



## LOW DOSE INTRATYMPANIC GENTAMICIN FOR THE TREATMENT OF MENIERE'S DISEASE- A PROSPECTIVE STUDY

Dr. S. Poornima<sup>1</sup>, Dr. Priyadershini Rangari<sup>2\*</sup>

<sup>1</sup>MS (ENT), Assistant Professor, Department of ENT, Akash Institute of Medical Sciences and Research Center, Devanhalli, Bangalore (Karnataka)

<sup>2\*</sup>M.D.S (Oral Medicine and Radiology), Assistant Professor, Department of Dentistry, Sri Shankaracharya Medical College, Bhilai, Durg (Chhattisgarh)

Conflicts of Interest: Nil

Corresponding author: Dr. Priyadershini Rangari

### Abstract:

**Background:** Intratympanic gentamicin therapy is an effective modality for control of vertigo in Meniere's disease (MD) and when given in low concentration (<30 mg/mL), once weekly minimizes its side effects like chronic vestibular insufficiency or hearing loss.

**Objective:** We studied the efficacy of low dose interval intratympanic gentamicin therapy in control of intractable vertigo, tinnitus and hearing loss. Other symptoms also evaluated.

**Methods:** Our study included 44 patients with Meniere's disease (MD). Maximum 4-6 doses of weekly intratympanic gentamicin injections of 0.5 ml of gentamicin. In three age group, all pre and post treatment follow up of symptoms were evaluated. Follow up period was evaluated on 4<sup>th</sup> week, 8<sup>th</sup> week and 12<sup>th</sup> week.

**Results:** Out of 44 patients, 32 (72.72%) subjects had vertigo on 4<sup>th</sup> week, 09 (20.45%) subjects had vertigo on 12<sup>th</sup> week. Hearing loss was observed in 35 (85.36%) subjects on 4<sup>th</sup> week and 10 (24.39%) subjects on 12<sup>th</sup> week. The fullness and tinnitus became significantly less intense after the therapy. Tinnitus was observed in 32 (80.0%) subjects on 4<sup>th</sup> week, 12 (30.0%) subjects had Tinnitus on 12<sup>th</sup> week. 25 (69.44%) subjects had headache on 4<sup>th</sup> week, 8 (22.22%) subjects had headache on 12<sup>th</sup> week. **Conclusion:** Low dose interval intratympanic gentamicin is a simple cost-effective office procedure for managing vertigo; tinnitus and hearing loss in patients with MD was statistically significant. Further studies needed with large number patients and control trials for definite conclusion.

**Keywords:** Gentamicin, Hearing loss, Intratympanic, Meniere's disease, Vertigo.

### Introduction:

Meniere's disease (MD), also called idiopathic endolymphatic hydrops, is one of the most common causes of dizziness originating in the inner ear. The typical clinical symptoms are frequent vertigo, sensorineural hearing loss, tinnitus, and/or feeling of fullness in the ear. Vertigo is typically the most debilitating symptom, and control of vertiginous episodes is the primary goal of therapeutic interventions for most patients.<sup>2</sup> Meniere's disease is manifested by episodic vertigo, tinnitus, fullness of ear, and fluctuating hearing loss. The treatment of patients with MD is usually directed at the most disabling symptom, which is the debilitating vertigo.

There are numerous available therapeutic options for MD including conservative treatments with dietary modifications, oral medication, procedural treatments with intratympanic therapies, and surgical treatments. A failure of conservative therapy often

introduces the need for a more aggressive therapy on the treatment algorithm. Surgical intervention or intratympanic aminoglycosides can be used in patients with vertigo, which, ideally, should control the vertigo while preserving the hearing level and balance. The side effects of aminoglycosides are like the risks of vestibular and cochlear toxicity, are mainly related to types of aminoglycosides, route of administration, duration of the therapy, total or cumulative dose, individual susceptibility, renal function, patient's age, etc.<sup>3,4</sup>

In 1948, Fowler first used systemic streptomycin to treat vertigo attacks in patients with intractable MD. The results showed that vertigo attack treatment carried the risks of bilateral vestibulopathy, nephrotoxicity, and unpredictable results. In 1957, Schuknekt may have been the first to use intratympanic streptomycin to alleviate vertigo attacks in patients with unilateral intractable MD, and it was firstly named "chemical labyrinthectomy".<sup>5</sup>

