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Main Article

Intratympanic methylprednisolone injections for subjective tinnitus

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Abstract

Objectives: This study aimed to determine whether intratympanically injected methylprednisolone is effective in treating subjective tinnitus refractory to medical treatment.

Study design: Prospective, randomised, placebo-controlled, single-blinded study.

Methods: Seventy adult patients with subjective tinnitus of cochlear origin were randomly assigned to receive intratympanic injection of either methylprednisolone or saline solution. The treatment protocol comprised three intratympanic injections, one per week for three weeks. Improvement in tinnitus severity was measured by a self-rated tinnitus loudness scale and by the tinnitus severity index, at baseline and two weeks after the last injection.

Results: Data for 59 patients were available for analysis. There was no significant difference between the two treatment groups regarding age, sex, pure tone average, pretreatment tinnitus intensity, tinnitus laterality or tinnitus duration. There was a significant post-treatment improvement in self-rated tinnitus loudness scale results in both groups. No significant post-treatment changes in the tinnitus severity index individual and total scores were observed in either group. The most frequently encountered side effects were pain during injection, vertigo, a burning sensation around the ear and in the throat, and a bitter taste. A burning sensation and bitter taste were observed more often in the methylprednisolone group compared with the placebo group

Conclusion: The results of this study indicate that intratympanic methylprednisolone has no benefit, compared with placebo, for the treatment of subjective tinnitus of cochlear origin refractory to medical treatment.

Key words: Methylprednisolone; Tinnitus

Introduction

Tinnitus is defined as the perception of sound without an external stimulus.[1] Subjective tinnitus represents the most common form of tinnitus; its incidence is estimated at approximately 10 per cent of the population.[2] Most cases are associated with hearing loss, but tinnitus can also occur with normal hearing.[1]

Subjective tinnitus is most commonly due to cochlear pathology, although other areas within the auditory pathway can also be responsible.[3] In cases in which the cochlea is the site of tinnitus, the most common diagnoses include presbycusis, noise-induced hearing loss and disorders associated with endolymphatic hydrops.[3]

Lack of knowledge about the exact pathophysiology of subjective tinnitus in patients with presbycusis limits our ability to implement effective therapy. Several different therapeutic interventions have been described for the treatment of tinnitus, including tinnitus retraining, tinnitus masking, biofeedback therapy, various drug treatments and, more recently, intratympanic injection therapy.[1,2,4]

Thus far, steroids have been one of the most popular agents used for intratympanic therapy. Steroids are known to have anti-inflammatory and electrolyte-altering effects.[4] Steroid receptors have been demonstrated in the inner ear in animal models and human temporal bones.[5,6] A significantly high level of various steroid medications has been demonstrated in the perilymph following transtympanic injection; this has the added benefit of avoiding systemic effects.[7] Of the various steroids assessed, methylprednisolone has been found to have the best pharmacokinetic profile.[8]

However, a review of the literature indicates conflicting results for the use of steroids in patients

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with subjective tinnitus. Sakata *et al.* reported retrospectively on 3041 patients who had undergone intratympanic dexamethasone injection.[9] A 75 per cent improvement in tinnitus was noted immediately after treatment. The only two prospective, randomised studies of the use of intratympanic steroids to treat tinnitus have been performed with dexamethasone. Silverstein *et al.* administered intratympanic dexamethasone to patients with Ménière's disease, and failed to demonstrate any significant changes in any measured parameter, including tinnitus.[10] Araújo *et al.* tested the effectiveness of dexamethasone injections as treatment for severe, disabling tinnitus, and found that the drug had no advantage compared with saline solution.[11]

On the other hand, intratympanic methylprednisolone has been used by Silverstein *et al.* in an uncontrolled preliminary study of patients with Ménière's disease, autoimmune inner-ear disease, sudden sensorineural deafness and presbycusis.[12] These authors suggested that intratympanic steroids may affect the symptoms of hearing loss and tinnitus in certain patients; 60 per cent of the patients reporting improvement had Ménière's disease.[12]

Application of intratympanic steroids has been shown to improve tinnitus in some patients; however, these studies were uncontrolled.[9,12] Additionally, although methylprednisolone has been shown to have a better pharmacokinetic profile in the inner ear than intratympanic dexamethasone, no controlled studies have investigated its effect on subjective tinnitus.[8] For this reason, we decided to undertake a prospective, controlled, randomised, single-blinded study to investigate intratympanic methylprednisolone injections as a treatment for subjective tinnitus refractory to medical treatment.

Methods

Study design

This was a randomised, single-blinded, placebo-controlled, prospective study. Patients were randomised to receive one of two treatments: intratympanic methylprednisolone or placebo (saline solution). The treatment protocol comprised three intratympanic injections, one per week for three weeks.

