Effectiveness of Intratympanic Dexamethasone with Lidocaine for Alleviation of Tinnitus

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ABSTRACT

Objective: To determine the effectiveness of Intratympanic Dexamethasone with Lidocaine in control of idiopathic tinnitus.
Study Design: Randomized control trial (Clinical Trials. gov Identifier: NCT04798391).
Place and Duration of Study: ENT Department, PAF Hospital, Sargodha Pakistan, from Apr 2017 to Jul 2019.
Methodology: 264 consenting patients with idiopathic unilateral tinnitus presenting at ENT Department PAF Hospital Sargodha were assessed for tinnitus severity using the modified tinnitus handicap inventory. The scores were recorded and subsequently administered intra-tympanicaly 2.0ml (milli-liter) of Dexamethasone and Lidocaine (1.5 ml Dexamethasone ± 0.5 ml 1% Lidocaine). The dose was repeated twice at weekly intervals. All the patients were reassessed on the modified tinnitus handicap inventory two weeks after the third Intra-tympanic administration, with patients divided into responsive and no-responsive groups depending on ten points or more improvement in tinnitus score.
Results: Mean modified tinnitus handicap inventory score pre-therapy was 29.6 ± 5.68, and post-therapy was 17.1 ± 7.45. Independent-sample T-test applied showed a *p*-value of <0.001.
Conclusion: Intratympanic Dexamethasone with lidocaine has a definitively positive outcome on tinnitus improvement.

Keywords: Dexamethasone, Intratympanic, Tinnitus.

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INTRODUCTION

Tinnitus is derived from "Tinnire", meaning ring (Hesse). Tinnitus, also known as phantom noise, is more aptly described as the anomalous perception of auditory impulses without external stimuli.[1] The most common site of abnormal auditory is the cochlea, but any part of the auditory pathway can generate this phenomenon.[2] The aberrant impulse is then transmitted to the auditory cortex, and conscious perception of sound starts. Due to the cessation of negative feedback response, the aberrant signal from the point of origin keeps on regenerating and thereby gives a tone. The tone varies from continuous to intermittent type, with varying intensities and character. The character has been described as roaring, hissing or even high-pitched whistles.

The use of steroids in treating sudden sensory neural hearing loss has been well documented. In sudden sensory neural hearing loss, steroids are used via a systemic route. Using the same analogy, it has been postulated that steroids introduced in the middle ear might positively affect the relief of tinnitus. Intra-tympanic steroids require a relatively small dose to be delivered to the cochlea without having systemic results.[4,5] Animal models show that steroids administered intra-tympanically into the middle ear cavity lead to a positive influence on the ionic balance in the endolymph, subsequently leading to up-regulation of K+/Na+ ion channels and water channels and stabilization of impulse generation from the inner ear. The water channels called aquaporins are involved in signal stability at the level of the inner ear and stria vascularis. The functioning of stria vascularis reverts to normal with intratympanic steroids in rat models, as seen by better circulation, which leads to increased clearance of end products of metabolism.[6]

The fact that Dexamethasone, a long-acting steroid, has a natural anti-inflammatory effect, which reduces endolymphatic hydrops after diffusion from oval and round windows, makes it an ideal drug solution for tinnitus therapy.[7] Furthermore, it stabilizes the cochlea's ionic disposition, leading to down regulation of Na+/K+receptors, leading to correction of aberrant signal generation.[6] The positive feedback related to aberrant signal generation is the originator of tinnitus pulses. These two mechanisms, coupled with increased blood supply to cochlea under the influence of Dexamethasone, make it a viable treatment option for tinnitus.[8,9] The intra-tympanic route for delivering a required amount of steroid is the most viable option and combining long-acting steroids like Dexamethasone with Lidocaine theoretically gives added advantage over steroid-alone infusion. This rationale was

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employed in this study with subjective measurement to improve tinnitus.

METHODOLOGY

This randomized control trial (Clinical Trials gov Identifier: NCT04798391) was carried out to determine alleviation in symptoms of tinnitus with the intratympanic installation of Dexamethasone and Lidocaine at ENT Department PAF Hospital Sargodha after approval of Institutional Review Board (File No: 11/J/Med) of from April 2017 - July 2019.

Inclusion Criteria: Patients scoring 20 or above on the modified tinnitus handicap inventory were included in the study.

