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Effectiveness of intratympanic dexamethasone on tinnitus: a clinical experience

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İntratimpanik deksametazonun tinnitus üzerine etkinliği: klinik deneyim

Amaç: Tinnituslu hastaların tedavisinde kullandığımız intratimpanik deksametazon (ITDex) enjeksiyonu deneyimlerimizi bildirmek.

Yöntem: Kliniğimize 2002 ile 2004 yılları arasında tinnitus tedavisi için gelen tüm hastaların kayıtları gözden geçirildi. Kırk hastanın bilgileri (29'u erkek, 11'i kadın; yaş ortalamaları 54, yaş aralığı 32-76) toplandı. Hastalar en az 6 aydır tinnitus nedeniyle tedavi görmelerine karşın yakınmaları devam eden; hipertansiyon, diabetes mellitus, hipo-hipertiroidi, hiperkolesterolemi, Meniere, otoskleroz ve kronik otitis media hastalıkları olmayan bireyler arasından seçildi. Enjeksiyonlar 4 mg/ml deksametazon içeren ampuller kullanılarak, iki gün arayla 5 kez yapıldı. Hastalara enjeksiyonlar başlamadan önce ve bittikten 5 gün sonra yüksek frekans dahil odyolojik tetkik ve tinnitus match testi yapıldı. Vizuel analog skala (VAS) ile tedaviden önce, 5 gün sonra ve geç dönemde tedavinin etkinliği sorgulandı. VAS'de 20 mm'lik düzelme anlamlı kabul edildi. İstatistik anlamlılığı ($p<0.05$) saptamak için paired t-test ve Wilcoxon işaret testleri kullanıldı.

Bulgular: Tedavi öncesi ve sonrasındaki, ve tedavi öncesindeki ve geç dönemdeki VAS değerleri karşılaştırıldığında, hastaların tinnitustan duydukları rahatsızlık anlamlı ölçüde azalmıştı (her iki $p< 0.001$). Bunun yanında, tedavi sonrasında ölçülen tinnitus şiddetleri anlamlı olarak azalmış ($p=0.049$), saf ses ortalamaları anlamlı olarak düşmüştü ($p=0.038$). Hastaların konuşmayı ayırt etme skorlarında bu tedavi nedeniyle anlamlı değişiklik saptanmadı ($p=0.865$). VAS'ye göre düzelme oranları; tedavi öncesi ve sonrası için %40 (40 hastanın 16'sı) ve tedavi öncesi ile geç dönem için %37 (35 hastanın 13'ü) olarak bulundu. Hastaların izlem süreleri 12 ile 33 ay arasında değişiyordu.

Sonuç: İşitme durumunu etkilemeksizin, ITDex tedavisi hastaların tinnitustan kaynaklanan rahatsızlıklarını ve duydukları sesin şiddetini azaltma yanında saf ses ortalamalarını da olumlu yönde etkilemiştir. Bu tedavi yöntemi tinnituslu hastaların tedavisinde başarılı ve güvenilir bir seçenek olarak görünmektedir.

Anahtar Sözcükler: Deksametazon, intratimpanik, tinnitus, VAS.

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Abstract

Objectives: To report our experience about intratympanic dexamethasone (ITDex) injection in the management of patients with tinnitus.

Methods: The records of all patients with tinnitus presenting for treatment at our institution between 2002 and 2004 were retrospectively reviewed. Forty patients' data (11 women and 29 men; aged 54±11 years; range, 32 to 76 years) were collected. Inclusion criteria consisted of having a minimum 6 months' medical therapy for tinnitus and being free of hypertension, diabetes mellitus, hypo-hyperthyroidism, hypercholesterolemia, Meniere's disease, otosclerosis, and chronic otitis media diseases. Intratympanic injections of 4 mg/mL dexamethasone had been performed 5 times at 2-day intervals. Before and 5 days after the injections, audiometry, including high-frequency and tinnitus-matching tests, had been performed. The efficacy of therapy was evaluated with a visual analog scale (VAS) before and 5 days after treatment and in the late period. A 20 mm improvement on the visual analog scale was considered to be significant. Paired-samples t and Wilcoxon signed-rank tests were used to determine statistical significance ($P<0.05$).

Results: When visual analog scale values before and after treatment, and before treatment and late period were compared, patients' annoyance from tinnitus was significantly decreased (both $P<0.001$). There were also significant decreases on tinnitus loudness ($P=0.049$) and pure tone averages ($P=0.038$). There was no significant difference regarding the speech discrimination scores of the patients ($P=0.865$). The improvement rates based on visual analog scale were 40% (16 of 40 patients) for before and after treatment and 37% (13 of 35 patients) for before treatment and late period. Follow-up varied from 12 to 33 months.

