Eur Arch Otorhinolaryngol (2016) 273:2271–2278
DOI 10.1007/s00405-015-3689-3

REVIEW ARTICLE

Intratympanic corticosteroids injections: a systematic review of literature

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Received: 29 December 2014 / Accepted: 12 June 2015 / Published online: 23 June 2015

Abstract The objective of the study was to determine the evidence of intratympanic steroids injections (ITSI) for efficacy in the management of the following inner ear diseases: Ménière's disease, tinnitus, noise-induced hearing loss (NIHL) and idiopathic sudden sensorineural hearing loss (ISSNHL). The data sources were literature review from 1946 to December 2014, PubMed and Medline. A systematic review of the existing literature was performed. Databases were searched for all human prospective randomized clinical trials using ITSI in at least one treatment group. The authors identified 29 prospective randomized clinical trials investigating the benefits of an intratympanic delivery of steroids. Six articles on Ménière's disease were identified, of which one favored ITSI over placebo in vertigo control. Of the five randomized clinical trials on tinnitus therapy, one study found better tinnitus control with ITSI. The only available trial on NIHL showed significant hearing recovery with combination therapy (ITSI and oral steroids therapy). Seventeen studies were identified on ISSNHL, of which 10 investigated ITSI as a first-line therapy and 7 as a salvage therapy. Studies analysis found benefits in hearing recovery in both settings. Due to heterogeneity in treatment protocols and follow-up, a meta-analysis was not performed. Given the low adverse effects rates of ITSI therapy and good patient tolerability, local delivery should be considered as an interesting adjunct to the therapy of the ISSNHL and NIHL. Only one article over six where ITSI therapy offers potential benefits to patients with Ménière's disease in the control of tinnitus and vertigo was found. ITSI does not seem to be effective in the treatment of tinnitus.

Keywords Ménière's disease · Noise-induced hearing loss · Tinnitus · Idiopathic sudden sensorineural hearing loss · Intratympanic steroid treatment · Transtympanic steroid treatment · Systematic review

Introduction

Intratympanic injections for inner ear disease were first described by Trowbridge in 1944 [1] and a variety of treatment protocols have since been suggested. The rationale of locally delivered steroids is to allow the drug to reach tissues of interest with a high dosage, yet avoiding the adverse effects of systemic administration. The semi-permeable properties of the round window membrane allow intratympanic steroids to access the perilymph by pinocytosis and diffusion [2]. This bypassing of the hemato-cochlear barrier results in up to 1.270-fold higher steroids concentrations into the perilymph [3] when compared to systemic administration.

Corticosteroid receptors have been identified in both cochlear and vestibular tissues, suggesting that gene expression can be altered to produce anti-inflammatory effects [4]. Dexamethasone intratympanic injections have been shown to increase cochlear blood flow by 29 % [5] and increase the expression of aquaporin-1 [6], a key regulator in perilymphatic fluid homeostasis. Therefore, the inner ear's physiology can be modulated by steroids and this explains why neurotologic disorders that have an inflammatory origin may respond to this drug.

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This article reviews published evidence on the use of locally delivered steroids for treatment of inner ear pathologies suspected to have an inflammatory or autoimmune physiopathology. The objective is to identify inner ear diseases for which patients can benefit from ITSI.

Method

After approval from our institutional review board committee, PubMed and Medline Databases were searched for all human prospective randomized clinical trials with a treatment arm receiving ITSI. The following research terms were used: *steroids*, *corticosteroids*, *prednisolone*, *methylprednisolone*, *dexamethasone glucocorticoids*, *intratympanic*, *transtympanic*, *inner ear disease*, *labyrinth diseases*. Inner ear diseases of interest were identified through article titles and individually added to the search protocol. Authors reviewed all potential papers based on available abstracts and complete articles analysis. Articles' references were also screened for potential additional studies. When multiple articles had been published by the same author for a growing series of patients, only the latest article, hence the one with the largest number of participants was included. Articles in languages other than English and French were also excluded. Database search included studies published between 1946 and December 2014.

