

Intratympanic dexamethasone as an adjuvant to oral imipramine hydrochloride (Tofranil, a TCA) 25 mg twice daily in management of idiopathic unilateral subjective tinnitus

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Received 31 October 2017

Accepted 5 May 2018

The Egyptian Journal of Otolaryngology 2019, 35:300–306

Background

In this report, we summarize our clinical experience with intratympanic (IT) dexamethasone treatment for control of idiopathic unilateral tinnitus when used as an adjunct treatment with Tricyclic antidepressant (TCA) imipramine hydrochloride 25 mg twice daily for 1 month.

Objectives

To assess the clinical benefit of adding dexamethasone by IT route to the tricyclic antidepressant imipramine hydrochloride in the management of idiopathic unilateral subjective tinnitus.

Study design

A prospective randomized clinical trial was conducted.

Results

Results from this study showed significant subjective improvement of patients with unilateral subjective tinnitus when comparing the two arms of the study, both to pretreatment assessment and between the two arms, giving significant advantage to the group treated with combination of intratympanic dexamethasone with imipramine hydrochloride 25 mg twice daily for 2 weeks using tinnitus handicap inventory questionnaire, subjective tinnitus loudness as measured by a visual analog scale, and tinnitus awareness score.

Conclusion

Intratympanic dexamethasone injection in combination with TCA imipramine maleate could be subjectively beneficial when compared with imipramine hydrochloride alone.

Keywords:

idiopathic, intratympanic dexamethasone, TCA, tinnitus

Egypt J Otolaryngol 35:300–306

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1012-5574

Introduction

Tinnitus by definition is the apparent sensation of sound without definite acoustic stimulation, and it represents one of the most common and distressing diagnoses in otology practice. Tinnitus is more prevalent in patients between the ages of 50 and 71 years, with men older than 65 years being affected more often than women of similar age (12 vs. 7%) [1].

Tinnitus can be classified as being either objective or subjective. Subjective tinnitus refers to a phantom auditory sensation for which no objective sound can be identified, and only the patient who has the tinnitus can hear it [2].

Many patients with tinnitus report associated symptoms such as frustration, annoyance, insomnia, anxiety, depression, irritation, and concentration difficulties, and these symptoms are highly relevant for the perceived tinnitus severity [2].

The available treatments for the management of the tinnitus patient are diverse. The most widely established treatment methods are counseling, cognitive behavioral therapy, and various forms of sound therapies. Frequently, these approaches are applied in combination [3].

Although most patients benefit from the currently available therapies to some degree, a big fraction of them are left untreated and in despair with the notion that ‘they have to learn to live with their tinnitus’ [4].

There is no specific pharmacological compound that has been approved for the treatment of chronic tinnitus [5].

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Antidepressants are frequently prescribed [6]. The main reason for the large use of antidepressants is the frequent co-occurrence of depressive disorders and tinnitus, as well as the overlap in symptomatology and pathophysiology of tinnitus and depression [7].

Intratympanic treatment of tinnitus with corticosteroids or gentamicin has been widely used as an option of treatment in selected patients with tinnitus, alone or in combination with standard modalities of management [8].

We conducted this study to evaluate the effect of combining antidepressant medications with intratympanic steroid injection trying to make a synergism between the effects of both lines of therapy for controlling unilateral idiopathic tinnitus in patients who have tinnitus for more than 3 months.

Patients and methods

Study design and patients

A prospective randomized clinical trial was conducted comparing intratympanic dexamethasone, 4 mg/ml three injections, when added as an adjunct to imipramine hydrochloride, 25 mg (Tofranil) twice daily for 1 month alone, in controlling resistant idiopathic subjective unilateral tinnitus in otherwise healthy individuals.

The study was conducted at two different hospitals in Egypt and KSA during the period from November 2014 to November 2016.

Patients

The study included 40 patients with age ranging from 18 to 60 years, comprising 26 females and 14 males, complaining of unilateral idiopathic continuous tinnitus for 6-month duration or more, with normal hearing or sensorineural hearing loss and normal middle ear function.

