

## Vestibular Rehabilitation with Intratympanic Drug Therapy in Meniere's Disease

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### ABSTRACT

**Objective:** To evaluate vertigo control and auditory rescue in patients with Meniere's disease treated with intratympanic Gentamicin and Dexamethasone.

**Study Design:** Randomized Control Trial (Clinical Trials. gov Identifier: NCT05355610).

**Place and Duration of Study:** ENT Departments CMH Quetta and Benazir Bhutto Hospital Rawalpindi Pakistan from Apr 2020 to Mar 2022.

**Methodology:** Ninety-three cases of unilateral Meniere's disease meeting the inclusion criteria were treated with intratympanic Gentamicin and Dexamethasone. Pre and post-treatment vertigo was assessed on Vestibular Deficit Index. Speech discrimination scores for auditory impact were also recorded pre and post-treatment.

**Results:** In the Ninety-three treated cases, there was a statistically significant improvement in the Vestibular Deficit Index (with a  $p$ -value of 0.001). Although all patients had a reduced speech discrimination score, it was not statistically significant ( $p$  value=0.08).

**Conclusion:** Control of vestibular symptoms can be achieved with intratympanic Gentamicin, and at the same time, the auditory system can be rescued with Dexamethasone.

**Keywords:** Dexamethasone, Gentamicin, Intratympanic.

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### INTRODUCTION

Meniere's disease is an uncommon condition of the inner ear with a prevalence of 120 per 100,000 persons. Meniere's disease affects both genders equally.<sup>1</sup> The peak incidence of the disease is in the third and fourth decade of life, and it follows a course over several years with fluctuating symptomatology.<sup>2</sup>

The disease process in Meniere's disease is of unknown aetiology. Pathophysiological changes observed in the cochlea are vestibular hydrops characterized by distension and dilatation of the scala media and saccule. At the same time, the utricle is involved in the latter stages. Distension of the scala media causes the reissner's membrane to bulge into the scala vestibuli. Symptoms of Meniere's disease become evident with rupture of the reissner's membrane, which causes the perilymph to escape into the endolymph canal (scala media).<sup>3</sup> The potassium-rich perilymph is highly toxic to both auditory and sensory epithelium, and this exposure leads to auditory and sensory symptoms in the form of fluctuating hearing loss and variable vertigo.<sup>3</sup> The symptoms settle with the spontaneous repair of the reissner's membrane. Vestibular hydrops can be graded on Magnetic Resonance Imaging from

Barath Grade-I, III. This imaging helps to grade the severity of the disease and plan appropriate treatment strategy.<sup>4</sup>

Treatment of Meniere's disease reflects the disease pathology and symptomatic relief. Rectification of pathology is twofold either a decrease in endolymph production by using steroids and betahistidine or an increase in absorption of endolymph using steroids.<sup>5</sup> Control of symptoms becomes necessary in advanced cases with intractable vertigo. In later stages of the disease, vestibular sedatives are of little help as the pathological gaps in the reissner's membrane become permanent as the disease progresses. Recently destructive therapies are gaining more popularity for control of severe vertigo. Among them, vestibulotoxic drugs have a prime role.<sup>6</sup> There are two problems with vestibulotoxic drugs, delivery of drug and collateral auditory damage. The adequate delivery mechanism is an intratympanic injection, and multiple injections are afforded by placing a grommet in the tympanic membrane. Associated auditory damage from vestibulotoxic agents can be prevented by concomitant use of Dexamethasone in the intratympanic injection.<sup>7</sup> This study was conducted to evaluate vertigo control and auditory rescue in patients with Meniere's disease treated with intratympanic Gentamicin and Dexamethasone.

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**METHODOLOGY**

This randomized control trial (Clinical Trials. gov Identifier: NCT05355610) was carried out to control intractable vertigo in Meniere's disease while at the same time trying to preserve the auditory function at the department of ENT CMH Quetta and Benazir Bhutto Hospital Rawalpindi, after approval of Institutional Review Board (File No: CMH QTA-IRB/531) from April 2020 to March 2022.

A sample size of Eighty-five patients was calculated with the Raosoft sample size calculator (power of test 80% and margin of error 5%), with a prevalence of 120 / 100000 cases as reported by Wu in 2018.<sup>1</sup> The patients were selected by non-probability consecutive convenience sampling technique.

