Intratympanic injection of dexamethasone for controlling subjective idiopathic tinnitus

Hussein Fared Weshahy, Enass Sayed Mohamed, Mohamed A. M. Salem, Marwa M. M. Hussein

ENT Department, Audiology Unit, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Enass Sayed Mohamed, MD, 40 Mohamed N. Serry Street, El-Gmhorea Avenue, Assiut, 71111, Egypt
Tel: +20 882 315 723, +20 100 336 2922; fax: 0020882333327;
e-mail: enasshassan40@yahoo.com.au

Received 19 June 2015
Accepted 24 July 2015

The Egyptian Journal of Otolaryngology
2015, 31:224–230

Background
Tinnitus is a common and distressing symptom that is characterized by the perceived sensation of sound without a corresponding external stimulus. Intratympanic (IT) dexamethasone injection is used for the treatment of tinnitus by introducing the substance through the tympanic membrane, resulting in reduced systemic toxicity and a higher perilymph steroid level.

Aim of the study
The aim of this study was to evaluate the effect of IT dexamethasone injection for controlling idiopathic tinnitus of cochlear origin.

Materials and methods
A total of 30 patients with subjective idiopathic tinnitus for at least 6 months were subjected to IT injection of dexamethasone, once per week for 4 weeks. Improvement in tinnitus was assessed using pure-tone audiometry, speech audiometry, tinnitus matching test, and Tinnitus Handicap Inventory by comparing the results before and after therapy.

Results
Pure-tone audiometry did not show significant improvement. However, there was a significant improvement in speech audiometry, tinnitus loudness, and Tinnitus Handicap Inventory after the end of the four injections and in the subsequent evaluations 1 and 3 months later.

Conclusion
IT dexamethasone injection could be a simple and effective method for controlling subjective idiopathic tinnitus. The tinnitus may not disappear, but will be alleviated, enabling the patient to cope more easily with the disease, and thus reducing their handicap.

Keywords:
intratympanic dexamethasone, subjective idiopathic tinnitus, Tinnitus Handicap Inventory

Egypt J Otolaryngol 31:224–230

1012-5574

Introduction

Subjective idiopathic tinnitus might be defined as the experience of noises in the ears or head without both aberrant etiology and external stimuli [1]. It is derived from the Latin word *tinnire*, which means to ring. This sound perception or noise emanating from the ears or head ranges from a barely noticeable annoyance to a debilitating chronic condition, which can interfere with a person's quality of life and may be extremely annoying [2].

Although tinnitus is a significant health and economic problem, there are no FDA-approved drugs to treat tinnitus [3], and few drugs reliably suppress or eliminate chronic tinnitus in the majority of patients. The lack of drug therapies is in part due to a limited understanding of the biological basis of tinnitus, the heterogeneity of the tinnitus population, the wide range of medical conditions that appear to cause tinnitus, and the huge cost associated with developing drugs to specifically treat tinnitus [4,5].

One of the principal advantages of intratympanic (IT) therapy is the ability to deliver therapeutic concentrations of the drug in a highly targeted manner to the inner ear, thus avoiding systemic side effects. Compared with IT doses, much higher systemic doses are required when action is intended on the inner ear, which is an end organ with blood–brain barrier [6].

The delivery of medications to the inner ear through the transtympanic route dates back to1935, when Barany [7] used IT lidocaine for the treatment of tinnitus. Since then, other molecules have been used and the indications have expanded. In 1956, streptomycin was used as an alternative to surgical unilateral labyrinthine ablation by Schuknecht [8]. In 1996, Sakata *et al.* [2] treated patients who had tinnitus by infusing dexamethasone solution into their middle ear. The authors reported good overall results in 77% of the ears immediately after the treatment and in 68% after 6 months.

Shulman and Goldstein [9] treated tinnitus with IT dexamethasone and obtained control of tinnitus in 50% of cases. In 2002, Cesarani and colleagues described 54 patients treated with IT dexamethasone injections. Of these patients, 34% experienced complete resolution of tinnitus, 40% experienced significant improvement, and 26% experienced no change [10].

However, Araújo *et al.* [11], in his randomized single-blind study, reported no difference between IT injection of dexamethasone and saline in patients with severe, disabling tinnitus. The same results were reported by Parelkar *et al.* [12] in a recent study.