The patients were excluded when they met the following criteria based on patient's history: (a) history of ototoxic drug use or otologic disease; (b) prior steroid use before treatment with intratympanic dexamethasone; (c) the presence of chronic otitis media, Meniere's disease, or retrocochlear lesion; (d) psychiatric or neurological diseases; (e) any current centrally acting medications on CNS such as sedatives, hypnotics, antidepressant, and antipsychotics; (f) tinnitus owing to para-auditory

causes such as vascular pulsating tinnitus of arterial or venous etiology, temporomandibular joint dysfunction, or palatal or stapedial myoclonus; (g) cases with acute subjective tinnitus accompanied by sudden SNHL, defined as more than or equal to 30 dB over three contiguous audiometric frequencies in less than 72 h; (h) bilateral, fluctuating, and intermittent tinnitus; and (i) hypertensive and diabetic patients.

A total of 40 patients who met all the criteria of unilateral idiopathic continuous tinnitus and completed questionnaires and pure-tone audiometry at the initial and final visits after treatment were included.

They were divided randomly into two equal groups (A and B), with 20 patients in each group.

Group A received imipramine 50 mg divided as twice daily+intratympanic injection of 4 mg/ml dexamethasone, administered as three injections in three successive weeks.

Group B received oral (tricyclic antidepressant) imipramine 50 mg divided as twice daily for 1 month.

Methods

All the following data were completed for all 40 patients at the initial pretreatment visit and the final posttreatment (3 month) follow-up visit: full history taking (pretreatment) regarding onset, course, and duration, laterality associated symptoms and associated symptoms of tinnitus, history of any systemic disease, and receiving any centrally acting medications; posttreatment history of the patient compliance regarding medications and any subjective change of tinnitus characteristics, severity, loudness, etc.; and pretreatment laboratory investigations, including complete blood picture to exclude anemia, blood lipid profile, and blood sugar.

Audiological assessment

Pure-tone air-conduction thresholds were determined for each ear at frequencies of 0.25, 0.50, 1, 2, 4, and 8 kHz over an intensity range of -10 to 120 dB, and bone-conduction thresholds tested at frequencies of 0.5, 1, 2, and 4 kHz, using pulsed stimulus to minimize confusion with the patient's own tinnitus. Hearing loss was defined as a pure-tone average of 25 dB or greater.

Speech reception threshold was assessed using Arabic spondee words [9] and speech discrimination scores using Arabic phonetically balanced words [10].

Immittancemetry included tympanometry and acoustic reflex thresholds. Patients with abnormal middle ear functions were excluded before treatment.

Subjective assessment of tinnitus before and after treatment was done by the following: tinnitus handicap inventory (THI) questionnaire Arabic version [11]. The questionnaire consists of 25 items (Appendix 1). There are three responses to each question: 'Yes' is awarded four points, 'Sometimes' is awarded two points, and 'No' is awarded zero points. The total score ranges between zero and 100 points, with higher scores representing greater perceived handicap. Overall, 20 points or greater change of THI total score is considered statistically significant [12].

Subjective tinnitus loudness is measured by a visual analog scale (VAS), where 0=no tinnitus and 10=the loudest tinnitus imaginable more than two point difference is considered statically significant.

Tinnitus awareness score (TAS) is defined as the percentage of time (in 10% intervals) the patient was aware of tinnitus within one day, where a more than 10-point difference is considered statically significant.

Treatment protocol

All patients (both groups A and B) received oral (tricyclic antidepressant) imipramine (Tofranil) 50 mg divided as twice daily.

Only patients in group A were scheduled for intratympanic injection of 4 mg/ml dexamethasone (long-acting corticosteroid), administered with 3 injections in three successive weeks starting after randomization.

Following institutional review board approval, the nature of the procedure was explained to the patients, and an informed consent was signed before the procedure. After confirming the tympanic membrane was normal, local anesthesia was induced using 10% lidocaine spray (Xylocaine Pump Spray; AstraZeneca, Sodertalje, Sweden) for 10 min.

Patients were placed in a supine position with their heads turned approximately 45° toward the unaffected side. Then, 0.4–0.6 ml of dexamethasone was injected into the middle ear using an operating microscope. Patients were instructed to refrain from changing position, swallowing, or talking for 30 min after the injection to allow the drug to diffuse into the cochlea through the round window membrane and to

prevent the steroid from leaking through the Eustachian tube.