**Inclusion Criteria:** Patients with age ranging from 35 to 65 years, of either gender with unilateral definitive Meniere's disease were included in the study.

**Exclusion Criteria:** Patients with actively discharging ear, Bilateral Meniere's disease, cholesteatoma, history of neurological diseases and head trauma were excluded from the study.

A total of ninety-three volunteer patients full filling the criteria were included. All patients had the pre-procedure assessment of vestibular dysfunction using the Vestibular Deficit Index. In addition, all patients had speech discrimination scores recorded using a pure tone audiogram. This was done at 1000 Hertz frequency on a pure tone audiogram. The patients have presented 20 single syllable words 20 decibels above their speech reception threshold. The percentage of words correctly repeated by the patients was recorded as their pre-procedure speech discrimination score.

Definitive Meniere's disease is a patient with two or more episodes of documented vertigo lasting more than 20 minutes with nystagmus and documented hearing loss in both attacks, accompanied by tinnitus and aural fullness.<sup>8</sup> Insertion of grommet for drug delivery was carried out in the main operation theatre of both hospitals by a consultant otorhinolaryngologist. A cotton pledget soaked in 10% lignocaine solution was placed directly on the ear drum using a zerodegree wideangle endoscope. The external auditory canal was packed with ribbon gauze soaked in 4% ligno-caine. After 15 minutes, a myringotomy incision was made in the anteroinferior quadrant of the tympanic membrane, and a 0.9-centimetre grommet was introduced. A 28 gauge pediatric cannula attached

to a 3-millilitre syringe was introduced through the grommet. A mixture of 1ml Gentamicin (40 mg/ml) and 1 ml of Dexamethasone (4mg/ml) was slowly injected into the tympanic cavity over 5 minutes. The drug delivery via grommet was repeated under local anaesthesia twice with one weekly interval. After the third injection, the grommet was removed, and the myringotomy opening was closed with a small sponge stone piece dipped in 0.5% ciprofloxacin ear drops.

After each procedure, patients were kept lying with treated ears up for 20 minutes. Post-procedure patients were advised tablet prochlorperazine (12.5 mg) and tablet Mefenamic acid (500 mg) thrice a day for three days. In addition, antibiotics in the form of capsule Cefimxime (400 Mg) were prescribed once daily for 05 days after the first procedure. Six weeks after the third instillation, all patients were assessed for vestibular deficit improvement using the Vestibular Deficit Index and auditory deterioration, if any, was checked by recording the speech discrimination score.

Data was analyzed using Statistical Package for the social sciences (SPSS) version 24. Mean±SD was calculated for a continuous variable like age, pre and post-procedure average vestibular deficit index. In addition, frequency and percentage were calculated for categorical variables, i.e. gender. Paired sample t-test was used for statistical significance. The *p*-value ≤ 0.05 was considered significant.

**RESULTS**

A total of ninety-three adult patients volunteered for the study. Among the study group, there were 15 (16.1%) females and 78 (83.9%) males. Age varied from 35 to 65 years, with a mean age of 51.96±7.77 years. Among the patients in this study, the pre-procedure average vestibular deficit index score was 8.97±1.08, and the post-procedure average vestibular deficit index score was 5.01±1.48. This improvement was significant, with a *p*-value of 0.001 on paired sample t-test (Table). Pre-procedure average speech discrimination was 71.66±8.88, and the average speech discrimination score percentage was 70.28±8.77. This reduction in speech discrimination score was insignificant (*p*-value -0.08) (Table).

**Table: Comparison of vestibular improvement and speech discrimination scores (n=93)**

Parameters	Study Group (Mean±SD)		<i>p</i> -value
	Pre-Procedure	Post-Procedure	
Vestibular deficit index	8.97±1.08	5.01±1.48	0.001
Speech Discrimination Score	71.66±8.88	70.28±8.77	0.080

## DISCUSSION

Vestibular disturbance in the form of vertigo is usually gauged with subjective questionnaires like "Vertigo Symptom Scale-short form" developed by Kondo,<sup>9</sup> Abbreviated Dizziness Questionnaire (Lauren),<sup>10</sup> Vertigo, Dizziness Imbalance Questionnaire (Martin),<sup>11</sup> and Pilot Questionnaire (Otmär).<sup>12</sup> However, none of these scales considers the objective assessment of vertigo. On the other hand, the vestibular Dysfunction Index incorporates objective and subjective symptomatic elements as perceived by the patient. This makes Vertigo Dysfunction Index a much more realistic approach to gauge vertigo.