We conducted this study to evaluate the effect of IT dexamethasone injection for controlling idiopathic tinnitus of cochlear origin.

Materials and methods

Thirty patients having persistent tinnitus for at least 6 months, refractory to medical line of management, in the age group of 30–60 years were selected from the ENT and Audiology outpatient clinics at Assiut University Hospitals, Egypt.

The study was conducted from April 2014 to March 2015. The study protocol was approved by the local ethics committee. Informed consent was obtained from all participants.

Tinnitus may be unilateral or bilateral, the ear with more annoying and louder tinnitus was chosen. Patients with sensorineural hearing loss (SNHL) of cochlear origin were included. Patients with a history of trauma, otitis media, otologic surgery, ototoxic drug intake, noise-induced hearing loss, Meniere's disease, systemic illness, and neurologic illness were excluded from the study.

A detailed history was taken from all patients. Otoscopic examination and neurologic examination were also carried out, after which they underwent a battery of tests.

Audiological assessment

Pure-tone audiometry was performed using a Madsen Orbiter 922 diagnostic audiometer, Madsen electronics, Denmark Madsen OB 822, Madsen electronics, Copenhagen, Denmark at frequencies between 0.25 and 8.0 kHz for air conduction and between 0.5 and 4.0 kHz for bone conduction. The four-frequency pure-tone average (4-PTA) for air conduction was calculated at frequencies of 0.5, 1.0, 2.0, and 4.0 kHz.

Speech audiometry was evaluated by measurements of speech reception threshold using Arabic spondee word List [13] and speech discrimination score was determined using Arabic phonetically balanced word [14] for each ear separately.

Impedence measurements were taken, including tympanometry and acoustic reflex testing.

Auditory brainstem response was evaluated when a retrocochlear lesion was suspected to be excluded.

Tinnitus matching [15]

The tinnitus matching test was carried out with an audiometer Madsen OB 822 and included the following:

(1) Pitch matching was measured by presenting two different frequencies of pure tone or narrow band noise, and the patient was asked to judge whether the pitch of the first or the second of the two successive tones is closer to the tinnitus the patient hears. The tone is presented to the contralateral ear with successive approximations until the most dominant frequency has been identified.
(2) Loudness matching was measured by presenting the external sound previously identified during pitch matching to the ear contralateral to the tinnitus and was increased or decreased in intensity until the patient judges that the loudness is equal to that of his or her tinnitus. The test for the intensity match is delivered in 1 dB steps.
(3) Minimal masking level was ascertained by determining the minimum level of white noise needed to achieve masking of the ongoing tinnitus. This test was performed monoaurally in the affected ear in 1 db steps. The test was stopped immediately if the stimulus became uncomfortably loud.
(4) Residual inhibition was carried out by presenting a white noise to the affected ear at 10 dB above the minimum masking level for 60 s. At the end of 1 min, the patient assesses whether the tinnitus is gone, diminished, unchanged, or louder. A complete residual inhibition was referred to if the tinnitus was completely absent after a 1-min exposure to the white noise; a partial residual inhibition was referred to if the tinnitus reduced but was not completely absent for a period of time; and negative residual inhibition was referred to if there was no change in tinnitus loudness.

Tinnitus Handicap Inventory

The patients responded to a specific tinnitus questionnaire, Tinnitus Handicap Inventory (THI),

which is a self-administered, 25-item questionnaire that is scored on a three-point scale (no = 0, sometimes = 2, and yes = 4). On the basis of the total THI score, tinnitus patients can be classified into five categories denoting handicap severity: slight handicap (0–16), mild handicap (18–36), moderate handicap (38–56), severe handicap (58–76), or catastrophic (78–100) [16].

Intratympanic injection of dexamethasone

One ear of each of the 30 patients was treated with IT dexamethasone injection under local anesthesia. The patients were placed in the supine position on the table with their heads turned about 30° away from the surgeon. An eutectic mixture of local anesthetic (EMLA) 2.5% lidocaine, 2.5% prilocaine in a cream base cream was applied for topical anesthesia in the outer ear canal and the tympanic membrane, and left for 30–45 min. The dexamethasone solution of 8 mg/ml was checked and warmed to body temperature before injection, and about 0.5 ml of dexamethasone was injected into the posteroinferior quadrant of the tympanic membrane using a spinal needle no. 22 under direct visualization through an operating microscope. The patient remained in the described position for 30 min [17]. Four injections were administered once per week for 4 weeks.

