

Intratympanic Steroids for Inner Ear Disorders: A Review

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Key Words

Intratympanic steroids · Deafness · Inner ear therapy · Ménière's disease · Sudden sensorineural hearing loss

Abstract

Background/Aim: The use of intratympanic steroids (ITS) has proliferated over the past 10–15 years to include treatments for inner ear disorders, like Ménière's Disease (MD) and sudden sensorineural hearing loss (SSNHL). The aim of this study was to review the clinical trials of ITS for inner ear disorders. **Methods:** PubMed and Ovid Medline databases were searched from 1966 to present for clinical trials on ITS in the treatment of MD and SSNHL. Studies were evaluated based on comparability and internal and external validity. **Results:** Thirty-eight studies were identified in total, 13 studies on MD and 25 studies on SSNHL. Most studies lacked placebo controls. Only 3 studies were double-blinded randomized prospective trials. Overall, there were heterogeneous steroid doses, treatment protocols, previous treatments, and definitions of disease and improvement. **Conclusion:** There are no good studies on ITS that meet the criteria of comparability, internal validity, and external validity. It is difficult to compare studies due to the heterogeneous nature of the data. More rigorously designed studies are required to determine the efficacy of this treatment, the optimal steroid to use, and the best treatment regimen.

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Introduction

The use of intratympanic steroids (ITS) for inner ear disorders has proliferated over the past 10–15 years to include treatment of sudden sensorineural hearing loss (SSNHL), Ménière's disease (MD) and autoimmune ear disorders [1]. This new tool in an otolaryngologist's armamentarium has allowed us to offer another treatment option to patients.

There are several advantages to using ITS. First, this is an office procedure that can be done under local anesthesia, and it is usually well tolerated. Second, it avoids the side effects of systemic steroids, like immune suppression, weight gain, osteoporosis, avascular necrosis of the hip, mood swings, and skin and endocrine changes. Although the mechanism of action of ITS is unclear at this time, it is believed to have little systemic absorption [2]. ITS enter the inner ear through the round window membrane [1], and typically travel down the eustachian tube to the gut. Third, ITS are directed locally, only towards the affected ear. Fourth, ITS produce significantly higher inner ear drug levels of steroids as compared to the systemic routes of administration [3, 4]. Fifth, this is relatively low cost in comparison to surgical management. Conversely, there are also some potential disadvantages to ITS, the most common of which is the pain and transient vertigo associated with the injections. There are also very low risks of persistent tympanic membrane perfora-

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tion, otitis media, otomycosis, mastoiditis, and potential for further hearing loss [5].

In weighing up the advantages and disadvantages of ITS, it is important for clinicians to understand the evidence behind this new treatment option. Our goal was to conduct a literature review of the clinical trials investigating ITS therapy for inner ear disorders.

Methods

We used the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) proposed guidelines for reporting the methods [6]. Although this literature review is not a meta-analysis, certain aspects of the MOOSE guidelines are applicable. One author (A.H.) reviewed all the studies. Ovid Medline and PubMed databases were searched for clinical trials on ITS from 1966 to January 1, 2009. We used the following search terms: labyrinth diseases, inner ear disease, steroids, intratympanic, Ménière's disease, sensorineural hearing loss, sudden hearing loss. The special feature 'explosion' was used with these key words in Ovid Medline. Additional studies were identified by hand searching the references of identified studies. The author was not blinded to the authors, institutions, journals of publication, or study results. In a study of blinding authors of meta-analyses, masking made no difference to the summary odds ratio [7]. Authors of the previous studies were contacted for any missing information, and 3 authors responded to our questions. We excluded articles that were published in a language other than English, abstracts, and unpublished studies. We selected clinical trials investigating ITS therapy for inner ear disorders (MD and SSNHL). There was not enough data to examine the indication of autoimmune ear disorders. The evaluation criteria of these clinical studies were similar to the recent review of Alles et al. [8]:

Comparability. Were the patients receiving the drug of study compared to a reference control group (e.g. placebo)?