Exclusion Criteria: Any patient with the history of head trauma, tympanic membrane perforation, depression and ear surgery was excluded from the study.

A sample size of two hundred and sixty-four consenting patients was calculated with the Raosoft sample size calculator with an incidence of 1.84 per 1000 reported by Moore *et al,* in a study population of 27,439 with 2517 new diagnoses per year (for the year 2001).[8] The patients were selected by the non-probability consecutive convenience sampled technique and divided into responsive and non-responsive groups depending on alleviation of tinnitus after intratympanic steroids instillation.

All the patients with idiopathic unilateral tinnitus were assessed for tinnitus severity using the modified tinnitus handicap inventory. The tinnitus handicap inventory introduced by Newman *et al,*[1] in 1996 was modified to include ten questions with a maximum score of 40. Patients were assessed on the modified tinnitus handicap inventory, and the scores were recorded.

All the patients were administered intra-tympanically 2.0 ml (millilitre) of Dexamethasone and Lidocaine (1.5ml Dexamethasone ± 0.5ml 1% Lido-caine) in the procedure room of the ENT department. Topical anaesthesia was given by placing a small cotton pledget soaked in 4% Lidocaine solution on the tympanic membrane for 15 minutes. The pledget was removed after 15 minutes, and 2.0ml of the drug was instilled into the tympanic cavity using a dental syringe slowly over 5 minutes. After drug instillation, patients were advised to lie prone with treated ear up for 30 minutes, followed with tablet Prochlorperazine Maleate 12.5 mg thrice daily, capsule Cefixime 400 mg once daily for 5 days and tablet Ibuprofen 400 mg if required up to a maximum of three tablets a day. Patients were advised to avoid driving and sudden neck movements immediately after the procedure for eight hours. The same procedure was repeated at weekly intervals for two weeks, making it three intratympanic infusions over two weeks duration. Two weeks after the last administration, all the patients were re-assessed on the modified tinnitus handicap inventory.[1] Patients with an improved score of 10 points were as responsive patients, and the rest were labelled as non responsive patients.

Statistical Package for Social Sciences (SPSS) version 20.0 was used for the data analysis. Independent sample t-test was used to test the significance of tinnitus tinnitus handicap inventory score among the responder and non-responder group after treatment. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 264 adult patients volunteered for the study. Age ranged from 28 to 69 years, with a mean age of 50.45 ± 11.9 years. There were 103 (39%) females and 161 (61) males in the study population. Out of 264 patients, 212 (80.3%) were grouped as responsive patients (Having a reduction in post therapy modified tinnitus handicap inventory score by 10 points or more), and 52 (19.7%) patients were grouped as non-responsive patients (having a reduction in post therapy modified tinnitus handicap inventory score by less than 10 points).

The mean of the modified tinnitus handicap inventory score assessed pre-therapy was 29.6 ± 5.68. The mean post therapy modified tinnitus handicap inventory score was 17.1 ± 7.45. The mean modified tinnitus handicap inventory score in the responsive-group was 29.08 ± 5.78 pre-therapy and 14.46 ± 5.07 post-therapy. The modified tinnitus handicap inventory score in the non-responsive group was 32.1 ± 4.51 pre-therapy and 28.15 ± 5.16 post-therapy.The mean post-therapy modified tinnitus handicap inventory score in the responsive group was 14.46 ± 5.07 and in the non-responsive group was 28.15 ± 5.16, with the *p*-value <0.001, as shown in Table.

Table: Tinnitus improvement in the study groups.

Parameters	Study Group (n=264)		*p*-value
	Responsive Group (n=212)	Non-Responsive Group (n=52)	
Post Treatment THI Score	29 ± 5.78	32.1 ± 4.51	<0.001

DISCUSSION

Tinnitus is a symptom rather than a disease. It is estimated that one in ten persons have experienced tinnitus transiently at least once in their lifetime. In cases of long-standing tinnitus, the symptom can be extremely bothersome and may even lead to depression.[9] Most patients who have experienced tinnitus discuss it as a roaring or high-pitched noise with varying intensities, often related to mood and surroundings. Patients usually complain of increasing intensities in serene surroundings.[10] Another debatable aspect of tinnitus is stress. Neuro-imaging and electroencephalogram recordings showed abnormal channels between the limbic system and auditory cortex when studied against the backdrop of tinnitus investigations in patients.