Conclusion: Without affecting hearing status, ITDex treatment can improve not only patients' annoyance from tinnitus and tinnitus loudness but also pure tone averages. This treatment appears to be a successful and safe alternative for the treatment of tinnitus.

Key Words: Dexamethasone, intratympanic, tinnitus, VAS.

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Introduction

Tinnitus is a sound sensed inside the head that cannot be localized and is generally presumed to be an auditory sense of a noise of internal origin. It affects approximately 17% of the population in general and 33% of elderly persons.[1] This study is concerned with subjective tinnitus, which cannot be heard from outside, existing only as tinnitus generated by para-auditory structures, reportedly created as a result of lesions formed mostly at the acoustic nerve and inner ear.

Many researchers have suggested medication for treatment of tinnitus. However, effective medications remain elusive, and this has led researchers to seek out new methods of treatment.[1,2] Intratympanic treatments are, in fact, an outcome of such research. The first intratympanic study was performed by Schuknecth in 1957 and has been used for various indications to date.[3] Intratympanic treatments have become more favorable in recent years owing to more-frequent use of ablative methods in the treatment of vertigo. In this method, medications are injected into the tympanic cavity through the oval window targeting the inner ear (inner-ear targeting therapy).

Use of steroids to cure inner-ear disorders dates back to 1979, when the procedure was first described by McCabe in the autoimmune inner-ear disease definition.[4] Particularly in recent years, some studies using steroids intratympanicly have been reported, when steroids are used, they almost invariably are dexamethasone.

The first clinical study using intratympanic steroids were performed by Itoh and Sakata between 1981 and 1987 and published in 1991.[5] Intratympanic steroids (mainly ITDex) have been used in patients for various inner-ear diseases (eg, Meniere's disease, autoimmune inner-ear disease, sudden sensorineural hearing loss, and labyrinthine vertigo) as well as tinnitus.[6-10]

In this experience, we used dexamethasone via an intratympanic route for treatment of tinnitus.

Materials and Methods

The records of all patients with tinnitus presenting for treatment at the Otolaryngology Clinics of Başkent University School of Medicine, in Adana and in Ankara, Turkey between 2002 and 2004 were retrospectively reviewed. Inclusion criteria consisted of having a minimum 6 months of medical therapy for tinnitus (eg, Ginkgo biloba extract EGb 761, beta histidine, or trimetazidine) and being free of hypertension, diabetes mellitus, hypo-hyperthyroidism, hypercholesterolemia, Meniere's disease, otosclerosis, and chronic otitis media diseases. Forty patients who met these criteria had undergone routine ENT examination. Further investigations with auditory brainstem response (ABR), electronystagmography (ENG), and internal acoustic canal magnetic resonance imaging had been performed when indicated. The tympanic membranes of all patients were intact. Subjects had been informed about tinnitus and the ITDex treatment, and informed consent forms had been voluntarily signed.

Injections had been given on a fixed protocol, 5 times at 2-day intervals, using ampules containing 4 mg/mL dexamethasone (Onadron® ampule, İ.E. Ulagay, Turkey). Audiologic investigations (including high frequency) and tinnitus match tests both before and 5 days after injections had been performed. The efficacy of treatment had been assessed using a visual analog scale (VAS) (0-99 mm) before and 5 days after injections and at late period. Audiologic investigations (including high frequency) and tinnitus match tests were not repeated in the late period.

Injection technique

Myringotomy had been performed under a microscope via an anterosuperior approach, folding the ear at a 45° angle, while keeping the patient's head straight, using a 27-gauge 1.5-inch dental injection needle. This had been followed by a second myringotomy via an anteroinferior approach, and the drug had been administered from this position. Injection had been terminated with the drug's inflow from the anterosuperior miringotomy.[11] Dexamethasone (0.5-1 mL) had been administered with every injection. Following injection, the patient had been placed on a bed for 60 minutes, with his or her head resting horizontally, making a 45° angle toward the other ear. No local or topical anesthetics had been used.

