Eur Arch Otorhinolaryngol (2015) 272:2777–2782
DOI 10.1007/s00405-014-3288-8

OTOLOGY

Intratympanic steroids as a salvage treatment for sudden sensorineural hearing loss? A meta-analysis

Jia Hui Ng · Roger Chun Man Ho · Crystal Shuk Jin Cheong · Adele Ng · Heng Wai Yuen · Raymond Yeow Seng Ngo

Received: 6 July 2014 / Accepted: 7 September 2014 / Published online: 13 September 2014

Abstract Sudden sensorineural hearing loss is typically treated with systemic steroids. The aim of this meta-analysis was to evaluate the efficacy of salvage intratympanic steroid treatment in patients who have initial treatment failure with systemic steroids. A MEDLINE literature search was performed, supported by searches of Web of Science, Biosis, and Science Direct. Articles of all languages were included. Selection of relevant publications was conducted independently by three authors. Only randomized controlled trials were considered. In one arm of the studies, the patients received salvage intratympanic steroids. In the other arm, patients did not receive further treatment. The standard difference in mean (SDM) amount of improvement in hearing threshold between patients who did and did not receive salvage intratympanic steroids was calculated. From an initial 184 studies found via the search strategy, 5 studies met inclusion criteria and were included. There was a statistically significant greater reduction in hearing threshold on pure-tone audiometry in patients who received salvage intratympanic steroids than in those who did not (SDM = −0.401, $p = 0.005$). Subgroup analysis showed that administration by intratympanic injection (SDM = −0.375, $p = 0.013$) rather than a round window catheter (SDM = −0.629, $p = 0.160$) yielded significant improvement in outcome. The usage of dexamethasone yielded better outcomes (SDM = −0.379, $p = 0.039$) than the use of methylprednisolone (SDM = −0.459, $p = 0.187$). No serious side effect of treatment was reported. In patients who have failed initial treatment with systemic steroids, additional treatment with salvage intratympanic dexamethasone injections demonstrate a statistically significant reduction in the hearing thresholds as compared to controls.

Keywords Sudden sensorineural hearing loss · Intratympanic · Steroids · Dexamethasone · Methylprednisolone · Injections · Salvage · Treatment

J. H. Ng
Department of Otolaryngology, Singhealth, Singapore, Singapore

R. C. M. Ho
Department of Psychological Medicine, National University Hospital, Singapore, Singapore

C. S. J. Cheong · R. Y. S. Ngo (✉)
Department of Otolaryngology, National University Hospital, 5 Lower Kent Ridge Road, 119074 Singapore, Singapore
e-mail: entnysr@nus.edu.sg

A. Ng
Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

H. W. Yuen
Department of Otolaryngology, Changi General Hospital, Singapore, Singapore

Introduction

Sudden sensorineural hearing loss (SSNHL) is an acute, unexplained hearing loss of at least 30 dB over at least three contiguous frequencies occurring within 72 h. A variety of treatments have been described for this condition, including vasoactive substances, hyperbaric oxygen, antivirals, vitamins, and even zinc [1–16]. However, ever since the 1980s when two double-blind trials [17, 18] showed efficacy of corticosteroids in the treatment of this condition, they have become the most commonly used agents in most centers worldwide, albeit with controversy.

The systemic routes of administration (oral or intravenous) are often used.

There are patients who do not respond sufficiently to this mode of treatment. For this group of patients, some studies have demonstrated benefit in the use of salvage intratympanic steroids [19, 20], whereas others have demonstrated no additional benefit [21–24]. In view of the lack of agreement of multiple retrospective and prospective studies, some authors have conducted randomized controlled trials (RCTs) on this subject. However, these RCTs are limited by their inability to obtain a sufficiently large sample size. To date, there has been no meta-analysis done on RCTs to investigate the efficacy of salvage intratympanic steroids. The aim of this study was to pool and perform a meta-analysis on all relevant RCTs done on this topic, to (1) evaluate the efficacy of salvage intratympanic steroid injections in treating SSNHL; and (2) determine the type of steroid, dose of steroid, and method of administration that has been used with most success.