The primary outcome measure was improvement in tinnitus severity, assessed by a self-rated tinnitus loudness scale and by the tinnitus severity index.[1] The outcomes of patients in the two groups were compared.

Patients completed the tinnitus loudness scale and the tinnitus severity index questionnaire at baseline and two weeks after the last injection.

Patients

Starting in June 2005, adult patients (i.e. older than 18 years of age) with subjective tinnitus for whom drug treatment had failed were enrolled in the study. New patients were enrolled over a 30-month period.

Informed consent was obtained from all patients prior to enrolment. The study protocol was approved by the institutional review board of our hospital.

Patients with otosclerosis, chronic otitis media, retrocochlear pathology, hypertension, diabetes mellitus, hypercholesterolaemia, hypo- or hyperthyroidism, or cancer were excluded. Patients with sudden sensorineural hearing loss were also excluded, since we considered it unethical to use a placebo in this group of patients.

Pretreatment evaluation

The initial patient assessment included a detailed history and otomicroscopic examination, followed by pure tone audiometry, speech discrimination and impedance testing. Brainstem evoked response audiometry or magnetic resonance imaging scanning was undertaken when there was suspicion of retrocochlear involvement. Laboratory studies included complete blood count, blood chemistry (including potassium, creatinine and glucose), serum cholesterol and triglyceride levels, and thyroid function tests.

Patients selected as eligible for the study were asked to complete a specific questionnaire regarding the affected ear, tinnitus duration, description of tinnitus (i.e. waterfall, whistle, crickets or other) and previous otological disease. Patients were then asked to complete a self-rated tinnitus loudness scale (using a one to 10 scale, with 10 being loudest) and a tinnitus severity index questionnaire in Turkish. The tinnitus severity index comprised a list of 12 questions regarding common situations related to tinnitus, including emotional distress, interference with work and leisure, sleep disturbance, and the patient's efforts to ignore their tinnitus.[1] Possible answers were 'never', 'rarely', 'sometimes', 'usually' and 'always', graded on a one to five scale, with one being 'never' and five being 'always'.

Treatment

Patients were randomly assigned to receive 0.3 to 0.4 ml intratympanic injections of either a 62.5 mg/ml methylprednisolone solution (Prednol-L; Mustafa Nevzat, Istanbul, Turkey) or isotonic sodium chloride (saline) solution. The intratympanic injection was performed with the patient lying supine with their head turned 45° to the unaffected side. Topical anaesthesia of the ear drum was induced using a cotton pledget soaked with Emla cream (Astra Zeneca, Istanbul, Turkey), placed under microscopic vision onto the lateral surface of the ear drum and left in place for 20 minutes. During this time, the solutions to be injected were warmed to body temperature to avoid vertigo. Using a 27-gauge needle and a 1 ml syringe, the solution was injected under microscopic vision into the middle ear via the anterosuperior quadrant of the tympanic membrane until the tympanic cavity was visibly filled with the solution. Another needle puncture was made superior to the first one for air escape, as previously described.[13] Patients were instructed to swallow as little as possible and to stay still for

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TABLE I

COMPARISON OF PATIENTS IN DRUG AND PLACEBO GROUPS

Parameter	Drug group	Placebo group	*p*
Patients (*n*)	30	29	
Age (mean (yrs))	49.9	55.3	0.063
Sex ratio (male/female)	2	1.5	0.628
Pure tone average (dB HL)*	45.25 ± 13.73	50.16 ± 15.37	0.609
Pretreatment tinnitus intensity score*†	7.70 ± 2.28	6.68 ± 2.02	0.077
Tinnitus laterality (unilat/bilat (*n*))	22/8	18/11	0.354
Tinnitus duration (mths)*	69.87 ± 121.4	90.48 ± 97.26	0.475

*Data shown as mean ± standard deviation. †self-rated tinnitus loudness scale. Yrs = years; unilat = unilateral; bilat = bilateral; mths = months

30 minutes. Any side effects were immediately recorded.

Statistical analysis

Statistical analysis was performed using the independent *t*-test, paired *t*-test and chi-square test. Significance was determined to be at the confidence level $p < 0.05$.

Results

Seventy patients with subjective tinnitus refractory to medical treatment were enrolled into the study. Eleven patients (five in the drug group and six in the placebo group) were excluded as they failed to return for follow up.

The aetiology of cochlear tinnitus in our patients was: presbycusis in 28 patients (47 per cent); acoustic trauma in seven (12 per cent); head and neck trauma in four (7 per cent); and ototoxicity in two (3 per cent). We were unable to determine tinnitus aetiology in 18 of our patients (31 per cent).

There was no significant difference between the treatment and control groups regarding age, sex, pure tone average, pretreatment tinnitus intensity, tinnitus laterality and tinnitus duration (Table I).