Audiometric tests

Audiologic examination and high-frequency audiometry had been performed using a soundless cabinet (Clinical Audiometer AC40 audiometry device, Interacoustics Co, Assens, Denmark), which carries the standards of the Industrial Acoustics Company. We had used Telephonics TDH-39P headphones (Telephonics Co, Farmingdale, NY, USA) for low frequency and Koss R-80 headphones (Koss Co, Milwaukee, WI, USA) for high frequency. Airway hearing thresholds had been determined by routine audiologic examination for values between 0.125-8 kHz and by high-frequency audiometry for values between 10-18 kHz. Levels of hearing loss had been evaluated by taking the hearing test results from the pure tone average [PTA=(500+1000+2000)/3] at low frequencies (125 Hz-8 kHz). The tinnitus matching method (the pitch-match frequency and loudness match - dB SL) had been used to determine the frequency and amplitude. A phonetically balanced word list consisting of 50 words each with single syllables had been used to determine the speech discrimination score (SDS) for each patient.

VAS (0 to 99 mm)

At the beginning of therapy and 5 days after and in the late period (mean 23.1± 5.90 months), patients had been asked, "How much does the sound you hear disturb you?" For the purpose of this survey, a VAS scale had been created consisting of a 10-cm long horizontal line split in two by a vertical line at the center, with "not at all" on one side of the line and "unbearable" on the other. Patients had been asked to mark their symptom levels on this scale. Decreasing VAS scores indicated favorable therapy outcomes while increasing scores indicated ineffective outcomes. A 20 mm improvement on the visual analog scale was considered to be significant.[9]

Statistical analyses

Data obtained before and after injections and in the late period were analyzed using the paired-samples *t* and Wilcoxon signed-rank tests. All analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc, Chicago, Ill, USA). A level of $P<0.05$ was considered statistically significant.

Results

Forty patients' data (11 women and 29 men; aged 54±11 years; range, 32 to 76 years) were collected. Injections had been performed in the left ear in 23 patients and in the right ear in 17. All 5 injections had been completed for all patients. At the study's end, no patients had been found to have tympanic membrane perforation, nor had been traces of development of external otitis or hearing disorders found. No increase in levels of tinnitus had been observed for any of the patients, yet some patients had reported vertigo, which occurred during injections only, and lasted for about 15 seconds. As local and topical anesthetics had not been used, patients felt a light, temporal pain during the first injection. VAS scores of late period could be collected only from thirty-five patients. Follow-up varied from 12 to 33 months (mean 23.1±5.90 months).

Data obtained before and 5 days after the injections and in the late period are shown in Table 1, together with *P* values. While a significant change was observed in the intensity of tinnitus ($P=0.049$), PTA (pure tone average) ($P=0.038$), VAS scores ($P<0.001$) before and after injections, and VAS scores ($P<0.001$) before treatment and in the late period; no changes were found in tinnitus frequency ($P=0.152$), average high frequency ($P=0.204$), SDS ($P=0.865$) values, and VAS scores ($P=0.078$) after treatment and in the late period.

The improvement rates based on visual analog scale (20 mm improvement) were 40% (16 of 40 patients) for before and after treatment and 37% (13 of 35 patients) for before treatment and in the late period.

Variations in VAS scores for each patient are shown in Figure 1. Both VAS scores after injection and in the late period are lower than the VAS scores before injection.

Discussion

A survey of the studies employing intratympanic steroids reveals that Itoh and Sakata[5] studied 322 patients with Meniere's disease and labyrinthine vertigo, from 1981 to 1987, in an effort to control vertigo. Schuknecht[12] sought to control vertigo in patients with Cogan's syndrome in 1994. Sakata et al.[13] treated tinnitus in 1214 patients in 1996; Arriaga and Goldman[14]

Tablo 1. Data obtained both before and after injections.

	Before treatment mean ± SD Median n = 40	After treatment mean ± SD Median n = 40	Late period mean SD median n=35	*P* (before and 5 days after treatment)	*P* (before treatment and late period)	*P* (5 days after treatment and late period)
Tinnitus loudness (dB)	60.625±26.19 62.5	55.375±27.69 57.5	–	0.049	–	–
Tinnitus frequency (Hz)	4.69±3.046 5	5.725±4.78 6	–	0.152	–	–
Pure-tone average (dB)	33.45±19.68 30	30.46±22.28 24	–	0.038		
High-frequency average (dB)	63.4±13.27 67	62.53±12.67 65	–	0.204	–	–
Visual analog scale (mm)	64.75±20.18 66.5	44.3±17.50 42.5	48.1±18.08 51.0	< 0.001	< 0.001	0.078
Speech discrimination scores (%)	92.5±12.06 98	93.23±10.84 100	–	0.865	–	–