Methodology

Search strategy and selection criteria

A MEDLINE literature search was performed using a combination of the low-specificity keywords "hearing loss", "steroid", and "intratympanic", supported by searches of Web of Science, Biosis, and Science Direct, to yield all possibly relevant results. The search was completed in May 2014. Articles of all languages were included.

We sought all RCTs that studied the efficacy of salvage intratympanic steroids in patients with SSNHL who have failed systemic steroid treatment. All RCTs fulfilling the following criteria were included: (1) conduct of human studies involving subjects with SSNHL who have failed systemic steroid treatment; (2) presence of a control arm (where no further treatment was prescribed) and a treatment arm (where salvage intratympanic steroids were given); (3) the average hearing threshold of each arm of the study was reported at the start and end of the treatment/observation period; (4) steroid treatment regimen was described.

Studies were excluded if they had incomplete reporting of pure-tone audiometry results pre- or post-intervention as this information was needed to calculate effect size. Attempts to obtain the required information from the authors were made, and these studies were only excluded if these attempts were unsuccessful.

All articles were de-identified (blinded title, authors, journal name, and year of publication) before selection. Selection of relevant publications was conducted independently by three authors, and any disagreements were resolved through discussions. The following information was extracted from each article: sample size of each study arm, mean age of the study group, gender distribution of the study group, type of steroid used, method of administering steroids, dose of steroid used, duration of therapy in treatment arm, and finally, pure-tone audiometry threshold pre- and post-study.

Statistical analysis

All statistical analyses were performed with Comprehensive Meta-Analysis Version 2.0, developed for support in meta-analysis. Meta-analysis of change scores using the random-effects model was performed. The random-effects model was used because it takes into account both variation caused by sampling error and also random variation of the underlying effect sizes between studies. A fixed-effect model would produce a confidence interval that may be artificially narrow as it only reflects the random variation within each trial, but not the potential heterogeneity between trials [25, 26]. Change in pure-tone audiometry scores between patients who did and did not receive salvage intratympanic steroids were calculated using a standardized mean difference (SMD) [27], together with its confidence interval and p value. Significant difference was set at $p < 0.05$ for all analyses. Tests of heterogeneity were conducted with the Q statistic that is distributed as a χ^2 variate under the assumption of homogeneity of effect sizes. Between-study heterogeneity was assessed with the I^2 statistic, which describes the percentage of variability among effect estimates beyond that expected by chance [28]. As a reference, I^2 values of 25 % were considered low, 50 % moderate, and 75 % high. Subgroup analyses were performed to investigate the role of steroid type and administrative method on outcome. Funnel plots and statistical tests (Egger's linear regression method) [29] for funnel plot asymmetry were performed to test for evidence of publication bias.

Results

From the initial 184 articles found via the search strategy, 6 studies fulfilled the inclusion criteria. One study did not report relevant data to calculate effect size (Fig. 1). The five studies were published between the years 2006 and 2011. Two studies were conducted in Western countries and three were conducted in Asian countries. All studies involved 203 patients with SSNHL who have failed systemic steroid treatment. One hundred and two patients underwent further treatment with intratympanic steroids (i.e. cases) and 101 patients received no further therapy

(i.e. controls). Other characteristics of the five studies are summarized in Table 1. Data from the five studies were pooled for meta-analysis. Results showed that patients who received salvage intratympanic steroids demonstrated a statistically significant reduction in the hearing thresholds (SDM = −0.401, SE = 0.143, 95 % CI −0.68 to −0.122, $p = 0.005$) as compared to controls, reflecting a greater amount of hearing improvement. Figure 2 shows the Forest plot and the standard mean difference in reduction of hearing thresholds in patients receiving salvage intratympanic steroids versus controls. No between-study heterogeneity was found ($\tau^2 = 0.000$, $Q = 2.751$, $df = 4$, $p = 0.600$, $I^2 = 0$). As a result, meta-regression was not performed. We undertook subgroup analyses to explore the relationship between the mode of administration and type of steroid on the hearing thresholds as compared to controls (Table 2). The subgroup analysis showed that administration by injection (SDM = −0.375, $p = 0.013$) rather than a catheter (SDM = −0.629, $p = 0.160$) caused significant reduction in hearing thresholds or grater magnitude in improvement. The use of dexamethasone (SDM = −0.379, $p = 0.039$) rather than methylprednisolone (SDM = −0.459, $p = 0.187$) caused significant reduction in hearing thresholds.