After treatment, the differences in each variable of tinnitus evaluation (audiological evaluation, DHI, tinnitus loudness measurement by VAS, TAS, and tinnitus matching) at the initial visit (before treatment) and 3 months from the last injection were analyzed.

Statistical analysis

IBM SPSS statistics (version 22.0, 2013; IBM Corp., Chicago, Illinois, USA) were used for data analysis. Data were expressed as mean±SD (2 SD) for quantitative parametric measures in addition to median percentiles for quantitative nonparametric measures and both number and percentage for categorized data. Data were analyzed using Stata (version 14.2; StataCorp LLC, College Station, Texas, USA) and MedCalc (version 15; MedCalc Software bvba, Ostend, Belgium).

Normality of numerical data distribution was examined using the Shapiro–Wilk test. Normally distributed numerical data were presented as mean and SD, and intergroup differences were compared using the unpaired *t* test. Paired numerical data were compared using the paired *t* test.

Nonnormally distributed numerical data were presented as median and interquartile, and intergroup differences were compared using the Mann–Whitney test.

Categorical data were presented as number and percentage, and between-group differences were compared using Fisher's exact test.

P value less than 0.05 was considered statistically significant.

Results

This study included 40 patients, comprising 14 males and 26 females. Mean age of the patients was 40.1 ±3.35 years. Unilateral tinnitus was present in 15 right and 25 left ears. The two groups of patients had no significant differences with respect to the demographic data (Table 1).

They were divided into two study groups. Group A included 20 patients who received imipramine hydrochloride (a tricyclic antidepressant medication) 50 mg oral daily dose divided as twice daily for 1 month

and IT dexamethasone injections 4 mg/ml in three successive injections separated by 1 week apart. Group B included 20 patients who receiving imipramine hydrochloride alone with the same dose and duration. Assessment of tinnitus using subjective rating of symptoms before treatment in either study groups using THI and TAS together with VAS showed no significant difference between both the study groups before treatment (Table 2).

After 3 months from the last injection date, assessment of tinnitus was repeated using the same measures, and TAS showed significant improvement of tinnitus in group A in comparison with group B (Table 3).

After 3 months of last injection, the three parameters of subjective assessment of tinnitus were repeated for all patients in either study groups by the same investigator and results were tabulated and statistically analyzed. The results showed statistically significant improvement in both study groups before and after treatment and between the two groups, giving advantage to group A (imipramine+dexamethasone

group) over group B (imipramine alone) (Table 3 and Fig. 1).

Hearing threshold was not affected by either protocols of treatment, as shown in Tables 4–6.

Discussion

Tinnitus is quite a disabling condition. Its subjective nature makes it difficult to study and quantify. Till now there is no universally accepted treatment protocol for subjective tinnitus [13].

The multifactorial basis for tinnitus generation and perception makes targeting therapy very difficult. All available treatment protocols are not able to reduce or eliminate the sensation of tinnitus on a consistent basis [14].

Steroids have long been used in the treatment of tinnitus, whether idiopathic tinnitus or tinnitus associated with noise trauma, and till to date, there is no solid evidence on the efficacy or safety of systemic steroid therapy in controlling all types of tinnitus [14,15].

The choice of an IT route for steroid administration in the treatment of tinnitus has two advantages: first, high perilymph levels are attained as a result of providing a direct passage through the round window membrane, and second, adverse effects of systemic administration of the drug are avoided [8].

Table 1 Characteristics of patients in either study group

Variables	Group A (N=20)	Group B (N=20)	P value
Age (years)	40±7	39±6	0.666 [†]
Sex (M/F)	8/12	6/14	0.741 [‡]
Affected ear (right/left)	7/13	8/12	1.000 [‡]

Data are mean±SD. [†]Unpaired t test. [‡]Fisher's exact test.