Pure-tone audiometry, speech audiometry, tinnitus matching, and THI were repeated after the end of the four injections, and then 1 and 3 months later.

Categorical variables were described as number and percentage (*N*, %), and continuous variables were described as mean and SD (mean, SD). Comparison between continuous variables was made using *t*-test and analysis of variance. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and Q–Q plots. A two-tailed *P* value less than 0.05 was considered statistically significant. All analyses were performed with the SPSS 20.0 software (SPSS version 20.0, IBM Corp. Armonk, NY).

Results

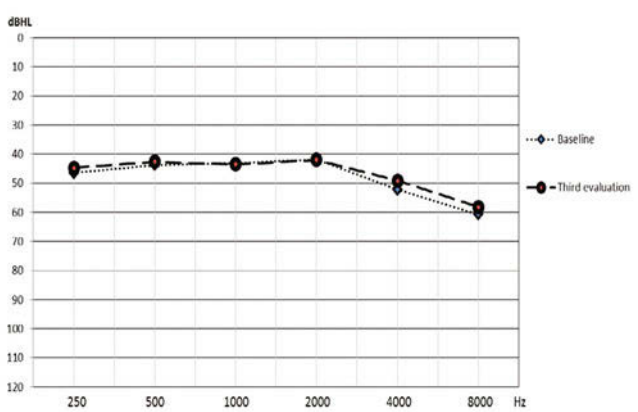
The mean age of patients was 45 ± 11, with an age range of 30–60 years. The study included 17 male and 13 female patients. The duration of tinnitus ranged from 6 months to 3 years with a mean of 18.7 ± 10.0. The tinnitus was bilateral in 22 patients and unilateral in eight patients.

There was no improvement in the mean pure-tone thresholds at different frequencies after dexamethasone injection in tinnitus patients (Fig. 1). The mean initial PTA level was 45.2 ± 21.7, and the mean post-therapy level was 44.3 ± 22.1. There was no significant difference between pretherapy and post-therapy levels (Table 1 and Fig. 1). However, there was a significant improvement in speech discrimination score after therapy (Table 1). A total of 18 (60%) tinnitus patients showed improvement in their SD%.

There was a significant reduction in tinnitus loudness level when measured subjectively, using tinnitus matching tests. Moreover, the minimum masking level was reduced significantly when comparing pretherapy and post-therapy levels (Figs 2 and 3). A total of 27 (90%) tinnitus patients showed reduction in their loudness level and minimum masking level.

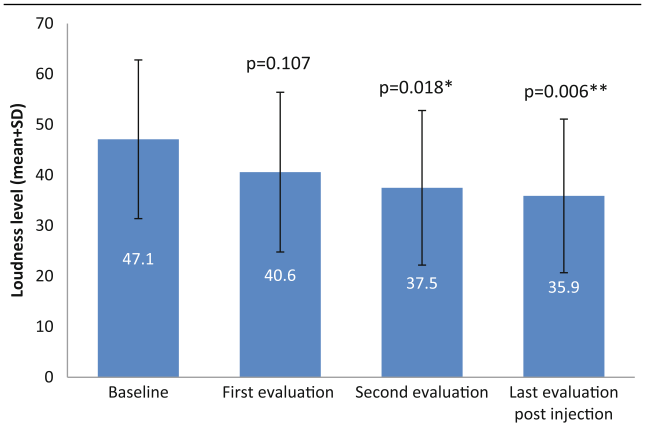
As regards residual inhibition (RI), only three patients changed from negative RI to partial RI; no patient changed to complete RI. There was no statistically significant difference between preinjection and postinjection RI ($P = 0.84$).

Figure 1



The mean of pure-tone thresholds at different frequencies before and after dexamethasone injection in tinnitus patients.

Figure 2



The mean and SD of loudness level of the study samples before and after dexamethasone injection.

The results of THI showed statistically significant improvement after dexamethasone injection. There was also an improvement in patients at the end of the therapy and subsequent evaluations (1 and 3 months later), but this improvement was not statistically significant (Table 2).