Results

Databases search identified four inner ear diseases for which ITSI was used in a prospective randomized clinical trial: Ménière's Disease, tinnitus, noise-induced hearing loss (NIHL) and idiopathic sudden sensorineural hearing loss (ISSNHL). After duplicates removal and screening, 29 articles remained for analysis.

For Ménière's Disease, 6 articles were identified and listed in Table 1. When feasible, extraction of study data followed the recommendations of the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery [7]. Of the selected articles, three [8–10] found no benefit of ITSI over placebo. One of these studies [10] compared a dexamethasone poloxamer gel to a placebo and found no statistical significance ($p = 0.086$) in the reduction of number of vertigo-days per month (-0.201 vs -0.124) and no statistical significance ($p = 0.055$) in the reduction of the tinnitus handicap inventory score (-15.0 vs -4.0).

One study [11] found that low-dose intratympanic gentamycin injections (ITGI) provided better vertigo control over ITSI and another found that vertigo was similarly controlled with ITGI, ITSI and endolymphatic sac decompression (ESD) [12].

In the remaining study, Garduno-Aaya et al. [2] found better vertigo control with ITSI over placebo (82 vs 57 %), a statistically significant improvement in subjective hearing (35 vs 10 %) and a statistically significant improvement in subjective tinnitus loudness and aural fullness (48 vs 20 %).

For tinnitus control, five prospective randomized trials were identified and listed in Table 2. Three studies [13–15] compared ITSI to placebo and found no benefit in tinnitus score improvement. One study [16] compared intratympanic dexamethasone, intratympanic prednisolone and oral carbamazepine and found no benefit in the ITSI groups. The study by Shim et al. [17] is the only study where tinnitus was improved in a statistically significant manner with ITSI (25.8 vs 9.8 % in control group).

In the treatment of NIHL, only one randomized clinical trial on humans was available [18] (Table 3). Of the 27 patients receiving combination therapy (systemic and ITSI), 51.9 % improved their pure tone average (PTA) by more than 15 dB and 66.7 % improved their speech discrimination score (SDS) by 15 % or more. Recovery rates for PTA and SDS were significantly better in the combination therapy group when compared to systemic therapy alone.

Ten studies investigated ITSI as first-line therapy for ISSNHL recovery (Table 4). Two studies [19, 20] found that ITSI therapy was equivalent to systemic therapy in hearing level (HL) improvement, and one [21] found that combination therapy was similar to systemic steroids. Of the two studies [22, 23] comparing systemic, ITSI and combination therapy, one found that combination therapy was superior to systemic treatment alone (87.5 vs 44.4 %). As for the four remaining studies, three [24–26] found that combination therapy was superior to systemic therapy and one [27] favored ITSI over placebo.

For salvage therapy in ISSNHL, 8 studies were identified (Table 5). All but one found that ITSI therapy was superior to control, placebo or systemic therapy.

Discussion

A meta-analysis of the identified literature was not performed due to the heterogeneous nature of the data. Studies used different treatment protocols, definitions of SSNHL and Ménière's disease, definitions of outcome criteria, and timeframes for follow-up. Reported studies described the use of different steroids: dexamethasone or methylprednisolone. A single study [16] in our review compared methylprednisolone to dexamethasone injections and found no difference in tinnitus control between groups. In their