Internal Validity. What was the level of evidence for the study? We used the Oxford Centre for Evidence-Based Medicine guidelines [9], which grades studies from levels 1–5. Level 1 is the highest level of evidence (e.g. randomized controlled trial); level 5 is the lowest level of evidence (e.g. expert opinion). Was the study prospective or retrospective? Which therapy was evaluated?

External Validity. Which criteria were used to confirm the diagnosis of SSNHL or MD? How long was the follow-up? Which criteria were used to evaluate the results?

Results

Thirty-eight studies were identified in total, 13 studies on MD and 25 studies on SSNHL. Table 1 lists the clinical trials for MD. Table 2 lists the study design for the SSNHL clinical trials. Table 3 lists the results for the SSNHL clinical trials. A meta-analysis of the existing literature was not performed due to the heterogeneous nature of the

data. Studies used different steroid doses, treatment protocols, definitions of SSNHL and MD, definitions of outcome criteria, and timeframes for follow-up.

Comparability: Were the Patients Receiving the Drug of Study Compared to a Reference Control Group (e.g. Placebo)?

The natural history of MD is a fluctuating course towards the resolution of symptoms. A longitudinal follow-up of MD patients found that 50% had complete vertigo resolution and 28% had partial vertigo resolution after 14 years from diagnosis [45]. Silverstein et al. [46] studied 50 patients who refused surgery for MD. Fifty-seven percent had vertigo resolution in 2 years and 71% had vertigo resolution in 8.3 years. Thus, the importance of a placebo control cannot be overemphasized in MD.

In reviewing the MD studies in table 1, only 4 studies had controls [10–13]. Only 1 study had a control that was a placebo in which patients did not receive any other therapy [10]. In the study of Sennaroğlu et al. [12], the controls were a group of intratympanic gentamicin patients and endolymphatic sac patients. The study of Silverstein et al. [11] was a cross-over study; thus, all patients received ITS, but in a randomized order. Therefore, the final results could be a carry-over effect from the first treatment. The control in the study of Itoh and Sakata [13] was lidocaine.

In reviewing the SSNHL studies in tables 2 and 3, 13 studies had controls [4, 23–34]; however, the controls were all some form of systemic steroids. None of the studies had placebo as their control. Systemic steroids have been deemed by some authors to be the gold standard treatment for SSNHL [47, 48]. The ethics of withholding a gold-standard treatment for research purposes is questionable; thus, it is difficult to design a study with placebo as the control. The reported spontaneous recovery rate of SSNHL ranges from 32 to 70% [49, 50]. Unfortunately, this statistic confounds our interpretation of these studies.

Internal Validity: What Was the Level of Evidence for the Study? Prospective or Retrospective? Which Therapy Was Evaluated?

Among the 13 MD trials, only 2 were level one evidence, 1 was level two, 1 was level three, and the remaining 9 were level four. The 2 level one studies were both double-blinded randomized prospective trials that used dexamethasone as the IT steroid [10, 11]. The sample sizes for both these studies were small: 22 [10] and 20 [11]. These 2 studies had diametrically opposite conclusions.