Table 2 Subjective rating of symptoms before treatment in either study group

Variables	Assessment tool	Group A (N=20)		Group B (N=20)		P value [†]
		Mean	SD	Mean	SD	
Subjective rating of symptoms before treatment	THI	44.7	10.3	47.8	7.3	0.281
	TAS ^a	53.5	12.7	57.5	12.1	0.314
	VAS	5.3	1.3	5.9	1.0	0.148

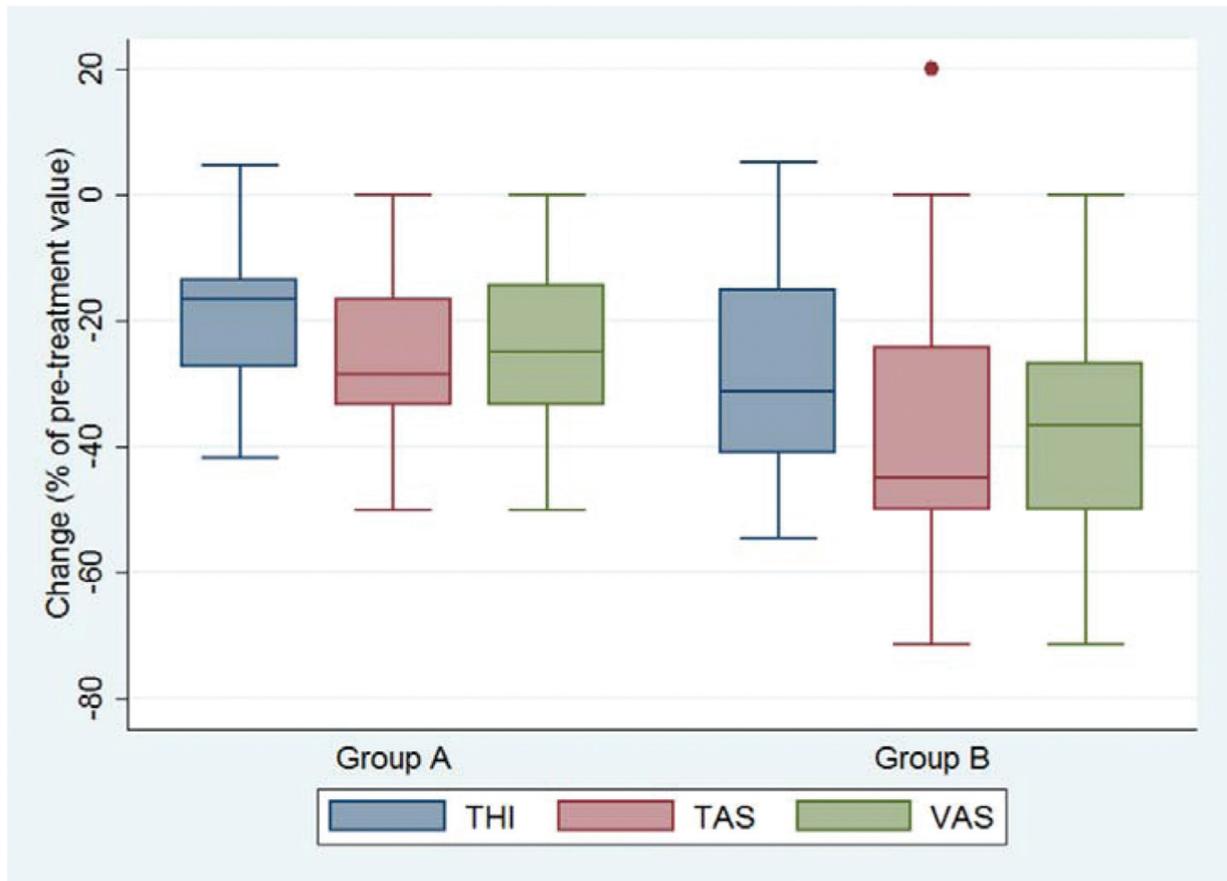
TAS, tinnitus awareness score; THI, tinnitus handicap inventory; VAS, visual analog scale. ^aTAS is defined as the percentage of the time the patient is aware of tinnitus for a day. [†]Unpaired t test.