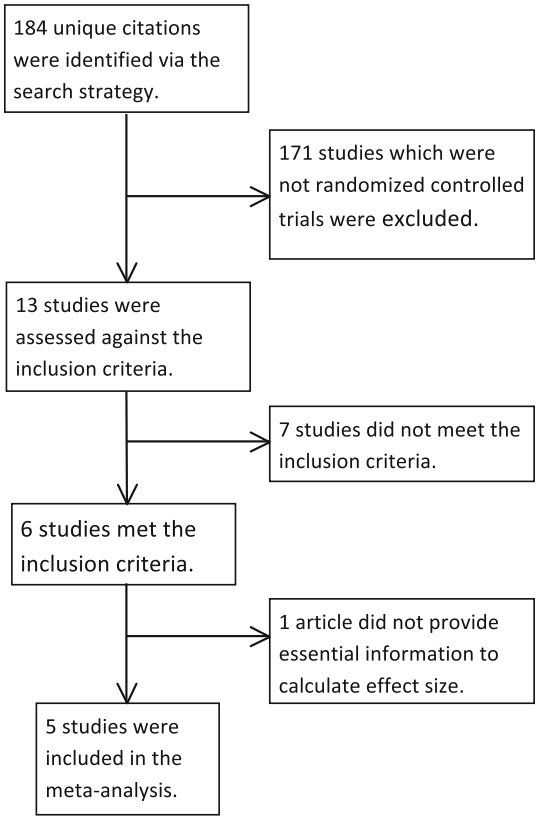

Fig. 1 Literature search profile

Side effects of intratympanic steroids were reported by four of the five studies. Minor side effects included transient dizziness, ear pain, and tinnitus. Of the 203 patients in these studies, three developed tympanic membrane perforation. Of the three, one healed spontaneously, one was treated successfully with a paper patch, and one required a myringoplasty (in this patient a round window catheter was used). No infective complications occurred. The presence of publication bias was tested by the Egger's regression method. There was no publication bias (intercept = −2.82, 95 % CI −9.71 to 4.07, $t = 1.30$, $df = 3$, $p = 0.28$).

Discussion

While there have been systemic reviews and meta-analyses previously done on the treatment of sudden sensorineural hearing loss, none has been performed specifically on RCTs evaluating the efficacy of salvage intratympanic steroids in patients who have previously failed systemic

Table 1 Study characteristics

References	Number of treated patients/ controls	Mean age (years)	Females (%)	Type of steroid	Weekly dose (mg)	Method	Days elapsed
Lee et al. [22]	21/25	44.7	60.9	Dexamethasone	4	Injection	56
Li et al. [24]	24/20	54.4	63.6	Methylprednisolone	80	Injection	56
Wu et al. [21]	27/28	47.4	67.9	Dexamethasone	4	Injection	42
Plontke et al. [23]	11/10	56.0	50.0	Dexamethasone	4	Catheter	14
Xenelli et al. [19]	19/18	50.4	55.6	Methylprednisolone	40	Injection	56