Table 1. Clinical trials on Ménière's disease

Study (first author)	Level of evidence	Dex. mg/ml	Treatment protocol	AAO-HNS 1995-defined MD	Outcome criteria	Follow-up	Sample size	HL %	Vertigo %	Tinnitus %	Aural fullness %
Garduño-Aaya, 2005 [10]	1	4	5 consecutive daily injections	+	AAO-HNS 1995 ^a , Dizziness Handicap Inventory, Tinnitus Handicap Inventory	2 years	11 ITS 11 placebo	35 10	82 57	48 20	48 20
Silverstein, 1998 [11]	1	8	3 days of injections, 3 weeks later cross-over	+	AAO-HNS 1995 ^a , Tinnitus Handicap Inventory, Florida Ear and Sinus Center tinnitus interview, modified AAO tinnitus scale	up to 13 weeks	20 (cross-over study)	n.s.	n/a	n.s.	n.s.
Sennaroglu, 2001 [12]	2	1	5 drops every 2 days for 3 months	-	AAO-HNS 1985 ^b ; hearing loss: improvement in hearing; vertigo: complete/substantial control; tinnitus and aural fullness: decrease or total disappearance	18 months	24 ITS 16 ITG 25 ESD	16 30 12	72 75 52	50 21 20	75 50 60
Itoh and Sakata, 1991 [13]	3	2	4-5 injections at intervals of 1-2 weeks	-	AAO-HNS 1985 ^{b,c}	n.a.	61 ITS 75 lidocaine	poor poor	80 81	74 70	n.a. n.a.
Boles-Auirre, 2007 [14]	4	12	injection as required at 1- to 4-month intervals	+	'survival' - did not seek other ablative treatment	2 years	129	n.a.	91	n.a.	n.a.
Barrs, 2004 [15]	4	10	injection 2 days in a row, weekly for 3 weeks, for a total of 5 injections in 1 month	+	complete control of vertigo; ≥15 dB pure tone average or ≥20% speech discrimination score	2 years	34	n = 1, n.s.	47 with ≥1 injection; 24 at 2 years	n.a.	n.a.
Hillman, 2003 [16]	4	16	1 injection every week for 3 weeks	+	AAO-HNS 1995 ^a	up to 20 months	50	40	n.a.	n.a.	n.a.
Barrs, 2001 [17]	4	4	injections twice a day, then weekly for 3 weeks	+	AAO-HNS 1995 ^a	3, 6, 12 months	21	n.s.	52 at 3 months 43 at 6 months	n.a.	n.a.
Sennaroglu, 1999 [18]	4	1	5 drops every 2 days for 3 months	-	AAO-HNS 1985 ^b same as previous paper [12]	3 months	24	17	72	42	75
Arriaga, 1998 [19]	4	8	1 injection	n.a.	AAO-HNS 1995 ^a	≥1 month	15	33	n.a.	n.a.	n.a.
Shea, 1997 [20]	4	16	1 injection + i.v. dex. for 3 days + p.o. dex. for 30-90 days	+	AAO-HNS 1995 ^a	≥2 years	48	35.4	63.4	n.a.	n.a.
Shea, 1996 [21]	4	16	1 injection + i.v. dex. for 3 days + p.o. dex. for 1 month	-	hearing loss: improvement, vertigo: absence of dizzy spells; tinnitus: decrease; aural fullness: reduction	1 year	28	67.9	96.4 at 1 year, 76 at 2 years	82.10	89.30
Silverstein, 1996 [22]	4	MP (80 mg/ml), dex. eye solution (1 mg/ml), or i.v. dex. (4 mg/ml)	≥2 injections, 2 drops twice per day instillation, or injections every Monday, Wednesday, Friday for 3-4 weeks	n.a.	AAO-HNS 1995 ^a	3, 6, 12 months	46 (22 MD)	41	n.a.	47	n.a.

AAO-HNS = American Academy of Otolaryngology-Head and Neck Surgery; ESD = endolymphatic sac decompression; ITG = intratympanic gentamicin; MP = methylprednisolone.

^a 1995 AAO-HNS criteria for outcome [48]. Vertigo: class A (complete control). Hearing: significant change is a ≥10-dB change in pure tone audiogram with pure tone averages at 0.5, 1, 2, and 3 kHz or ≥15% change in speech discrimination score.

^b 1985 AAO-HNS criteria for outcome. Numeric value = average number of definitive spells/month in 24-month period after therapy/average number of definitive spells/month in 6-month period before therapy × 100. Scoring: 0 = complete control of definitive spells; 1-40 = substantial control of definitive spells; 41-80 = limited control of definitive spells; 81-120 = insignificant control of definitive spells; ≥121 = worse control of definitive spells. Vertigo: complete and substantial control.

^c AAO 1972 and Sakata's criteria were also used in this paper in addition to the 1985 AAO-HNS criteria for outcome; however, no significant differences were found between these 3 criteria, so only the 1985 AAO-HNS criteria were quoted in this review.