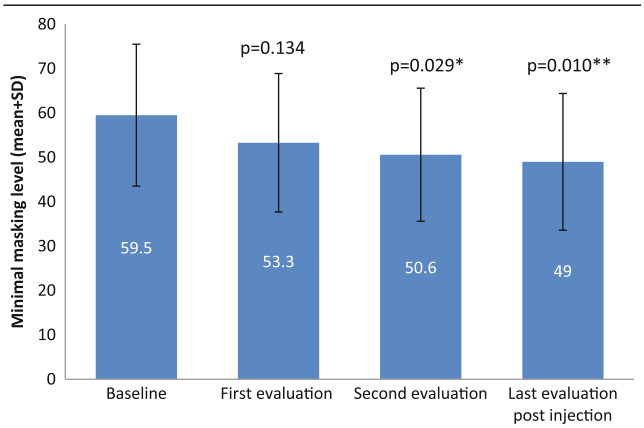
Before injection, tinnitus patients had mainly severe or catastrophic handicap, but their scores reduced significantly after therapy to slight, mild, or moderate handicap (Fig. 4). (The χ^2-test was used for comparison, $P = 0.001^{***}$).

However, the patients did not report full recovery of tinnitus, neither after the end of injections nor during the follow-up period.

Discussion

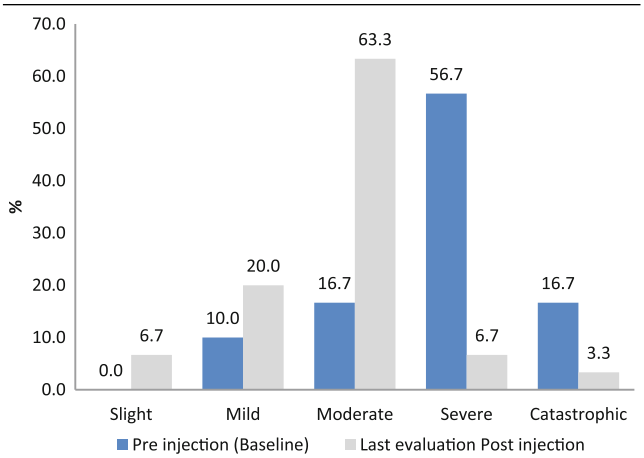
In the present study, no significant changes were encountered in PTA, but SD% tended to improve significantly. Yilmaz *et al.* [18] studied IT dexamethasone injection in 40 patients with nearly the same inclusion and exclusion criteria and reported no significant changes in average high-frequency and SD% and a significant reduction in PTA, which agreed partially with our results. Our results were in agreement with those of Parelkar *et al.* [12], who reported no change in the hearing levels before and after treatment as per the pure-tone audiogram reports in the patient group. Hamid in his study on Meniere's disease noticed a significant gain in speech discrimination (30–60%) that has been associated with IT dexamethasone perfusion. He suggested

Figure 3



The mean and SD of minimal masking level (MML) of the study samples before and after dexamethasone injection.

Figure 4



Total Tinnitus Handicap Inventory (THI) score of the study samples before and after dexamethasone injection.

Table 1 Mean (*X*), SD, and *P* level of pure-tone average, and speech discrimination score for the study samples before and after dexamethasone injection

Audiometric tests	Mean ± SD				*P* value
	Before injection	First evaluation after injection	Second evaluation after injection	Third evaluation after injection	
PTA	45.2 ± 21.7	43.5 ± 22.0	44.1 ± 21.9	44.3 ± 22.1	0.877 (NS)
SD%	81.5 ± 18.3	91.4 ± 7.9	88.7 ± 11.6	87.5 ± 12.4	0.049*

ANOVA test used to obtain *P* value; ANOVA, analysis of variance; PTA, pure-tone average; NS, no significant difference ($P > 0.05$); *Significant difference ($P < 0.05$).

Table 2 Mean (*X*), SD, and *P* level of Tinnitus Handicap Inventory for the study samples before and after dexamethasone injection.