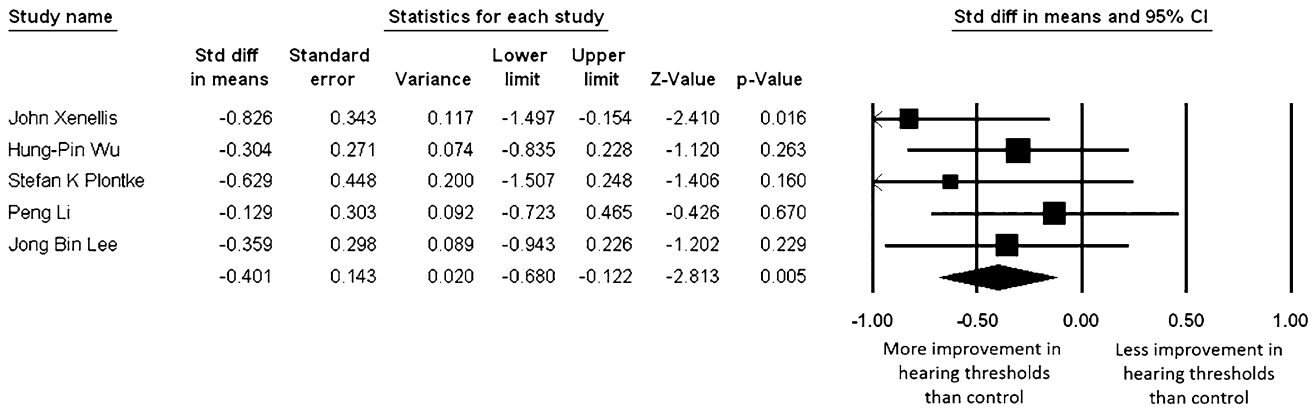

Fig. 2 Standard difference in mean amount of change in hearing threshold (reduction equals improvement) in patients receiving further steroids versus controls

Table 2 Subgroup analysis based on type of steroid and mode of administration

Subgroups	No. of studies	SDM	Standard error	*p* value
Dexamethasone used	3	−0.379	0.183	0.039
Methylprednisolone used	2	−0.459	0.348	0.184
Steroid administration: IT injection	4	−0.375	0.150	0.013
Steroid administration: round window catheter	1	−0.629	0.448	0.160

steroid treatment. A systemic review published by Spear et al. in 2011 [30] did include a section on this subject. However, a mixture of prospective studies and RCTs was used in their meta-analysis, which also did not include three randomized controlled trials [21, 22, 24] that were published in 2011, as their literature search was completed earlier. With the three additional RCTs published in 2011, it is now feasible to pool these studies with two previous RCTs [19, 23] to perform a new meta-analysis that only includes RCTs on this subject, so as to derive better evidence.

There have been previous meta-analyses done on related topics that we chose not to reexplore in this study. For example, Conlin et al. [32], Wei et al. [31], and Labus et al. [33] performed meta-analyses to evaluate the efficacy of systemic steroids versus no treatment in sudden sensorineural hearing loss. None of the three meta-analyses showed a statistically significant improvement in outcome when patients with sudden sensorineural hearing loss were treated with systemic steroids. However, the presence of individual RCTs [17, 18] that show the contrary, and the low incidence reported of adverse outcomes associated with treatment makes it a common practice for most centers in the world to treat these patients with systemic steroids nonetheless. Other studies have been performed to evaluate the efficacy of primary treatment with intratympanic steroids [34–38] or with combined systemic and intratympanic steroids [34, 39–44]. This meta-analysis did not include these studies, as it is more difficult to justify the first-line use of more invasive treatment before a trial of medical therapy.

This meta-analysis found that salvage intratympanic steroids is superior to no further treatment in patients with sudden sensorineural hearing loss who have failed systemic systemic steroids. Failure of systemic steroids was defined by the studies included as either (1) pure-tone average of worse than 30 dB; or (2) worse than 10–20 dB from the contralateral ear. Patients failing systemic steroid therapy by this criteria are therefore ideal candidates to be considered for intratympanic steroid therapy. Subgroup analysis showed that administration of dexamethasone via intratympanic injections yields the best outcomes. We did not analyze the effect of duration of salvage intratympanic steroid therapy on outcomes as this was 14–15 days for all five studies. Also, apart from the one study where dexamethasone was administered continuously via a round window catheter, all studies administered the intratympanic steroid injections four times over the treatment period, at a dose of 20 mg/injection (methylprednisolone) or 1.5–2 mg/injection (dexamethasone). In all studies, intratympanic steroids were performed within 1 month of the onset of sudden sensorineural hearing loss, after systemic steroids were completed. Patients who received intratympanic injections were all instructed post-injection to keep their heads still and turned to the opposite side for 20–45 min, and to refrain from swallowing in that time. The above measures may serve as a useful guide for clinicians performing intratympanic steroid injections.