Table 1 Intratympanic steroid injections in Ménière's disease

References	Dosage	Groups	HL	Vertigo	Tinnitus	Fullness
Lambert [10]	Dex 3 mg or 12 mg in poloxamer-407	14 Dex (3 mg)	ND	V-D/M	THI reduction	NA
		16 Dex (12 mg)		−0.147	−12.2	
		14 placebo		−0.201 ($p = 0.086$)	−15.0 ($p = 0.055$)	
				−0.124	−4.0	
Casani [11]	Dex 4 mg/mL	28 ITSI	ND	CC	NA	NA
	Genta 27.6 mg/mL	32 ITGI		42.9 %		
				81.3 %^{SS}		
Garduño-Aaya [2]	Dex 4 mg/mL	11 ITSI 11 placebo	SI	CC	SI	SI
			35 %^{SS}	82 %^{SS}	48 %^{SS}	48 %^{SS}
			10 %	57 %	20 %	20 %
Paragache [9]	Dex 0.2 mg/mL	20 ITSI 20 Medical tx	SDS	Good control	CC(I)	CC
			15 %^{NSS}	85 %^{NSS}	10 % (60 %)^{NSS}	15 %^{NSS}
			10 %	80 %	15 % (50 %)	25 %
Sennaroğlu [12]	Dex 1 mg/mL	24 ITSI 16 ITGI 25 ESD	PTA	CC	CC(I)	PI
	Genta 20 mg/mL		16^{NSS}	42 %^{NSS}	8 % (50 %)^{NSS}	75 %^{NSS}
			30^{NSS}	50 %^{NSS}	7 % (21 %)^{NSS}	50 %^{NSS}
			12^{NSS}	28 %^{NSS}	5 % (20 %)^{NSS}	60 %^{NSS}
Silverstein [8][a]	Dex 8 mg/mL	10 ITSI	PTA and SDS ND	ND in ENG studies	ND	NA
		10 Placebo				

HL hearing loss; *DEX* dexamethasone, *Genta* gentamycin, *ITSI* intratympanic steroids injection, *ITGI* intratympanic gentamycin injection, *ESD* endolymphatic sac decompression, *NA* not available, *CC* complete control, *CC (1)* complete control (improvement), *SI* subjective improvement, *PI* partial improvement, *PTA* pure tone average, *SDS* speech discrimination score, *ENG* electronystagmography, *SS* statistically significant, *NSS* not statistically significant, *ND* no difference, *V-D/M* vertigo-days per month, *THI* tinnitus handicap inventory

[a] Results before crossover

Table 2 Intratympanic steroid injections in tinnitus treatment

References	Patient selection	Dosage	Groups	Results
Choi [13]	Refractory	Dex 5 mg/mL	15 ITSI	THI
			15 Salin	33.3 %^{NSS}
				40 %
Shim [17]	Idiopathic <3 months	Dex 5 mg/mL	42 Ala	Cure rate
			46 Ala + ITSI	9.8 % 25.8 %^{SS} 20.0 %^{SS}
			44 Ala + ITSI + PSTG	
Topak [15]	Refractory	MP 62.5 mg/mL	30 MP	SATLSI
			29 Salin	21 %^{NSS}
				22 %
She [16]	Refractory	MP 0.25 mg/mL	35 MP	Control rate
		Dex 5 mg/mL	24 Dex	45.7 %^{NSS}
		CBZ 300 mg	25 Carb	29.2 %^{NSS}
				36.0 %
Araujo [14]	Refractory + severe and disabling	Dex 4 mg/mL	21 ITSI	TVASI
			14 Salin	33 %^{NSS}
				29 %

DEX dexamethasone, *MP* methylprednisolone, *CBZ* carbamazepine, *THI* tinnitus handicap index, *Ala* alazopram, *PSTG* prostaglandin, *ITSI* intratympanic steroids injection, *CC* complete control, *SS* statistically significant, *NSS* not statistically significant, *TQ* tinnitus questionnaire, *SATLSI* self-assessed tinnitus loudness scale improvement, *TVASI* tinnitus visual analog scale improvement

Table 3 Intratympanic steroid injections in noise-induced hearing loss

References	Level	Dosage	Follow-up	Groups	PTA Improvement >15 dB	SDS improvement >15 %
Zhou [18]	1	MP 40 mg/mL	8 weeks	27 ITSI + PO	51.9 %	66.7 %
				26 PO	23.1 % ($p = 0.047$)	30.8 % ($p = 0.014$)