Table 2. Study design of clinical trials on SSNHL

First author	Level of evidence	Definition of SSNHL	Study type	Steroid and dose, mg/ml	Previous or concurrent treatment other than ITS	Treatment protocol
Battaglia, 2008 [23]	1	≥20 dB of unilateral SSNHL in at least 3 freq. occurring w/in 3 days	initial	dex. (12)	prednisone p.o. concurrently for 14 days	3 weekly injections
Ahn, 2008 [24]	1	SSNHL 30 dB in 3 contiguous freq. over several days	initial	dex. (5)	MP p.o. concurrently for 14 days	3 injections (days 1, 3, 5)
Xenellis, 2006 [25]	1	SSNHL at least 30 dB in 3 contiguous freq. in ≤3 days	salvage	MP (80 mg/2 ml)	prednisolone i.v. for 10 days; acyclovir	4 injections over 15 days
Ho, 2004 [26]	1	unilateral severe or profound idiopathic SSNHL over 24 h	salvage	dex (4)	MP p.o. for 10 days, vasodilators, vit. B, benzodiazepines for 10 days, carbogen inhalation for 5 days	1 injection/week for 3 weeks
Kilic, 2007 [27]	2	sudden onset HL history	salvage	MP (62.5)	MP i.v. for 3 days, prednisolone p.o. for 21 days	5 injections at 3-day intervals
Plaza, 2007 [28]	2	unilateral deafness, w/in 3 days, ≥30 dB at 3 consecutive freq.	salvage	MP (20)	MP (120 mg) i.v. for 5 days	3 weekly injections
Van Wijck, 2007 [29]	2	SSNHL ≥30 dB at 3 subsequent 1-octave steps in freq. w/in 3 days	salvage	MP (62.5)	MP i.v. for 1 day, then MP p.o. for 9 days; naftidrofuryl, diazepam, LMWH	microcatheter – 3 drops b.i.d. for 3 weeks
Kakehata, 2006 [30]	2	n.a. ¹	initial	dex. (4)	dex. i.v. for 10 days in comparative group	1 injection/day for 8 days
Lauterman, 2005 [31]	2	monoaural sudden idiopathic profound HL	initial	MP (32)	concurrent prednisolone i.v. for 10 days + rheologic infusion therapy	5 injections on 5 consecutive days via ventilation tube
Roebuck, 2006 [32]	3	SSNHL ≥20 dB over 3 freq. in ≤72 h	salvage	dex. (24)	Medrol dosepak for 5–7 days before, controls received prednisolone for 20 days	1 injection
Choung, 2006 [33]	3	idiopathic SSNHL	salvage	dex. (5)	prednisolone p.o. for 10 days and other medication (gingko, antiviral, hydrochlorothiazide)	2 injections/week for 2 weeks
Haynes, 2006 [5]	3	decline over 3 days, ≥3 freq. affected by at least 30 dB	salvage	dex. (24)	systemic steroids (85% antiviral, 27% diuretics)	1 injection
Plontke, 2005 [34]	3	SSNHL w/in 72h	salvage	MP (40) or dex. (4)	prednisolone i.v. for 10 days, pentoxifylline for 10 days	RW microcatheter MP (10 µl/h) or dex. (5 µl/h) for 4 weeks
Dallan, 2006 [35]	4	≥20 dB SSNHL over at least 3 contiguous freq. occurring w/in 3 days	salvage	MP (40)	MP i.v. for 10 days + pentoxifylline for 10 days; 2 patients received LMWH	1 injection
Banerjee, 2005 [36]	4	SSNHL at least 30 dB in 3 contiguous freq. in ≤3 days	initial or salvage	MP (40) or dex. (4)	depends on outside referring ENT specialist	2 injections/week until plateau in hearing; average 3.8 (2–11)
Slattery, 2005 [37]	4	SSNHL at least 30 dB in 3 contiguous freq. over 24 h	salvage	MP (62.5)	prednisone for 14 days	4 injections, 4 days apart, within 2 wks
Herr, 2005 [38]	4	>20 dB SSNHL at any freq. w/in 72h	salvage	dex. (10) or MP (62.5)	high-dose systemic steroids	microwick dex. (3 drops /day) for 1 week; if not better, RW microcatheter infusion MP or dex. (10 µl/h for 10–13 days)
Battista, 2005 [39]	4	PTA >90 dB	initial	dex. (24)	concurrent MP p.o. for 11 days	4 injections over 2 weeks
Gouveris, 2005 [40]	4	HL w/in >3 days, >30 db SSNHL	salvage	dex. (8)	prednisone i.v. and vasoactive agents (pentoxifylline and HES)	average 2.7 injections (range 1–7) every 2 days