This study has several strengths. First, there was no heterogeneity and publication bias in our results. Second, as a meta-analysis of RCTs, it provides a good level of evidence that salvage intratympanic steroids are

efficacious in the treatment of refractory sudden sensorineural hearing loss. The main limitation of this meta-analysis is the small number of trials involved. This is related to the nature of the topic as only patients with refractory sudden sensorineural hearing loss are considered; the meta-analysis mentioned above performed by Spear et al. [30] also included a similar number of trials. Also, although all the studies included were randomized controlled trials, only one was blinded and placebo controlled. Although subgroup analysis found that dexamethasone rather than methylprednisolone, administered via intratympanic injections rather than a round window catheter tended to demonstrate better outcomes, we should view this result as preliminary. Although this study yielded statistical significance, the degree of clinical significance is still debatable due to the limitations mentioned above. Also, the studies included in this meta-analysis did not report the correlation statistic between pre and post-treatment audiometry scores. As such, we are unable to calculate the weighted raw mean difference in dB improvement in patients who underwent salvage intratympanic steroids. Should all five studies be assigned the same weight, patients who underwent salvage intratympanic steroids were found to have improved a mean of 10.0 dB more than patients who did not. The significance of this amount of improvement is debatable.

Salvage intratympanic steroids is currently not routinely practiced in many otology centers. Although it is acknowledged that the results of this study should be interpreted with appropriate caution, it is hoped that this study would encourage more clinicians to consider the use of this modality of treatment in patients who have failed initial systemic steroid treatment. With more widespread use of intratympanic steroids, more robust evidence may be generated of its efficacy.

Conclusion

In conclusion, this meta-analytical review provides evidence that for patients who have failed initial treatment with systemic steroids, salvage intratympanic steroid injections demonstrate statistically significant improvement and reduction in the hearing thresholds as compared to controls. The subgroup analysis showed that administration by injection rather than a catheter or the use of dexamethasone rather than methylprednisolone caused more significant reduction in hearing thresholds or grater magnitude in improvement. Clinicians may consider the use of salvage intratympanic dexamethasone injections in patients who have experienced treatment failure with systemic steroids.

Acknowledgments No financial support was received from any parties for this study.

Conflict of interest None.