MP methylprednisolone, *ITSI* intratympanic steroids injection, *PO* per Os, *PTA* pure tone average, *SDS* speech discrimination score

pharmacokinetics studies in 1999, Parnes et al. [28] compared these two molecules. They found that methylprednisolone was superior to dexamethasone as peak concentrations were higher and remained higher for longer duration. Other authors have argued that higher concentrations of methylprednisolone were sampled in the endolymph due to decreased absorption by cochlear and vestibular tissues. To this day, no clinical data favors one over the other.

Given the natural evolution of Ménière's disease, it has been suggested that study protocols always include a placebo group. Of the listed studies in Table 1, only 3 included a placebo group. The studies by Lambert et al. [10] and Garduno-Aaya et al. [2] were both of Level 1 evidence [29], but only the latter suggested benefits in vertigo and tinnitus control over placebo. The study by Silverstein et al. [8] found no difference between ITSI and placebo, but was criticized for being a crossover study. No benefits were found at 3 weeks, before the crossover, the only time point unbiased by the potential carry-over effect.

Paragache et al. [9] compared ITSI to medical therapy, comprising salt, caffeine, nicotine and alcohol restriction with cinnarizine and betahistidine hydrochloride. No difference was measured between the two groups in vertigo, tinnitus or hearing loss recovery (Table 1). However, the patients in the ITSI group were instilled the lowest dexamethasone concentration of all reported studies in this review: 20 times less than the usually used concentration of 4 mg/mL. With the expected dose–response relationship of inflammatory and autoimmune diseases to steroids, one can expect that the used steroid concentration was too low to produce any therapeutic effect.

The two remaining randomized studies interested in Ménière's disease compared ITSI to ITGI. Together with our previously published local experience [30], ITGI seems to offers better vertigo control over ITSI. However, given the potential cochlear toxicity of gentamycin, ITGI should only be considered for patients with non-serviceable hearing.

In tinnitus therapy, one study [17] found benefits of ITSI over a control group. Patients were selected for having

Table 4 Intratympanic steroid injections as first-line therapy of idiopathic sudden sensorineural hearing loss

References	Treatment	Sample	PTA	SDS	Comment
Lim [22]	Dex 5 mg/mL bid × 14 days, Pred PO × 10 days	20 PO 20 ITSI 20 PO + ITSI	Imp >10 dB 60 % 60 %^{NSS} 55 %^{NSS}	NA	ITSI = oral = CT
Arastou [24]	Dex 4 mg/mL twice a week for 2 weeks	36 ITSI + PO 41 PO	Imp > 15 dB 75 %^{SS} 41.4 %	NA	CT > oral
Koltsidopoulos [21]	Dex 4 mg/mL 3 TI + 9 days of IV pred	46 ITSI + IV 46IV	Imp > 10 dB 67.4 %^{NSS} 52.2 %	Gain > 15 % 32 %^{NSS} 18 %	ITSI = CT; when profound HL excluded: CT > IV
Gundogan [25]	MP 62.5 mg/mL 4 TI	37 ITSI + PO 37 PO	Imp > 15 dB 89 %^{SS} 61 %	Score Imp 41.08 %^{SS} 20.06 %	CT > oral
Filipo [27]	MP 62.5 mg/mL 3 TI	25 ITSI 25 Placebo	Imp >10 dB 96 %^{SS} 20 %	NA	ITSI > placebo
Rauch [19]	MP 40 mg/mL 1 mL every 4 days for 2 weeks	113 ITSI 108 PO	Mean Imp 28.7 dB^{NSS} 30.7 dB	Mean Imp 35.5 %^{NSS} 36.3 %	ITSI not inferior to oral
Arslan [26]	MP 125 mg/mL, 1 TI every 2 days, 5 total	85 ITSI + IV 73 IV	Imp > 10 dB NA[a] (21.8)^{SS} NA[a] (13.0)	NA	CT > systemic
Hong [20]	DEX 5 mg/mL Every day for 8 days	32 ITSI 31 PO	Imp > 15 dB No significant difference[a]	NA	ITSI = oral
Battaglia [23]	DEX 12 mg/mL 1 TI once a week for 3 weeks	19 ITSI + PO 20 ITSI 21 PO	Imp > 15 dB 87.5 %^{SS} 70.6 %ST 44.4 %	Mean Imp 44 %^{SS} 36 %ST 20 %	CT > oral; Trend of ITSI > oral
Ahn [35]	Dex 5 mg/mL, 3 TI total	60 ITSI + PO 60 PO	Imp > 15 dB 73.3 %^{NSS} 70.0 %	NA	CT = oral