Table 2 (continued)

First author	Level of evidence	Definition of SSNHL	Study type	Steroid and dose, mg/ml	Previous or concurrent treatment other than ITS	Treatment protocol
Lefebvre, 2002 [41]	4	SSNHL >30 dB for 3 consecutive 1-octave freq. steps w/in 24 h	salvage	MP (62.5)	MP i.v. for 1 day, then MP p.o. for 15 days; carbogen, naphhydrofuryl, diazepam, LMWH	RW microcatheter infusion 10 µl/h for 8–10 days
Chandrasekhar, 2001 [42]	4	change in hearing w/in 12 h to 3 days ¹	salvage	dex. (4)	'other meds', suboptimal doses of either Medrol dosepak or p.o. prednisone, or no treatment	1–15 injections
Gianoli, 2001 [43]	4	>20 dB SSNHL in ≥3 contiguous audiometric freq. occurring w/in 3 days	salvage	dex. (25) or MP (125)	high-dose systemic steroids (prednisone 1 mg/kg/day for min. 1 week or equivalent)	4 injections over 10–14 days
Kopke, 2001 [44]	4	HL on awakening or w/in 72 h	salvage or initial	MP (62.5)	prednisone p.o. for 2 weeks	RW microcatheter infusion 10 µl/h for 14 days
Parnes, 1999 [3]	4	n.a.	salvage	MP (40) or dex	'conventional medical measures' depending on referring physician	2–29 injections
Silverstein, 1996 [22]	4	n.a.	salvage	MP (80), dex. eye solution (1), or i.v. dex. (4)	'conventional treatment'	every Monday, Wednesday and Friday for 3–4 weeks

PTA = Pure tone average; HL = hearing loss; RW = round window; LMWH = low molecular weight heparin; HES = hydroxyethyl starch.
¹ Accuracy of data cannot be confirmed.

Garduno-Anaya et al. [10] reported that ITS treatment of MD patients resulted in an 82% complete vertigo control rate over placebo (57%). There was also a subjective improvement in tinnitus (48%), hearing loss (35%), and aural fullness (48%) compared with 20, 10, and 20%, respectively, in the placebo group. Silverstein et al. [11] reported that ITS treatment of MD patients showed no benefit over placebo for the treatment of hearing loss or tinnitus. As mentioned before, this was a cross-over study; thus, the final results could be a carry-over effect from the first treatment. Only 2 other studies were prospective [11, 17], while the remaining studies were retrospective. For the purposes of this review, let us define a positive study as one that concluded that steroids were beneficial for the treatment of MD. A negative study is one that concluded that steroids were not beneficial, but not harmful either, for the treatment of MD. Among the 13 MD studies, 8 were positive [10, 12–14, 18, 20–22] and 5 were negative [11, 15–17, 19].

Among the 25 SSNHL studies, 4 were level one evidence, 5 were level two, 4 were level three, and the remaining 12 were level four. Among the SSNHL studies, the Battaglia et al. [23] study was the only double-blinded study. Their goal was to evaluate the combination therapy of ITS + oral steroids. One group received ITS + oral pla-

cebo pills. A second group received oral steroids + intratympanic saline. A third group received ITS + oral steroids. The Battaglia et al. [23] study showed that patients treated with the combination of ITS + oral steroids had a higher likelihood of hearing recovery than those treated with oral steroids alone. There are some weaknesses to this study, as described in a Letter to the Editor from Rauch and Reda [51]. The first weakness was the small sample sizes of 17, 18 and 16 in each group. Their original sample size calculation was 141 patients in each group for a total of 423 patients. Their revised sample size calculation was 54 patients per group, but allowing for a 15% dropout rate, they estimated 64 patients per group. Their actual sample size is much smaller than their sample size calculations. The second weakness was that their primary outcome measure of improved pure-tone average showed no significant difference between the 3 groups. Thus, by initial design, their study outcome was negative and there may be flaws with the reassignment of their outcome criteria. Their secondary outcome measure of proportion of subjects showing improved pure tone average was significant. It showed that combination therapy was significantly better than ITS alone. Despite these weaknesses, this was a rigorously designed elegant study of level one evidence.