Repeated Intratympanic administration of drugs has always been difficult due to recurrent damage to the tympanic membrane. Using a grommet is beneficial as it provides a conduit for the repeat of the procedure without surgical intervention in every drug delivery.<sup>13</sup> Ototoxic drugs that ablate labyrinthine vestibular organs carry an inherent risk of collateral damage to cochlea.<sup>14</sup> This concomitant damage to the cochlea can be dampened with simultaneous use of steroids in the form of Dexamethasone. This study documented auditory collateral damage using speech discrimination scores in pre and post-procedure settings.

It was observed that there was a statistically significant improvement in vestibular symptoms after three intratympanic courses of Gentamicin. Although the speech discrimination score fell after the three procedures, it was not statistically significant and can be attributed to the simultaneous use of Dexamethasone and Gentamicin.

Ardic *et al*, in a retrospective case review study of twenty-five cases, used Gentamicin and Dexamethasone in intratympanic injections to gauge vertigo control. The number of injections varied in each case and were tailored to the suppression of vertigo individually in every patient. The authors found that the combination of Gentamicin and Dexamethasone gave significant control of vertigo and the same time, spared the cochlea from concomitant toxicity.<sup>15</sup>

A meta-analysis by Ahmedzai *et al*, reviewed eighteen expert-nominated studies with 1231 patients regarding using pharmacological agents to control Meniere's disease symptomatology. These drugs included betahistidine, diuretics, diphenidol, dimenhydrinate, Intratympanic Gentamicin and steroids delivered orally and intratympanically. Intratympanic steroids were conclusively shown to alleviate

vestibular symptoms like vertigo and imbalance and reduce the number of attacks of Meniere's disease. In addition, the combination of intratympanic steroids and Gentamicin reduced the vestibular symptoms and protected the hearing.<sup>16</sup>

Geng *et al*, treated 139 patients with intratympanic Gentamicin and Dexamethasone and studied the drug's effects in the case-control trial. They found that treated patients had a marked reduction in circulating IgG and IgM antibodies, tinnitus, vertigo, and instability decreased in the treated group compared to the age and gender-matched control group. This study gives credibility to the immune complex-mediated theory of Meniere's disease.<sup>17</sup> Immune-mediated disease process thus has a favourable outcome with steroids. The use of steroids in Meniere's disease not only alleviates vestibular symptoms but have a protective effect on the cochlea.

In a retrospective cohort study, Guan *et al*, studied patients from 2006 to 2019. All the patients were treated with intratympanic Gentamicin. The patients were reassessed every month, and those with persistent symptoms were re-treated with intratympanic Gentamicin four times. Any patient who had intractable relapses after four treatments were followed with labyrinthectomy. The authors found that chemical labyrinthectomy with Gentamicin was equally effective as surgical labyrinthectomy and avoided auditory loss.<sup>18</sup> Histological evidence of Dexamethasone-induced cochlear function preservation was demonstrated by Guneri *et al*, when two groups of rats were used, and one group was given intratympanic Gentamicin and the second intratympanic Gentamicin and Dexamethasone. The intratympanic Gentamicin group showed apoptotic changes in the cochlea and spiral ganglion, whereas the combination group was not affected at the cellular level.<sup>19</sup> In a meta-analysis of steroid use in Meniere's disease by Patel, there was overwhelming evidence that steroids, when used alone, have a beneficial effect on vertigo control. This effect is enhanced when steroids are delivered intratympanically. Additionally, steroids show a protective effect on cochlea when combined with ototoxic drugs for chemical labyrinthectomy.<sup>20</sup>

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## CONCLUSION

Control of vestibular symptoms can be achieved with the use of intratympanic Gentamicin in Meniere's disease,

and at the same time auditory system can be rescued with intratympanic Dexamethasone.

**Conflict of interest:** None.

**Author's Contribution**

ZA: Conception, design, AHA:, AAK: Data analysis, KAAB: Substantial.

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