References

1. Kubo T, Matsunaga T, Asai H et al (1988) Efficacy of defibrinogenation and steroid therapies on sudden deafness. Arch Otolaryngol Head Neck Surg 114:649–652
2. Byl FM (1984) Sudden hearing loss: eight years' experience and suggested prognostic table. Laryngoscope 94 Pt 1(5):647–661
3. Chandrasekhar SS (2003) Updates on methods to treat sudden hearing loss. Oper Tech Otolaryngol Head Neck Surg 14:288–292
4. Reisser CH, Weidauer H (2001) Gingko biloba extract EGb 761 or pentoxifylline for the treatment of sudden deafness: a randomized, reference-controlled, double blind study. Acta Otolaryngol 121(5):579–584
5. Ogawa K, Takei S, Inoue Y et al (2002) Effect of prostaglandin E1 on idiopathic sudden sensorineural hearing loss: a double-blind clinical study. Otol Neurotol 23(5):665–668
6. Cinamon U, Bendet E, Kronenberg J (2001) Steroids, carbogen or placebo for sudden hearing loss: a prospective double-blind study. Eur Arch Otorhinolaryngol 258(9):477–480
7. Probst R, Tschopp K, Ludin E et al (1992) A randomized, doubleblind, placebo-controlled study of dextran/pentoxifylline medication in acute acoustic trauma and sudden hearing loss. Acta Otolaryngol 112(3):435–443
8. Kronenberg J, Almagor M, Bendet E et al (1992) Vasoactive therapy versus placebo in the treatment of sudden hearing loss: a double-blind clinical study. Laryngoscope 102(1):65–68
9. Burschka MA, Hassan HA, Reineke T et al (2001) Effect of treatment with Ginkgo biloba extract EGb 761 (oral) on unilateral idiopathic sudden hearing loss in a prospective randomized double-blind study of 106 outpatients. Eur Arch Otorhinolaryngol 258(5):213–219
10. Gordin A, Goldenberg D, Golz A et al (2002) Magnesium: a new therapy for idiopathic sudden sensorineural hearing loss. Otol Neurotol 23(4):447–451
11. Nageris BI, Ulanovski D, Attias J et al (2004) Magnesium treatment for sudden hearing loss. Ann Otol Rhinol Laryngol 113(8):672–675
12. Suckfüll M (2002) Hearing Loss Study Group. Fibrinogen and LDL apheresis in treatment of sudden hearing loss: a randomized multicentre trial. Lancet 360(9348):1811–1817
13. Mann W, Beck C, Beck C (1986) Calcium antagonists in the treatment of sudden deafness. Arch Otorhinolaryngol 243(3):170–173
14. Joachims HZ, Segal J, Golz A et al (2003) Antioxidants in treatment of idiopathic sudden hearing loss. Otol Neurotol 24(4):572–575
15. Mora R, Barbieri M, Mora F et al (2003) Intravenous infusion of recombinant tissue plasminogen activator for the treatment of patients with sudden and/or chronic hearing loss. Ann Otol Rhinol Laryngol 112(8):665–670
16. Topuz E, Yigit O, Cinar U et al (2004) Should hyperbaric oxygen be added to treatment in idiopathic sudden sensorineural hearing loss? Eur Arch Otorhinolaryngol 261(7):393–396
17. Wilson WR, Byl FM, Laird N (1980) The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study. Arch Otolaryngol 106:772–776