Table 3 Within-group comparison of subjective rating of symptoms before and after treatment

Variables	Assessment tool	Time	Group A (N=20)			Group B (N=20)		
			Mean	SD	P value [†]	Mean	SD	P value [†]
Subjective rating of symptoms	THI	Before treatment	44.7	10.3	<0.001	47.8	7.3	<0.001
		After treatment	36.4	10.2		34.4	8.2	
	TAS	Before treatment	53.5	12.7	<0.001	57.5	12.1	<0.001
		After treatment	40.5	14.3		36.0	13.1	
	VAS	Before treatment	5.3	1.3	<0.001	5.9	1.0	<0.001
		After treatment	4.0	1.1		3.6	1.0	

There was statistically significant improvement of tinnitus symptomatology posttreatment in either study groups. TAS, tinnitus awareness score; THI, tinnitus handicap inventory; VAS, visual analog scale. [†]Paired t test.

Figure 1



Box plot showing the percentage of change in subjective rating of symptoms in either study group. Box represents the range from the first quartile to third quartile (interquartile range). Line inside the box represents the median (second quartile).

Table 4 Hearing threshold in affected ear before and after treatment in either study group

Variable	Frequency	Group A (N=20)		Group B (N=20)		Before treatment P value [†]	After treatment P value [†]
		Before treatment Mean±SD	After treatment Mean±SD	Before treatment Mean±SD	After treatment Mean±SD		
Hearing threshold in affected ear before and after treatment (dB)	0.25 kHz	25.5±10.6	24.0±11.0	25.3±8.0	23.3±8.0	0.934	0.806
	0.5 kHz	26.5±11.0	26.8±10.7	26.0±8.0	25.3±8.7	0.871	0.628
	1 kHz	27.5±12.2	27.8±12.9	26.5±9.3	25.3±10.2	0.772	0.501
	2 kHz	31.3±11.1	31.0±11.2	30.3±9.4	29.5±9.1	0.760	0.644
	4 kHz	34.3±12.5	33.3±12.2	32.8±11.4	31.5±10.8	0.694	0.633
	8 kHz	34.0±13.2	34.5±13.2	33.3±12.6	33.3±11.3	0.855	0.749

[†]Unpaired t test.

Empirical treatment of idiopathic tinnitus with antidepressant medications has been used by many otologists, and results are encouraging [16].

In this study, a combination of antidepressant medication with intratympanic dexamethasone injection was used trying to make a synergism between the effects of both lines of therapy and to reduce the expected adverse effects using both medications in one arm of the study groups and an antidepressant alone in another arm as a control group.

This hypothesis was evaluated through a prospective, randomized, controlled trial on 40 patients. There was female predominance in both groups, and left ears were affected more than right ears in both study groups. Average age was 40±7 years in group A and 39±6 years in group B, with no statistically significant differences regarding age or sex between both study groups (Table 1). These patients were presented to the outpatient clinic complaining of unilateral tinnitus. Patients who met the inclusion criteria were randomly allocated into two study groups: group A

Table 5 Within-group comparison of hearing threshold in affected ear before and after treatment

Variables	Frequency	Assessment time	Group A (N=20)			Group B (N=20)		
			Mean	SD	P value [†]	Mean	SD	P value [†]
Hearing threshold in tinnitus ear (dB)	0.25 kHz	Before treatment	25.5	10.6	0.06	25.3	8.0	0.25
		After treatment	24.0	11.0		23.3	8.0	
	0.5 kHz	Before treatment	26.5	11.0	0.66	26.0	8.0	0.61
		After treatment	26.8	10.7		25.3	8.7	
	1 kHz	Before treatment	27.5	12.2	0.57	26.5	9.3	0.39
		After treatment	27.8	12.9		25.3	10.2	
	2 kHz	Before treatment	31.3	11.1	0.66	30.3	9.4	0.29
		After treatment	31.0	11.2		29.5	9.1	
	4 kHz	Before treatment	34.3	12.5	0.16	32.8	11.4	0.17
		After treatment	33.3	12.2		31.5	10.8	
	8 kHz	Before treatment	34.0	13.2	0.18	33.3	12.6	1.00
		After treatment	34.5	13.2		33.3	11.3	

[†]Paired t test.