PTA pure tone average, *SDS* speech discrimination score, *Dex* dexamethasone, *MP* methylprednisolone, *Pred* prednisolone, *TI* transtympanic injections, *Imp* improvement, *ITSI* intratympanic steroids injection, *CT* combination therapy, *PO* per os, *ITSI* intratympanic steroids injection, *SS* statistically significant, *NSS* not statistically significant, *ST* statistical trend, *NA* not available

[a] Numbered results not reported

unilateral idiopathic tinnitus for less than 3 months. The authors hypothesized that in the early stage of disease; the cochlear lesion causing tinnitus can be reversed. Because minimal plastic change has occurred in the central auditory pathway, early administration of ITSI may enable cochlear lesion recovery and restore neural hyperactivities of the central auditory pathway. Unfortunately, there was no placebo group in this study so results were not compared to the natural evolution of the disease. Also, patients' last follow-up was at 3 months, so long-term benefits were not assessed. Yet, this study suggests that patients might benefit from a reduced time between tinnitus onset and therapy.

Zhou et al. [18] found that combination therapy was superior to systemic steroids alone for patients exposed to noise trauma who had shown no spontaneous recovery within the first 72 h. Eighty-one percent of the recruited patients had been exposed to fireworks or military training noise. The therapeutic effects of steroids are thought to arise from their protective effects on injured cells [31, 32] by stabilization of cellular membranes, scavenging of oxygen free radicals and by inhibition of phospholipase A_2. This first human study on ITSI therapy for NIHL shows promising results. However, sample size was small (53 patients) and

Table 5 Intratympanic steroid injections as salvage therapy of idiopathic sudden sensorineural hearing loss

References	Treatment	Sample	PTA Imp >15 dB (mean IMP in dB)	SDS Imp >15 %	Comment
Zhou [36]	MP 40 mg/mL, 1 TI/day for 4 days	37 ITSI	45.9 %^{SS}	43.2 %^{SS}	ITSI > control
		39 control	20.5 %	17.9 %	
Li [33]	MP 40 mg/mL, 1 TI every 3 days, 4 total	24 ITSI	37.5 %^{SS} (9.7)	NA	ITSI > control
		21 ear drops	NA[a] (0.9)		
		20 controls	0 % (0.9)		
Wu [37]	DEX 4 mg/mL, 4 TI in 2 weeks	27 ITSI	44.4 %^{SS} (9.7)	NA	ITSI > placebo
		28 placebo	10.7 % (4.5)		
Lee [38]	Dex 5 mg/mL 1 TI twice a week for 2 weeks	21 ITSI	47.6 %^{SS}(11.4)	NA	ITSI > control
		25 control	16.0 % (1.7)		
Plontke [34]	DEX 4 mg/mL perfusion by microcatheter 0.58 mg/day for 14 days	11 ITSI	54.5 %^{NSS} (13.9)	24.4	ITSI = placebo
		10 placebo	50 % (5.4)	4.5 $p = 0.07$	
Xenellis [39]	MP 40 mg/mL 4 TI over 15 days	19 ITSI	47.4 %^{SS} (14.9)	NA	ITSI > control
		18 control	0 % (−0.8)		
Ho [40]	DEX 4 mg/mL once per week for 3 weeks	15 ITSI	54 %^{SS} (28.4)	NA	ITSI > control
		14 control	7 % (13.2)		