THI	Range	Mean ± SD	P_1	P_2	P_3
Before injection (baseline)	36–94	64.3 ± 14.8			
First evaluation after injection	14–76	46.5 ± 14.6	0.000***		
Second evaluation after injection	14–78	43.7 ± 13.2	0.000***	0.422 (NS)	
Last evaluation after injection	14–78	40.9 ± 12.7	0.000***	0.124 (NS)	0.441 (NS)

THI, Tinnitus Handicap Inventory; P_1: comparison between baseline and each one of other evaluations using *t*-test; P_2: comparison between first evaluation and each one of other evaluations using *t*-test; P_3: comparison between second evaluation and last evaluation using *t*-test; (NS, no significant difference ($P > 0.05$))

that dexamethasone offers a new treatment modality leading to significant speech discrimination recovery. He reported that steroids improve the stria vascularis ion transport system [19]. Disturbance in the ion transport system or ion homeostasis affects the inner ear function, which includes hair cell function, endolymph and perilymph composition, and nerve impulse conductance. Corticosteroids restore the ion homeostasis in the inner ear [20]. Improvement in cochlear function, especially the hair cell function and nerve impulse conductance, could be the possible cause of improvement in SD%.

In our study, the tinnitus loudness level and minimal masking level reduced significantly on tinnitus matching test evaluation after IT dexamethasone injection, with improvement of these parameters in 27 (90%) patients. These results are in agreement with those of Mahmoud and Hafize, who reported a significant difference between the study group and the control group (tinnitus patients without IT dexamethasone injection) for the two parameters, loudness level and minimal masking level, and concluded that the tinnitus matching test could be used as a subjective evaluation for tinnitus and outcome measure of the therapy [21].

THI scores were also improved significantly after the therapy. Most of the patients changed from severe and catastrophic handicap to slight, mild, and moderate handicap; however, none of the tinnitus patients showed full recovery of tinnitus. An *et al.* [22] also reported that the mean THI scores were significantly reduced at 3 months after IT dexamethasone injection.

Our results are in agreement with the studies of Sakata *et al.* [2], Shulman and Goldstein [9], and Cesarani *et al.* [10], who used IT dexamethasone injection in tinnitus and reported recoveries of 71, 70, and 74%, respectively. However, Cesarani and colleagues reported 34% full recovery of the tinnitus. This could be attributed to the difference in the inclusion criteria of their study group in which the duration of tinnitus did not exceed 3 months.

She *et al.* [23] compared the efficacies of IT prednisolone injection, IT dexamethasone injection, and carbamazepine by means of oral administration for subjective tinnitus. The effective rate of the prednisolone group, dexamethasone group, and the carbamazepine group was 48.6, 33.3, and 44.0%, respectively, and the control rate half a year after the treatment was 45.7, 27.8, and 36.0%, respectively. They reported that prednisolone may be better than dexamethasone in IT perfusion for subjective tinnitus. They concluded that IT steroid injection has a positive effect on subjective tinnitus and may be considered to be an alternative treatment to it. The advantage of prednisolone over dexamethasone was explained by Parnes *et al.* [24], who showed that methylprednisolone had a higher concentration and longer duration in the perilymph after transtympanic administration compared with hydrocortisone or dexamethasone. However, Hamid [19] reported that dexamethasone is more effective, because it is absorbed faster than other steroids; he used a higher concentration of dexamethasone (24 mg/ml) in his study.

In contrast, Araujo *et al.* studied the effectiveness of IT dexamethasone injection as a treatment for severely disabling cochlear tinnitus, in their randomized, prospective, single-blind study [25]. They concluded that there was no advantage in IT injections of dexamethasone over saline solution in the treatment of severely disabling tinnitus, and both solutions produced a placebo-like improvement in about 30–40% of patients. They attributed their results to the inclusion of patients with severely disabling tinnitus, which is different from common forms of tinnitus; the symptoms are intense, with a high annoyance level and an affective component that renders the patient incapable of performing daily tasks efficiently. In 1989, House [26] severed the cochlear nerves of patients with Ménière's disease who were undergoing vestibular nerve section and who also had severe tinnitus. Considering that tinnitus in Ménière's disease certainly has a cochlear origin, it was surprising to learn that a large percentage of these patients continued to experience the unaltered symptom after the cochlear nerve was severed. Somehow, the central auditory pathways kept the symptom of tinnitus alive after cochlear deafferentation. A lack of central suppression of spontaneous auditory pathways could explain the noise permanence. The central component of severely disabling tinnitus even when of cochlear origin, makes the IT injections of dexamethasone inefficient in some group of patients, especially in those with severely disabling tinnitus.