SD: Standard deviation

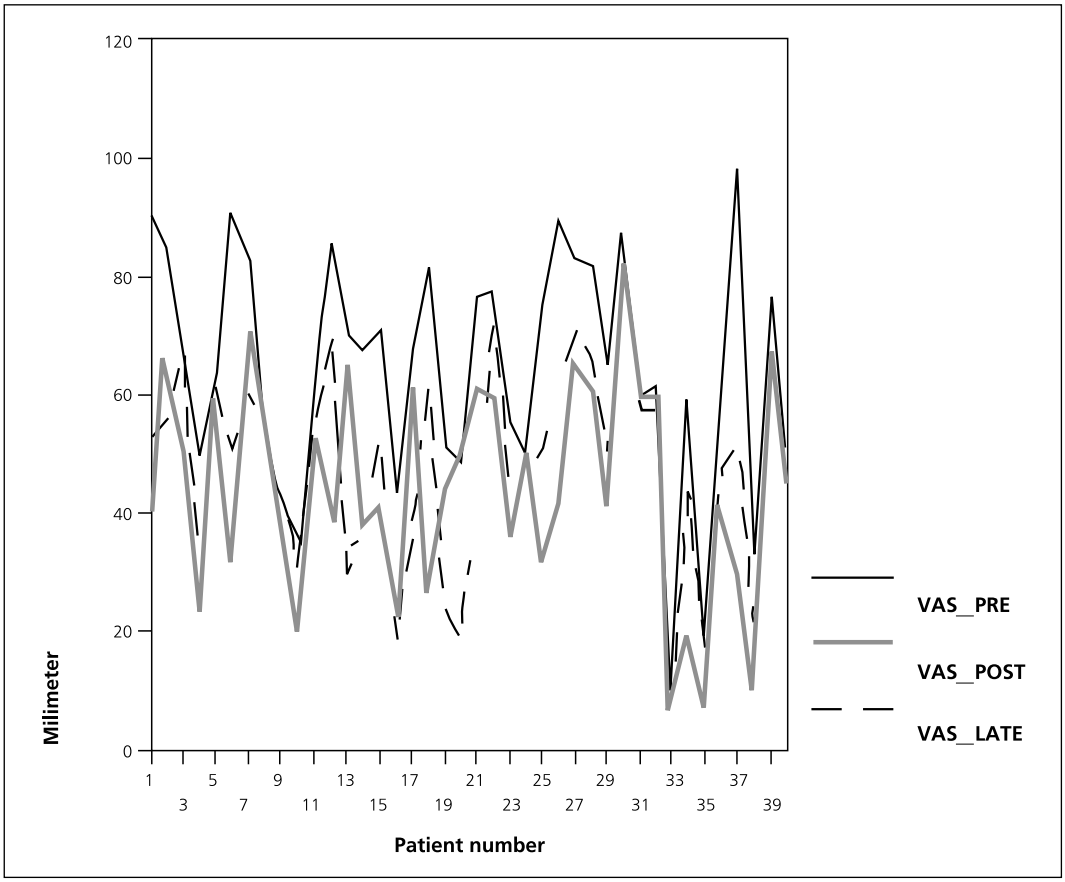

Figure 1. Patients' pre- and postinjection and late period VAS scores.

sought to improve hearing in 21 patients with endolymphatic hydrops in 1998; Silverstein et al[15] sought to control vertigo in 20 patients with unilateral Meniere's disease; Parnes et al.[16] sought to improve the symptoms in 37 patients with sensorineural hearing loss (SNHL) due to various reasons in 1999; Chandrasekhar,[11] in 2001, attempted to improve hearing in 10 patients with sudden SNHL; Barrs et al.,[17] in 2001, studied vertigo control in 21 patients with Meniere's disease that could not be easily controlled; Cesarani et al.[8] studied subjective idiopathic tinnitus control in 54 patients in 2002; and Ho et al.[18] sought to resume hearing in 39 patients with sudden SNHL.

Recovery rates of various tinnitus treatments are as follows: Duckert and Rees[19] (40% using intravenous lidocaine), Briner et al.[19] (33% using misoprostol), Davies et al.[19] (16% using oral nimodipine), Sprenger[19] (36% using gingko biloba), House and Brackmann[19] (25% using vestibulocochlear nerve section), Warrick[19] (27% using stellate ganglia block or section), Hatton et al.[19] (46% employing extracochlear electric suppression), Portmann et al.[19] (66% applying positive current to the oval window), Vernon et al.[19] (22% setting transcutaneous electrodes in the preauricular and postauricular regions of the ear), House and Brackmann[19] (79% in patients with cochlear-implant [intracochlear study]), Berliner et al.[19] (53% using cochlear-implant), Tyler and Kelsay[19] again (81% using cochlear-implant), Mann[19] (5% employing acupuncture techniques), Jastrebof and Hazell[19] (80% using their suggested treatments aimed at habituation), and Yilmaz et al.[1] (39% using misoprostol). In several studies using ITDex in tinnitus, Sakata et al.[13] and Cesarani et al.[8] reported recoveries of 71% and 74%, respectively, with 34% full recovery in the latter. In our experience, both VAS (P<0.001) and tinnitus loudness (P=0.049) scores tended to decrease significantly. The improvement rates (40% early period, 37% late period) show the efficiency of our treatment, which is in accordance with above literature.