18. Moskowitz D, Lee KJ, Smith HW (1984) Steroid use in idiopathic sudden sensorineural hearing loss. Laryngoscope 94:664–666
19. Xenellis J, Papadimitriou N, Nikolopoulos T et al (2006) Intratympanic steroid treatment in idiopathic sudden sensorineural hearing loss: a control study. Otolaryngol Head Neck Surg 134(6):940–945
20. Ho HG, Lin HC, Shu MT et al (2004) Effectiveness of intratympanic dexamethasone injection in sudden-deafness patients as salvage treatment. Laryngoscope 114(7):1184–1189
21. Wu HP, Chou YF, Yu SH et al (2011) Intratympanic steroid injections as a salvage treatment for sudden sensorineural hearing loss: a randomized, double-blind, placebo controlled study. Otol Neurotol 32(5):774–779
22. Lee JB, Choi SJ, Park K et al (2011) The efficiency of intratympanic dexamethasone injection as a sequential treatment after initial systemic steroid therapy for sudden sensorineural hearing loss. Eur Arch Otorhinolaryngol 268(6):833–839
23. Plontke SK, Löwenheim H, Mertens J et al (2009) Randomized, double blind, placebo controlled trial on the safety and efficacy of continuous intratympanic dexamethasone delivered via a round window catheter for severe to profound sudden idiopathic sensorineural hearing loss after failure of systemic therapy. Laryngoscope 119(2):359–369
24. Li P, Zeng XL, Ye J et al (2011) Intratympanic methylprednisolone improves hearing function in refractory sudden sensorineural hearing loss: a control study. Audiol Neurootol 16(3):198–202
25. Mak KK, Kong WY, Mak A et al (2013) Polymorphisms of the serotonin transporter gene and post-stroke depression: a meta-analysis. J Neurol Neurosurg Psychiatry 84(3):322–328
26. Sutton AJ, Abrams KR, Jones DR et al (1999) Systematic reviews of trials and other studies. Health Technol Assess 2:1–276
27. Cochrane Handbook for Systematic Reviews of Interventions, Part 9.2.3.2. http://handbook.cochrane.org/index.htm#chapter_9/9_2_3_2_the_standardized_mean_difference.htm. Accessed 2 Jan 2014
28. Bridle C, Spanjers K, Patel S et al (2012) Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry 201:180–185
29. Egger M, Davey Smith G, Schneider M et al (1997) Bias in meta-analysis detected by a simple graphical test. BMJ. 315:629–634
30. Spear SA, Schwartz SR (2011) Intratympanic steroids for sudden sensorineural hearing loss: a systematic review. Otolaryngol Head Neck Surg. 145(4):534–543
31. Wei BP, Mubiru S, O'Leary S (2006) Steroids for idiopathic sudden sensorineural hearing loss. Cochrane Database Syst Rev (1):CD003998
32. Conlin AE, Parnes LS (2007) Treatment of sudden sensorineural hearing loss: II. A meta-analysis. Arch Otolaryngol Head Neck Surg 133(6):582–586
33. Labus J, Breil J, Stützer H et al (2010) Meta-analysis for the effect of medical therapy vs. placebo on recovery of idiopathic sudden hearing loss. Laryngoscope 120(9):1863–1871
34. Battaglia A, Burchette R, Cueva R (2008) Combination therapy (intratympanic dexamethasone + high-dose prednisone taper) for the treatment of idiopathic sudden sensorineural hearing loss. Otol Neurotol 29(4):453–460
35. Rauch SD, Halpin CF, Antonelli PJ et al (2011) Oral vs intratympanic corticosteroid therapy for idiopathic sudden sensorineural hearing loss: a randomized trial. JAMA 305(20):2071–2079
36. Hong SM, Park CH, Lee JH (2009) Hearing outcomes of daily intratympanic dexamethasone alone as a primary treatment modality for ISSHL. Otolaryngol Head Neck Surg 141(5):579–583
37. Han CS, Park JR, Boo SH et al (2009) Clinical efficacy of initial intratympanic steroid treatment on sudden sensorineural hearing loss with diabetes. Otolaryngol Head Neck Surg 141(5):572–578
38. Kara E, Cetik F, Tarkan O et al (2010) Modified intratympanic treatment for idiopathic sudden sensorineural hearing loss. Eur Arch Otorhinolaryngol 267(5):701–707
39. Zhou Y, Zheng H, Zhang Q et al (2011) Early transtympanic steroid injection in patients with 'poor prognosis' idiopathic sensorineural sudden hearing loss. ORL J Otorhinolaryngol Relat Spec 73(1):31–37
40. Kakehata S, Sasaki A, Futai K et al (2011) Daily short-term intratympanic dexamethasone treatment alone as an initial or salvage treatment for idiopathic sudden sensorineural hearing loss. Audiol Neurootol 16(3):191–197
41. Arslan N, Oğuz H, Demirci M et al (2011) Combined intratympanic and systemic use of steroids for idiopathic sudden sensorineural hearing loss. Otol Neurotol 32(3):393–397
42. Fu Y, Zhao H, Zhang T et al (2011) Intratympanic dexamethasone as initial therapy for idiopathic sudden sensorineural hearing loss: Clinical evaluation and laboratory investigation. Auris Nasus Larynx 38(2):165–171
43. Gouveris H, Schuler-Schmidt W, Mewes T et al (2011) Intratympanic dexamethasone/hyaluronic acid mix as an adjunct to intravenous steroid and vasoactive treatment in patients with severe idiopathic sudden sensorineural hearing loss. Otol Neurotol 32(5):756–760
44. Lautermann J, Sudhoff H, Junker R (2005) Transtympanic corticoid therapy for acute profound hearing loss. Eur Arch Otorhinolaryngol 262(7):587–591