Table II gives patients' pre- and post-treatment tinnitus severity index scores and self-rated tinnitus loudness scores, and compares changes. We failed to find any significant post-treatment differences in any of the individual tinnitus severity index question scores, for either the drug group or the placebo group ($p > 0.05$ for all). When we assessed post-treatment improvements in individual tinnitus severity index question scores, comparing the drug versus the placebo groups, there were no significant differences ($p > 0.05$ for all) (Table II).

The average total tinnitus severity index score in both groups also failed to show any significant difference, comparing pre- and post-treatment results ($p = 0.112$ in the drug group, $p = 0.935$ in

TABLE II

TINNITUS SCORES: TINNITUS SEVERITY INDEX AND SELF-RATED TINNITUS LOUDNESS SCALE

Assessment point	Drug group			Placebo group			Drug *vs* placebo group; *p**
	Pretreatment	Post-treatment	*p*	Pretreatment	Post-treatment	*p*	
Tinnitus severity index†							
Does your tinnitus. . .							
make you feel irritable and nervous?	3.00 ± 1.20	2.59 ± 1.28	0.276	3.19 ± 1.03	3.06 ± 0.97	0.690	0.547
make you feel tired or stressed?	3.38 ± 1.18	2.94 ± 1.34	0.254	2.67 ± 0.97	2.71 ± 0.77	0.893	0.102
make it difficult for you to relax?	2.34 ± 1.37	2.00 ± 1.37	0.414	2.05 ± 1.07	2.24 ± 1.09	0.598	0.513
make it uncomfortable to be in a quiet room?	2.90 ± 1.71	2.41 ± 1.46	0.328	3.20 ± 1.36	3.12 ± 1.17	0.846	0.711
make it difficult to concentrate?	2.63 ± 1.27	1.94 ± 1.25	0.078	2.33 ± 1.15	2.29 ± 0.92	0.910	0.793
make it harder to interact pleasantly?	2.13 ± 1.38	1.94 ± 1.34	0.646	1.38 ± 0.50	1.24 ± 0.44	0.350	0.808
interfere with required activities?	2.24 ± 1.30	2.00 ± 1.37	0.554	1.52 ± 0.81	1.41 ± 0.71	0.658	0.773
interfere with social activities?	2.31 ± 1.39	1.63 ± 0.96	0.087	1.57 ± 0.81	1.35 ± 0.70	0.387	0.165
interfere with overall enjoyment of life?	2.69 ± 1.54	2.19 ± 1.42	0.288	2.38 ± 1.40	2.18 ± 1.13	0.629	0.641
interfere with sleep?	3.30 ± 1.51	2.71 ± 1.40	0.191	3.24 ± 1.26	3.00 ± 1.12	0.547	0.866
How much effort is it to ignore tinnitus?	3.31 ± 1.49	2.75 ± 1.69	0.256	3.25 ± 1.25	3.71 ± 2.11	0.422	0.426
How much discomfort do you experience when tinnitus is present?	3.41 ± 1.45	2.69 ± 1.62	0.131	3.10 ± 1.21	3.13 ± 1.15	0.950	0.182
Total score	33.00 ± 11.09	27.24 ± 12.75	0.112	29.43 ± 8.54	29.24 ± 5.26	0.935	0.507
Self-rated tinnitus loudness scale‡	7.70 ± 2.28	6.12 ± 1.80	0.018	6.68 ± 2.02	5.21 ± 1.35	0.004	0.198

Data are given are means ± standard deviation. *Change in scores, drug group *vs* placebo group. †Scale of 1 to 5; ‡scale of 1 to 10.

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TABLE III
ADVERSE EFFECTS IN DRUG AND PLACEBO GROUPS

Symptom	Group		*p*
	Drug	Placebo	
Pain (%)	67	52	NS
Burning sensation (%)	57	17	0.002
Vertigo (%)	57	38	NS
Bitter taste (%)	40	7	0.003

NS = nonsignificant

the placebo group). An assessment of post-treatment changes in average total tinnitus index severity score, comparing the drug versus the placebo group, indicated no significant difference ($p = 0.507$) (Table II).

Assessment of self-rated tinnitus loudness scores showed a significant improvement in both groups, comparing pre- and post-treatment results ($p = 0.018$ in drug group, $p = 0.004$ in placebo group) (Table II). However, assessment of post-treatment changes in the self-rated tinnitus loudness score, comparing the drug versus the placebo group, showed no significant difference ($p = 0.198$) (Table II).

Adverse events

Patients were questioned about the occurrence of any adverse events. Pain during injection was the most commonly reported adverse event, followed by vertigo, burning sensation around the ear or in the throat, and a bitter taste. A burning sensation and a bitter taste were reported more often in the drug group than the placebo group ($p = 0.002$ and $p = 0.003$, respectively). There was no significant difference in the two groups in terms of pain during injection and vertigo (Table III).