In our report, no significant changes were encountered in average high-frequency and SDS values, and PTAs tended to reduce significantly. This indicates that the therapy administered had no adverse effects on patients' hearing. These results were in agreement with our previous study which suggested that ITDex does not cause any measurable adverse effect with OAE on the outer hair cell (OHC) functions.[20] Further, with the use of dexamethasone through the intratympanic route, not only high perilymph levels were attained, but the potential adverse effects of systemic use were avoided. We used a 27-gauge dental needle for ITDex injection, which has the advantage of being less invasive and more cost efficient than catheter implantation and tube insertion. Furthermore, ITDex treatment has been accepted as a relatively safe procedure compared with other agents like gentamycin and lidocaine. However, there remains a paucity of audiologic and histologic research in the field of dexamethasone ototoxicity.[7] Our study's use of a 4-mg/mL dexamethasone dose is, of course, not one of the higher doses (eg, Hamid's 24-mg/mL dexamethasone study),[21] and there remains a need for audiologic and histologic animal studies at higher doses.

An increase in neural activity of the peripheral auditory system leading to tinnitus has been suggested by Jastreboff and Hazell.[22] Jastreboff believes that the afferent activity is not only produced by inner hair cells (IHC) but by the perceptual intensity of neural activity, which would increase in the case of a probable decrease in cochlear gain by the OHCs. According to Chery-Croze et al.,[23] in the region where IHC damage occurs, any efferent inhibition of OHCs will lead to a reduction in afferent input, and the reduction in efferent inhibition due to damaged IHCs will create a highly active domain in the basilar membrane, resulting in tinnitus. However, according to LePage,[24] even if the IHCs are intact, tinnitus may occur on a portion of the basilar membrane involving damaged OHCs. Loss of motility in the OHCs may repress the ability/capacity of the IHCs to work properly, resulting in a sound input that is not real. Therefore, activity that is not normally heard will be experienced as tinnitus. If functional OHCs are present adjacent to this dysfunctional OHC region, the audiometric sensitivity loss will not occur. In another study[25] focusing on the role of OHCs in tinnitus, the authors claimed that significant OHC dysfunction causes an excessive release of glutamate from

the IHCs, which then leads to an increase in the endocochlear potential, and this phenomenon results in tinnitus.

The choice of an intratympanic route in the treatment of tinnitus theoretically has two advantages: First, high perilymph levels are attained as a result of providing a direct passage via the oval window membrane; and second, adverse effects of systemic administration of the drug are avoided.[7]

"Intratympanic steroid" commonly refers to corticosteroids. Corticosteroids have been used to decrease inflammation on the neuroepithelium of the inner ear associated with autoimmune dysfunctions.[26] Some of the mechanisms suggested for this decrease in inflammation are that steroids passing through the oval window rectify cellular edema and metabolic disorders and stabilize the membrane, and that they suppress the irritated or hypersensitive status of the sensor cells in the inner ear.[5] The decreases we observed in VAS scores and tinnitus loudness are based on the hypothesis that steroids might reduce the increased neural activity of hypersensitive OHCs that produce tinnitus[5] or that they might decrease glutamate release at stress concentration of Dex.[27]

Conclusion

In their 1993 article, Jastreboff and Hazell argue that scientists have said to patients with tinnitus, "There is nothing that can be done. The you sound hear will be with you for your lifetime, so you should learn to live with it."[22] As global conditions improve, patient's look for improved treatment. Today, patients expect a more comprehensive approach from contemporary medicine, one that not only helps them sustain their lives but also improves their quality of life. The underlying idea of this experience is that further steps can be taken to improve the quality of life for patients with a condition that has not been sufficiently addressed in many clinics. According to our improvement rates (40% early period, 37% late period), intratympanic use of dexamethasone is a successful treatment option for tinnitus. Future studies with regard to both reliability and efficiency of the technique are warranted.

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