Table 3. Results of clinical trials on SSNHL

First author	Definition of improvement	Sample size	Hearing loss improvement	Follow-up	Pos./neg.
Battaglia, 2008 [23]	15 dB PTA	17 ITS 18 p.o. prednisone 16 ITS + p.o. prednisone	31 dB PTA, 36% SDS, 12/17 patients 21 dB PTA, 20% SDS, 8/18 patients 40 dB PTA, 44% SDS, 14/16 patients	4 weeks	+
Ahn, 2008 [24]	>15 dB gain + final hearing <45 dB	60 ITS 60 controls	73.3% 70%	3 months	-
Xenellis, 2006 [25]	10 dB PTA	19 ITS 18 controls	47% 0%	1.5 months	+
Ho, 2004 [26]	30 dB PTA	15 ITS 14 controls	53% 7.1%	2.6 ± 1.6 months (ITS) 2.3 ± 1.7 months (control)	+
Kilic, 2007 [27]	10 dB PTA	19 ITS 18 controls	73.6% 0%	24.9 (7–30) months	+
Plaza, 2007 [28]	15 dB PTA, 15% SDS	9 ITS 9 controls	55% (44 dB PTA) 0% (2.3 dB PTA)	6 months	+
Van Wijck, 2007 [29]	10 dB PTA	12 ITS 12 controls	66% (24.5 dB PTA) 8.3% (1.1 dB PTA)	30 days	+
Kakehata, 2006 [30]	complete recovery, or at least 30 dB	10 ITS 21 controls	70% 62%	10 days ¹	+
Lauterman, 2005 [31]	calculated PTA gains; full, partial and none recovery scales	13 ITS 14 controls	15 dB PTA 11 dB PTA	10 days ¹	-
Roebuck, 2006 [32]	10 dB PTA, 15% SDS	31 ITS 30 controls	30% (PTA criteria); 38.7% (SDS criteria) 17% (PTA criteria); 10% (SDS criteria)	4 weeks	+
Choung, 2006 [33]	10 dB PTA, 15% SDS	33 ITS 33 controls	39.4% 6.1%	8 weeks	+
Haynes, 2006 [5]	20 dB PTA, 20% SDS	40	27.50%	271 (22–1460) days control	+
Plonke, 2005 [34]	calculated PTA improvement	23 ITS 23 controls	15 dB PTA 9 dB PTA	1 year	+
Dallan, 2006 [35]	15 dB PTA	8	75%	6 months	+
Banerjee, 2005 [36]	calculated dB and % SDS improvement	26	27.2 ± 5.7 dB PTA 25.4 ± 6.2% SDS	5.4 (1–52) months	+
Slattery, 2005 [37]	improvement in treated ear to 50% of baseline difference between the treated and untreated ear; 10 dB PTA, 12% SDS	20	5% improved to near-normal hearing 55% significant improvement in PTA and SDS	3 months	+
Herr, 2005 [38]	10 dB PTA, 20% SDS	17	53%	6 weeks	+
Battista, 2005 [39]	complete = final PTA w/in 10 dB of baseline; partial = final PTA w/in >50% of hearing	25	8% full, 12% partial	6 months	-
Gouveris, 2005 [40]	complete recovery: w/in 10 dB of unaffected ear; partial recovery: >10 dB improvement; no recovery: <10 dB improvement	9 high freq. ISSHL; 10 sudden deafness or profound SHL; 21 pantonal ISSHL	high freq: 33.3% CR, 39.1% PR, 28.6% NR pantonal: 0% CR, 31% PR, 55.5% NR	last audio test at the end of intratympanic steroid therapy	+
Lefebvre, 2002 [41]	16.25–25 dB PTA	6	100%	~5 days after completion of treatment	+
Chandrasekhar, 2001 [42]	increase in SDS, decrease in PTA	10 (11 ears)	73%	3 weeks to 4 years	+

