioration, tongue paresthesia, mild dysgeusia, and acne represent additional minor complications which are rarely encountered, and resolve either with time, or conservative treatment. The present analysis identified tympanic membrane perforation in 57 patients, out of a total population of 1,351 who received intra-tympanic steroid treatment for SSNHL (4.2%). Thirty-four of these patients had undergone procedures which involved round window membrane perfusion systems, leaving 23 patients out of the 1,351 (1.7%) with tympanic membrane perforation secondary to standard intra-tympanic steroid injection. Only four cases required a formal myringoplasty. One patient with a window membrane perfusion system developed chronic otitis media, which had necessitated tympano-mastoid surgery. Dislocation of the perfusion system, headaches, or ear canal skin defects, have also been reported, although rarely, in the latter group of patients.

Conclusion

Intra-tympanic steroids appear to be effective as primary treatment in SSNHL (strength of recommendation A), however, their superiority in comparison to systemic steroids still needs to be reproduced in Level I studies, before they can replace them as the mainstay treatment modality of this condition. Intra-tympanic steroid administration is also effective as a salvage therapy in patients with SSNHL (strength of recommendation B), however, the proportion of patients who will benefit from this intervention is still not clearly defined. It is difficult to draw definite conclusions regarding the efficacy of combination therapy for SSNHL.

There is also not enough evidence to suggest that the permeability of the round window membrane is the primary reason of treatment failure after local steroid administration for SSNHL

Most complications of intra-tympanic treatment for SSNHL reported in the literature are minor, temporary, and conservatively managed. Round window membrane perfusion systems are associated with higher complication rates, without evidence of superior outcome than standard intra-tympanic injections.

Conflict of interest None declared.

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