PTA pure tone average, *SDS* speech discrimination score, *Imp* improvement, *ITSI* intratympanic steroids injection, *MP* methylprednisolone, *NA* not available, *NSS* not statistically significant, *SS* statistically significant, *TI* transtympanic injection, *NA* not available, *CT* combination therapy

[a] Numbered results not reported

patient selection was heterogeneous. Further studies are needed to confirm these benefits.

The use of ITSI for treatment of ISSNHL has been studied in two settings: as first-line and as salvage therapy. Given the unethical considerations of offering placebo as first-line therapy to patients suffering from ISSNHL, most studies compared combination to systemic therapy.

Four of these studies found that combination therapy was superior to systemic therapy alone and three found that combination therapy was equivalent to systemic treatment. Hence as first-line therapy of ISSNHL, adding ITSI to systemic therapy significantly improved patients' outcome in more than half of the available studies. The used steroid concentrations in the positive studies ranged from methylprednisolone 12 mg/mL to dexamethasone 12 mg/mL (Table 4). Furthermore, Rauch et al. [19] designed a non-inferiority trial involving 205 patients and found that ITSI alone was not inferior to oral therapy. Hence, with recovery rates ranging from 55 % [22] to 96 % [27] the added benefits of ITSI need to be considered. The addition of ITSI to ISSNHL therapy may allow the use of lower systemic doses, thereby minimizing their adverse effects.

When considering salvage therapy in ISSNHL, ITSI groups had PTA improvement of 15 dB or more that ranged from 37.5 % [33] to 54.5 % [34]. The benefits on hearing levels were also significantly higher with ITSI in all but one study. Hence the available evidence supports the use of ITSI in salvage therapy.

In the six positive studies reported in Table 5, salvage therapy was administered, if no response was noted, 10–13 days after first-line systemic therapy. The used steroid concentration ranged from methylprednisolone 40 mg/mL to dexamethasone 5 mg/mL. Therefore, physicians should consider offering ITSI to patients suffering from ISSNHL after as little as 10 days into an unsuccessful first-line systemic therapy regiment.

Adverse events of ITSI therapy include ear pain at time of injection, caloric vertigo, dizziness, infection and persistent tympanic perforation. All of these side effects are either transient or easily curable. Pain and caloric vertigo can be, respectively, minimized with the use of fine needles and adequate steroid temperature at time of injection. Hence, when compared to systemic administration of steroids, intratympanic delivery is safe and can easily be managed by otolaryngologists.

Conclusion

Due to heterogeneity in treatment protocols and follow-up, a meta-analysis was not performed. Our review found only one article over six where ITSI therapy offers potential benefits to patients with Ménière's disease in the control of tinnitus and vertigo. Patients affected with ISSNHL seem to benefit from ITSI in both first-line and salvage therapy. Only one human study was found on NIHL and its results

showed a statistically significant improvement on hearing thresholds. Furthermore, our review showed that ITSI does not seem to be effective in the treatment of tinnitus.

Given the low adverse effects rates of ITSI therapy and good patient tolerability, local delivery should be considered as an interesting adjunct to the therapy of the idiopathic sudden sensorineural hearing loss and noise induced hearing loss. However, despite the number of published studies on this delivery modality, it is yet difficult to recommend a specific treatment protocols for these inner ear conditions. A tailored approach based on patient's tolerance and response seems most appropriate. The inner ear diseases presented in this study are all thought arise from an inflammatory or an autoimmune process. Therefore, expect a dose–response relationship with ITSI therapy and future local delivery devices offering increased and prolonged release might improve recovery rates.

Acknowlegments No funding received for this work from any of the following organizations: NIH, Welcome Trust, HHMI or other.

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