Table 3 (continued)

First author	Definition of improvement	Sample size	Hearing loss improvement	Follow-up	Pos./neg.
Gianoli, 2001 [43]	10 dB PTA, 10% SDS	23	44% improved in PTA 21% improved in SDS	1–2 weeks	+
Kopke, 2001 [44]	10 dB PTA, 15% SDS	6 (early group, within 6 weeks of SSNHL) 3 (late group, >6 weeks)	83% (5/6 early) 0% (late group)	n/a ¹	+
Parnes, 1999 [3]	'normal thresholds', 'serviceable hearing'	37 (20 dex., 17 MP)	13/37 = 35.1% overall 7/13 = 54% SSNHL	n/a	+
Silverstein, 1996 [22]	10 dB PTA, 15% SDS	46 (8 SSNHL)	41%	12 months	+

SNHL = Sensorineural hearing loss; SSNHL = sudden sensorineural hearing loss; HL = hearing loss; PTA = pure tone average; SDS = speech discrimination score; CR = complete recovery; PR = partial recovery; NR = no recovery.

¹ Accuracy of data cannot be confirmed.

We consider a positive SSNHL study to be one which demonstrated significant overall hearing improvement following ITS compared to pretreatment hearing, though amongst the published studies there is no uniform definition of improvement. The 4 level one evidence studies were all prospective randomized studies [23–26]. Three of these studies were positive [23, 25, 26], while the fourth was negative [24]. The sample sizes for these studies varied: 120 [24], 51 [23], 37 [25], and 29 [26]. Among the 25 SSNHL studies, 22 were positive and 3 were negative.

To answer the question 'Which therapy was evaluated?', tables 1 and 2 display the heterogeneous nature of the steroids used and treatment protocols. Dexamethasone and methylprednisolone were used in different concentrations. Parnes et al [3] conducted an animal study on guinea pigs to evaluate the inner ear fluid pharmacokinetics of intratympanic dexamethasone, hydrocortisone, and methylprednisolone. Methylprednisolone had the highest concentration for the longest duration in both endolymph and perilymph. Unfortunately, clinical application of this drug can cause burning discomfort in the ear and throat in some patients. Therefore, lidocaine is added by some investigators to relieve these side effects [3]. Currently, there is no treatment protocol (duration, frequency, or amount) that is deemed to be superior. Some studies examined ITS for salvage therapy; others examined ITS for initial therapy of SSNHL. Previous treatments that patients had received before initiating ITS were very heterogeneous and unclear in some studies. The interval between the sudden hearing loss and start of treatment, which is a known variable to affect recovery, was also heterogeneous among the studies.

A previous report by Alles et al. [8] reviewed the different methods of administering ITS. In most studies, steroids were administered by transtympanic injection under local anesthesia [3, 16, 18, 20–22]. Some performed a second myringotomy to allow air to escape [19, 20, 39]. Some injected the steroids onto absorbing material in the round window niche [20, 21]. Some used inner ear medical delivery devices, like the Round Window Microcatheter or the Silverstein Microwick [42]. Some inserted a ventilation tube in the tympanic membrane through which steroids were delivered [12, 17]. None of the techniques has been shown to be superior. All of these variables hinder our ability to compare these studies.

External Validity: Which Criteria Were Used to Confirm the Diagnosis of MD or SSNHL? How Long Was the Follow-Up? Which Criteria Were Used to Evaluate the Results?