Parelkar *et al.* [12] reported that, although IT therapy is a highly efficacious and tempting mode of drug delivery, IT dexamethasone injections are not effective for refractory tinnitus and do not alter the hearing loss; this study was also conducted on patients with severely disabling tinnitus. They also referred the failure of IT injection in a group of patients to the poor round window membrane permeability.

The mechanism of action of this therapeutic modality is multifactorial, including anti-informatory effects, a metabolic improving effect, an edema-relieving effect, and suppress the irritated or hypersensitive hair cells in the inner ear, which are believed to cause

tinnitus [2,27]. Pondugula *et al*. pointed at other mechanism of action for IT dexamethazone injection in tinnitus patients, which suggest that steroid perfusion of labyrinthine tissues can affect sodium and fluid transport *in vitro* studies [28]. The choice of an IT route in the treatment of tinnitus has two advantages: first, high perilymph levels are attained as a result of providing a direct passage through the oval window membrane, and, second, adverse effects of systemic administration of the drug are avoided [29].

Local side effects, may include injection-site pain, dizziness, caloric vertigo, infection, persistent tympanic membrane perforation, or possible vasovagal or syncopal episodes during injection [30–32]. In our study, no side effects except for transient injection-site pain in few patients were noted. Sufficient warming of the drug, the use of fine needles and appropriate local anesthesia, a gentle rate of injection, and avoidance of excessive injection volumes seem to be key factors for good local tolerance [33].

Conclusion

IT dexamethasone injection could be a simple and effective method for controlling subjective idiopathic tinnitus. The tinnitus may not disappear, but will be alleviated, thereby enabling the patient to cope more easily with the disease, and thus reducing their handicap and improving their quality of life. The lack of a control group is one limitation of this study, as a placebo-controlled study would not be ethically acceptable. However, further double-blind, controlled studies with larger numbers of patients are recommended to confirm these results. Studying the effect of different therapeutic molecules on control of subjective idiopathic tinnitus is also recommended.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Nondahl DM, Cruickshanks KJ, Wiley TL, Klein R, Klein BE, Tweed TS. Prevalence and 5-year incidence of tinnitus among older adults: the epidemiology of hearing loss study. J Am Acad Audiol 2002; 13:323–331.

2 Sakata E, Itoh A, Itoh Y. Treatment of cochlear-tinnitus with dexamethasone infusion into the tympanic cavity. Int Tinnitus J 1996; 2:129–135.

3 Vio MM, Holme RH. Hearing loss and tinnitus: 250 million people and a US$10 billion potential market. Drug Discov Today 2005; 10:1263-1265.

4 Dobie, RA. A review of randomized clinical trials in tinnitus. Laryngoscope 1999; 109:1202–1211.

5 Robinson SK, Viirre ES, Stein MB. Antidepressant Therapy for Tinnitus. In: Snow J Jr., editor. Tinnitus: Theory and Management. BC Decker; Hamilton, Canada: 2004. chapter 20, p. 278–293.

6 Jahnke K. The blood–perilymph barrier. Arch Otorhinolaryngol 1980; 228:29–34.

7 Barany R. The control of tinnitus by injecting intravenous local anesthetics. Acta Otlaryngol 1935; 23:201–203.

8 Schuknecht HF. Ablation therapy for the relief of Meniere's disease. Laryngoscope 1956; 66:859–870.

9 Shulman A, Goldstein B. Intratympanic drug therapy with steroids for tinnitus control: a preliminary report. Int Tinnitus J 2000; 6:10–20.

10 Cesarani A, Capobianco S, Soi D, Giuliano DA, Alpini D. Intratympanic dexamethasone treatment for control of subjective idiophatic tinnitus: our clinical experience. Int Tinnitus J 2002; 8:11–113.

11 Araújo MF, Oliveira CA, Bahmad FM Jr. Intratympanic dexamethasone injections as a treatment for severe, disabling tinnitus: does it work? Arch Otolaryngol Head Neck Surg 2005; 131:113–117.

12 Parelkar K, Thorawade V, Jagade M, Nagle S, Nataraj R, Pandare M, *et al*. Intratympanic injections: an unsolved mystery. Int J Otolaryngol Head Neck Surg 2015; 4:124–132.

13 Soliman S, Fathalla A, Shehata W. Development of Arabic suggested spondiac words test. Ain Shams Medical Congress 1985; 2:1220.