The adverse events reported were generally mild. Patients reported that pain, burning sensation and bitter taste resolved in approximately 10–20 minutes following the injection. Vertigo resolved spontaneously in all patients approximately 2 minutes after the injection. No changes in hearing level were noted in either group after treatment. None of the patients developed otitis media, otitis externa or persistent perforation of the tympanic membrane.

Discussion

The results of this study indicate no benefit of intratympanic methylprednisolone over placebo for the treatment of subjective tinnitus refractory to medical treatment. Intratympanic treatment resulted in significant improvement in self-rated tinnitus loudness scoring in both the drug and the placebo groups. However, there was no improvement in scores for any of the questions of the tinnitus severity index questionnaire.

The potential success of intratympanic methylprednisolone for tinnitus treatment is based on the theory that glucocorticoid receptors exist in human cochlear tissue.[14] The interaction of the drug with these glucocorticoid receptors leads to alteration of specific target genes, producing metabolic and anti-inflammatory effects.[15,16] Steroids may also affect the vascularity of the inner ear. Shirwany *et al.* showed that transtympanic injection of dexamethasone in the guinea pig led to a 29 per cent increase in cochlear blood flow.[7] Expression of aquaporin 1 (an intrinsic membrane protein which increases the ability of water to pass through an epithelial cell layer) has been shown to increase following intratympanic steroid injection.[17]

Intratympanic application of steroids has been used for the treatment of various inner-ear and vestibular pathological conditions, including sudden sensorineural hearing loss, Ménière's disease and tinnitus.[10,12,18,19,20,21]

Transtympanic steroid therapy for tinnitus is supported by a body of literature.[9,22] Sakata *et al.* used intratympanic dexamethasone in 1214 patients with cochlear-type tinnitus, and achieved a 71 per cent effectiveness rate.[9] Shulman and Goldstein used either dexamethasone or hydrocortisone to treat 10 patients with cochlear-type tinnitus, and achieved a 70 per cent rate of tinnitus control.[22]

Despite the theoretical benefits of intratympanic steroid treatment and the clinical success of the aforementioned studies, the current study failed to show any significant benefit of intratympanic methylprednisolone application in patients with subjective cochlear tinnitus. There are several possible reasons for a lack of success in our study.

First of all, there is no standard protocol in the literature for intratympanic steroid injection – i.e. the frequency of injections, concentration and type of corticosteroid, and the method of injections. Our approach to intratympanic delivery of methylprednisolone may have resulted in poor diffusion into the inner ear.

- **Lack of knowledge about the exact pathophysiology of subjective tinnitus in patients with presbycusis limits our ability to implement effective therapy**
- **Application of intratympanic steroids has been shown to improve tinnitus in some patients; however, these studies were uncontrolled**
- **This paper reports a prospective, controlled, randomised, single-blind study investigating intratympanic methylprednisolone injections as treatment for subjective tinnitus refractory to medical treatment**
- **The results indicated no benefit of intratympanic methylprednisolone over placebo for the treatment of subjective tinnitus of cochlear origin refractory to medical treatment**

Another possible cause for a lack of significant improvement following intratympanic methylprednisolone may relate to our study population, most of which comprised patients with presbycusis.

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Intratympanic application of steroids has been shown to be more effective in patients with labyrinthine hydrops and chronic otitis media, compared with other causes of subjective cochlear tinnitus.[9,23] Unfortunately, we were not able to obtain consent for the inclusion of any patients with labyrinthine hydrops, and patients with chronic otitis media were excluded.

Another factor that may have affected our results relates to the increasing evidence suggesting that tinnitus is generated in the central nervous system as a result of deprivation of input or abnormal input from the ear. Alterations in neuronal input are suggested to lead to structural and functional changes in the central nervous system, resulting in tinnitus.[1,24] Such theories may explain why individual responses to intratympanic methylprednisolone and to saline were equivalent.

Finally, we would like to emphasise the fact that the use of a self-rated tinnitus loudness scale as an outcome measure in tinnitus studies may not be reliable, as shown in the current study. In our study, treatment resulted in an improvement in this scale in both the drug and the placebo groups. However, the additional use of the detailed tinnitus severity index questionnaire clearly showed that, in fact, our intervention had had no positive effect on patients' subjective experience of tinnitus. The tinnitus severity index is a better tool with which to define and quantify tinnitus, compared with a self-rated tinnitus loudness scale, and thus may be more helpful for the clinical assessment and management of patients with subjective tinnitus.

Conclusion

The current study of patients with subjective tinnitus refractory to medical treatment found that the placebo effect of transtympanic methylprednisolone injection was very high, but that in fact there appeared to be no actual benefit of this treatment over placebo in the treatment of such patients.

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