Ever since the establishment of abnormal auditory pathways as the cause of aberrant signals that led to tinnitus, it has been widely studied to see the effect of neuro-modulating drugs and anti-inflammatory drugs alleviate tinnitus. From oral prescription to intravenous drug administration, it was found that some pharmaceutical agents did relieve tinnitus but at the cost of severe side effects.[11,12]

Due to increased side effects associated with systemic drug delivery, the intratympanic route was increasingly studied as a viable drug delivery system with lesser side effects. Within the middle ear cavity, the presumable pathway for drug entry into the labyrinth is the round window, oval window and preformed vascular pathways. Once the drugs are introduced in the middle ear, the preferred pathway is a round window membrane as it has a thickness of only 60 micrometres. The cuboidal lining on the middle ear around the round window membrane and the loose collagen and elastocysts help in the permeability. Both Dexamethasone and Lidocaine have excellent permeability across these membranes. Dexamethasone molecules with a size of less than 1µm and lidocaine molecules of 0.3 µm can quickly diffuse from the middle ear space into the perilymph of Scala Tympani.[13] Lidocaine acts on different ionic receptors and channels on an intracellular level in the membranous labyrinth. These different channels include voltage regulated potassium, sodium, and calcium channels. Other ligand-gated receptors involved are Glutamic acid, glycine, gamma-aminobutyric acid (GABA), capsaicin receptor and vanilloid receptor.[1] Altered ionic movement across these channels is involved in neuroplasticity of the auditory system, thereby expressing abnormal signal expression as tinnitus. Lidocaine is shown to down-regulate the abnormal ionic movement across these channels and stabilize hair cell membranes, thereby positively affecting tinnitus.[14]

The homeostatic environment of the stria vascularis is closely related to the potassium equilibrium within the cochlea manifested by endolymph-perilymph ionic transport. Disrupted potassium regulation in the stria vascular can have a negative impact on the auditory signalling mechanism, and it has been shown that steroids and lidocaine stabilize this disruption and thereby stabilize the tinnitus initiating mechanism. Dexamethasone, the long-acting steroid, is an ideal drug delivered via the intratympanic route in relieving tinnitus.[15]

In a meta-analysis conducted by Hamid *et al*, steroid use in Meniere's disease and sudden sensory neural hearing loss has shown improvement in tinnitus and having a positive effect on hearing loss recovery. The improvement in tinnitus started after four weeks and was maximum at six months, and stayed stable for two years. Hamid also detailed the intratympanic movement of steroids with the biochemical changes occurring in stria vascularis leading to disease improvement.[16]

Over two years, a prospective study by Garduno-Anaya *et al*, studied twenty-two patients suffering from Meniere's disease and tinnitus. Eleven patients were given intra-tympanic Dexamethasone, and eleven other patients were given a placebo. Before and after intra-tympanic dexamethasone infusion, all patients were assessed on Tinnitus Handicap Inventory. Over the two years, 100% of patients given intra-tympanic Dexamethasone reported marked improvement in tinnitus. Other symptoms of Meniere's disease improved to variable extents.[17]

Memari *et al*, in a prospective trial of 100 patients of Meniere's disease, used intra-tympanic steroids in weekly intervals for three doses and found that steroids instilled intra-tympanically had a significant positive impact in relieving tinnitus. The patients were assessed for tinnitus pre-therapy and three weeks after the last intra-tympanic infusion.[18]

A randomized prospective study conducted by Elzayat *et al*, in a double-blinded method studied 44 patients. Twenty patients were given a combination of intra-tympanic steroids with Lidocaine, and the other half were given intra-tympanic steroids. Over six months, these forty-four patients were assessed for tinnitus, and at the end of six months period, a significant and

appreciable relief in tinnitus was found in patients treated with the combination of Dexame-thasone and Lidocaine as compared to dexamethasone alone.[19]

CONCLUSION

Combining Dexamethasone with Lidocaine delivered in an intra-tympanic route has a significantly positive impact in relieving idiopathic chronic intractable tinnitus.

Conflict of Insterest: None

Author's Contribution

ZA: Drafting, study, conceptualization, AA: Data Collection, result Interpretation, FA: Drafting, analysis, ML: Referencing, data analysis, MSAM: Result compilation, discussion, NA: Referencing, data analysis.

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