The Committee on Hearing and Equilibrium of the AAO-HNS has established criteria for the diagnosis of MD [52]. This committee also recommends comparing the 6-month period before treatment to the period between 18 and 24 months after treatment; thus, a 2-year follow-up is recommended. To evaluate results, the 1995 AAO-HNS criteria for a clinically significant change in hearing is 10 dB or more in pure tone average or 15% or more of change in word recognition score. Guidelines are also published by the AAO-HNS for vertigo and functional level. In reviewing table 1, the majority of papers used the 1995 AAO-HNS definition of MD as an inclusion criteria [10, 11, 14–17, 20]. One paper used the Shea staging system [21]. Two papers used the symptom complex of ep-

isodic vertigo, aural fullness, tinnitus, and hearing loss [12, 18]. Three papers did not specify their diagnostic criteria for MD [13, 19, 22]. For follow-up length, the more recent papers ensured 2 years of follow-up [10, 14, 15, 20]. The other papers ranged in follow-ups from as short as 1 month [19] to up to 20 months [16]. For evaluating the results, most papers used the 1995 version [10, 11, 16, 17, 19, 20, 22] or 1985 version [12, 13, 18] of the AAO-HNS guidelines. Boleas-Aguirre et al. [14] used a novel outcome criterion. They used Kaplan-Meier survival curves and defined survival as 'sufficient satisfaction with vertigo control that the subject did not wish to have subsequent ablative treatment' and failure as 'poor control and the choice to proceed to ablative treatment'. They reported a 91% acceptable vertigo control rate ('survival'). Some papers also used validated questionnaires to report results on tinnitus, dizziness, and aural fullness [10–12, 22].

The US National Institute for Deafness and Communication Disorders (NIDCD) defines SSNHL as the idiopathic loss of hearing of at least 30 dB over at least 3 contiguous test frequencies occurring within 3 days [53]. Among the SSNHL studies in table 2, only 5 of the 25 studies used the NIDCD definition of SSNHL [5, 25, 28, 29, 36]. Two studies did not mention their audiologic definition of SSNHL [3, 21]. A recent review of the randomized controlled trials on the treatment of SSNHL also found that only 2 of their 20 reviewed studies used the NIDCD definition of SSNHL [54]. Follow-up in the studies in table 3 also varied from 10 days to 24.9 months. There is no uniform definition of improvement and this also varied greatly in table 3. This heterogeneity hinders our ability to compare these studies.

Discussion

There are no good studies on ITS that meet the criteria of comparability, internal validity, and external validity. In reviewing the literature, it is difficult to interpret these studies for 4 reasons. Firstly, the data is heterogeneous with respect to steroid doses, treatment protocols, previous treatments, and definitions of disease and improvement. Secondly, the natural history of MD and SSNHL is towards spontaneous resolution. Thirdly, there is a lack of placebo controls in many of the studies. Without placebo controls, the effect of the treatment cannot be separated from the natural history of the disease. Fourthly, the sample sizes for the studies are small. The inclusion and exclusion criteria of the studies also limit the generalizability of the conclusions.

ITS is also used to treat autoimmune ear disorders, like Cogan's disease. Since these diseases are so rare, there are only case reports of using ITS to treat these patients [3, 21]. A discussion of ITS for this indication is outside the scope of this review.

This is a comprehensive systematic review of all the clinical trials to date for ITS in the treatment of MD and SSNHL. There are 2 limitations to this review. Firstly, we reviewed studies published only in the English language. This may bias the review towards practices in North America and Europe. Secondly, we decided to include retrospective studies. We believe that retrospective studies also impact clinical practice. If we were to limit our review to prospective double-blinded randomized controlled trials, then we could only include 2 MD studies and 1 SSNHL study [10, 11, 23]. We are limited by the quality of the studies in this field.

More research needs to be performed to study the efficacy and optimal steroid/treatment protocols, while using the uniform and widely accepted definitions of disease and improvement. Studies should be randomized and controlled to eliminate selection biases and the placebo effect. Currently, the National Institutes of Health is conducting a multicentre prospective double-blinded randomized controlled trial on the use of oral versus ITS corticosteroids for the initial treatment of SSNHL (www.suddendeafness.org). More such rigorously designed studies will help to advance our understanding of ITS treatment. However this study, like all before it, uses systemic steroids against which IT treatment outcomes are measured. As pointed out by Conlin and Parnes [55] in their meta-analysis, systemic steroids cannot be considered the gold-standard treatment of SSNHL, given the severe limitations of the landmark study [48] supporting their use.

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