14 Soliman S. Speech discrimination audiometery using Arabic phonetically balanced words. Ain Shams Med J 1976; 27:27–30.

15 Sandlin RE, Olsson RT. Subjective tinnitus: it's mechanism and treatment. In: M Valenete, H Hosford, GR Ross, editors. *Audiology treatment*. New York: Thieme; 2000. 691–697.

16 McCombe A, Baguley D, Coles R, McKenna L, McKinney C, Windle-Taylor P, British Association of Otolaryngologists, Head and Neck Surgeons. Guidelines for the grading of tinnitus severity: the results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. Clin Otolaryngol Allied Sci 2001; 26:388–393.

17 Sakata H, Kojima Y, Koyama S, Furuya N, Sakata E. Treatment of cochlear tinnitus with intratympanic infusion of 40% lidocaine into the tympanic cavity. Int Tinnitus J 2001; 7:46–50.

18 Yilmaz I, Ozluoglu LN, Cagici CA, Akkuzu G, Ozgirgin N, Yavuz H, Yalcintas D. Effectiveness of intratympanic dexamethasone on tinnitus: a clinical experience. Turk Arch Otolaryngol 2006; 44:81–87.

19 Hamid MA. Intratympanic dexamethasone perfusion in Meniere's disease. Presented at the spring meeting of the American Neurotology Society, Palm Desert, CA, May 2001:12.

20 Dennis RT. Ion homeostasis and inner ear disease. In: Hamid M, Sismanis A, editors. *Medical otology and neurotoyology. A clinical guide to auditory and vestibular disorders*. New York: Thieme; 2006. 21–32.

21 Mahmoud EA, Hafize ME. Transtympanic dexamethazone treatment for control of subjective idiopathic tinnitus. El-minia Med Bull 2004; 15:240–252.

22 An YH, Yu KK, Kwak MY, Yoon SW, Shim HJ. Prognostic factors for the outcomes of intratympanic dexamethasone in the treatment of acute subjective tinnitus. Otol Neurotol 2014; 35:1330–1337.

23 She W, Dai Y, Du X, Chen F, Zhang Q, Jiang P, Cui X. A short term study on the efficacies of intratympanic prednisolone and dexamethasone injection for subjective tinnitus. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2008; 22:871–873. 877

24 Parnes LS, Sun AH, Freeman DJ. Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. Laryngoscope 1999; 109:1–17.

25 Araújo MFS, Oliveira CA, BahmadJr FM. Intratympanic Dexamethasone Injections as a Treatment for Severe, Disabling Tinnitus. Arch Otolaryngol Head Neck Surg 2005;131:113–117.

26 House JW. Therapies for tinnitus. Am J Otol 1989; 10:163–165.

27 Itoh A, Sakata E. Trearment of vestibular disorders. Acta Otolaryngo 1991; 481:617–623.

28 Pondugula SR, Sanneman JD, Wangemann P, Milhaud PG, Marcus DC. Glucocorticoids stimulate cation absorption by semicircular canal duct epithelium via epithelial sodium channel. American Journal Physiol Renal Physiol 2004; 286:1127–1135.

29 Chandrasekhar SS, Rubinstein RY, Kwartler JA, Gatz M, Connelly PE, Huang E, *et al*. Dexamethasone Pharmacokinetics in the Inner Ear: Comparison of Route of Administration and Use of Facilitating Agents. Otolaryngology—Head and Neck Surgery 2000; 122:521–528.

30 Topak M, Sahin-Yilmaz A, Ozdoganoglu T, Yilmaz, HB, Ozbay M, Kulekci M. Intratympanic Methylprednisolone Injections for Subjective Tinnitus. Journal of Laryngology & Otology 2009; 123:1221–1225.

31 Rauch SD, Halpin CF, Antonelli PJ, Babu S, Carey JP, Gantz BJ, *et al*. Oral vs Intratympanic Corticosteroid Therapy for Idiopathic Sudden Sensorineural Hearing Loss: A Randomized Trial. J Am Med Assoc 2011; 305:2071–2079.

32 Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM, *et al*. Clinical practice guideline: sudden hearing loss. Otolaryngol Head Neck Surg 2012; 146: S1-S35.

33 Belhassen S, Saliba I. Pain assessment of the intratympanic injections: a prospective comparative study. Eur Arch Otorhinolaryngol 2012; 269:2467–2473.