Table 6 Percentage of change in subjective rating of symptoms in either study group

Variables	Assessment tool	Group A (N=20)		Group B (N=20)		P value [†]
		Median	IQR	Median	IQR	
Change in subjective rating of symptoms (% from baseline)	THI	-17	-30 to -13	-31	-47 to -15	0.041
	TAS	-29	-33 to -17	-45	-50 to -24	0.049
	VAS	-25	-33 to -14	-37	-50 to -27	0.007

The subjective improvement of tinnitus was more significant in GROUP A in comparison with GROUP B. IQR, interquartile range; TAS, tinnitus awareness score; THI, tinnitus handicap inventory; VAS, visual analog scale. [†]Mann-Whitney test.

comprised 20 patients who received imipramine hydrochloride (a tricyclic antidepressant medication) 50 mg oral daily dose divided as twice daily for 1 month and IT dexamethasone injections 4 mg/ml in three successive injections separated by 1 week apart, and group B included 20 patients who received imipramine hydrochloride alone with the same dose and duration.

Assessment of tinnitus using subjective rating of symptoms before treatment in either study groups (Table 2) using THI and TAS together with VAS showed no significant difference between both study groups before treatment.

After 3 months from the last injection date, assessment of tinnitus was repeated using the same measures, hearing threshold was not affected by either protocols of treatment as shown in Tables 4–6. After 3 months of last injection, the three parameters of subjective assessment of tinnitus were repeated for all patients in either study groups by the same investigator, and results were tabulated and statistically analyzed. The results showed statistically significant improvement in both study groups before and after treatment and between the two groups, giving advantage to group A (imipramine+dexamethasone group) over group B (imipramine alone) (Table 3 and Fig. 1).

An *et al.* [17] reported that the mean THI scores were significantly reduced at 3 months after IT dexamethasone injection alone. Their patients received intratympanic steroids alone without tricyclic medications. Their results agreed with the current study. Sakata *et al.* [18], Shulman and Goldstein [19], and Cesarani *et al.* [20] used IT dexamethasone injection alone in managing idiopathic tinnitus and reported some objective recoveries of 71, 70, and 74%, respectively and these results match also with the results of this current study.

In contrary to the previously mentioned studies, Araújo *et al.* [21] studied the effectiveness of IT dexamethasone injection as a sole treatment for severely disabling cochlear tinnitus in a randomized, prospective, single-blind study, and they concluded that there was no advantage of IT injections of dexamethasone over saline solution in the treatment of severely disabling tinnitus, and both solutions produced a placebo-like improvement in ~30–40% of patients. Parelkar *et al.* [22] reported that although IT therapy was a highly efficacious and tempting mode of drug delivery, IT dexamethasone injections were not effective for refractory tinnitus. This can be explained by looking at the inclusion and exclusion criteria of these studies and the assessment of patients after treatment using only

tinnitus loudness levels and minimal masking levels before and after treatment. Moreover, they did not use any subjective measures to assess tinnitus before and after treatment. The subjective nature of tinnitus makes it difficult to assess objectively.

The combination of intratympanic steroid injection and a tricyclic antidepressant is believed to have a positive effect on tinnitus control. There is no clear explanation why patients who received both medications reported such significant subjective relief. This may point to the subjective nature of this symptom which till now has got no clear pathological explanation. It is well accepted that the majority of tinnitus is triggered by cochlear damage and here comes the steroid action of immune suppression, anti-inflammatory, and ion homeostasis that would be expected to help repair of cochlear damage [23,24].

The control of tinnitus-associated anxiety alone that might be achieved by the use of the oral antidepressant or its placebo effect alone cannot explain the significant difference between the two arms of the study, which excludes the possibility of the sole action of the oral medication without a strong positive effect of intratympanic steroid.

Conclusion

This study showed a better clinical outcome of IT steroid administration together with Tricyclic antidepressant (TCA). This combination could be subjectively beneficial for alleviating idiopathic subjective unilateral tinnitus.

For more convincing conclusions, this combination requires more evidence provided by larger study groups and longer periods of follow-up to establish stricter criteria of those patients who would probably benefit from this combination.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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