Intratympanic gentamicin (ITG) for the treatment of severe vertigo was reported by Lange.<sup>2-6</sup> The initial approach was complete vestibular ablation to control the vertigo which can cause a greater risk to the hearing. At present, intratympanic injection of gentamicin is probably the most effective and most popular non-surgical treatment to eradicate vertigo in MD. Compared with the treatment regimen decades ago, several modifications for ITG treatment have emerged regarding the concentration of the gentamicin solution, the frequency of injections, and the method of delivery. In this chapter, the history, background, and progression of ITG treatment for MD are discussed, as well as the basic science, therapeutic method, treatment efficacy, indications, contraindications, and complications.<sup>7</sup>

Aminoglycoside antibiotics have a well-documented history of cochleotoxic and vestibulotoxic effects. Administration of intratympanic aminoglycoside antibiotics to patients with MD is based on the notion that the patient's vestibular symptoms are due to the damaged and distorted vestibular signals emanating from their ear and that they are better off with no signal than with a damaged and distorted signal. The objective of ITG is to weaken vestibular signals in the Meniere's ear to the point at which they are no longer strong enough to generate a vertigo attack. Ideally, aminoglycosides would act to reduce vestibular function, and thus alleviate the patient's symptoms of vertigo, while preserving hearing. Other aminoglycosides, such as amikacin, are considered to be relatively more cochleotoxic and thus are not used transtympanically. The best evidence for this is the simple clinical observation that patients undergoing systemic gentamicin or streptomycin therapy experience vestibulopathy much more commonly than hearing loss. Use of streptomycin has been largely replaced by gentamicin which is thought to be more selectively vestibulotoxic and better able to preserve residual hearing in patients with unilateral MD refractory to medical management.<sup>8</sup>

The aim of this study was to verify the efficacy of low dose intratympanic gentamicin in reduction of common symptoms of Meniere's disease.

## MATERIAL AND METHODS

This was a prospective study conducted in the outpatient department of ENT, Akash institute of medical sciences and research center, Devanhalli, Bangalore, Karnataka; in the period of 6 months since

January 2019 to July 2019. Study comprised about analysis of Intratympanic gentamicin (ITG) for the treatment of Meniere's disease (MD) 44 adults of age range between 30-50 years. The study was approved by the Institutional Research Ethics Committee and written informed consent was obtained from parents of all participants.

Patient inclusion criteria-

- History of recurrent episodes of vertigo, hearing loss and tinnitus; headache and a feeling of fullness in the ears atleast for last one year.
- No response to medical treatment (diuretics, betahistine),
- Unilateral hearing loss, with a good hearing in the opposite ear,
- Moderate or worse sensorineural hearing loss in the affected ear,
- Dynamic patient with normal vision and no alcohol addiction (no age limits),
- No drug allergies or idiosyncrasy.

**Procedure:** Direct injection method by gentamicin 2 mL ampul (40 mgr/mL) following surface anesthesia, approximately 1 mL of buffered gentamicin solution (30.7 mg/mL) was injected directly into the middle ear using a 26" G spinal needle when the patient was lying on his/her back, and his/ her head slightly turned towards the opposite side. The patient was asked not to gulp, and he/she stayed at this position for half an hour. This procedure was performed once a week, for 4-6 weeks.

Data was collected from patients in a specially designed case record form by taking detailed history, performing relevant examination and investigations.

Pretreatment evaluation included complete ontological, cardiovascular, ophthalmological and cervical spine examination; pure tone audiogram with speech discrimination score (SDS), glycerol test, electronystagmography with caloric test. Intratympanic gentamicin was administered as an outpatient procedure. Gentamicin was administered as we have previously described [Minor, 1999]. The mid-posterior aspect of the tympanic membrane was anesthetized and punctured, and the middle ear was filled with a buffered gentamicin solution (0.5 mL of 40 mg/mL typically injected) with 1.5-inch long 26 gauge needle and injected through postero-inferior quadrant of the tympanic membrane till middle ear is completely filled and tympanic membrane was seen bulging Patients remained supine with the head

angled slightly head down and turned to the contralateral side for 30 min to continually and is told to avoid any swallowing movements during this period. Patient is also instructed to keep the ear dry for 2 weeks. The same was repeated weekly for a maximum of 6 doses. Each patient received only 1 injection during this first round. Five days after the first gentamicin administration, cochlear and vestibular function tests were performed. Pre- and post treatment pure tone average (PTA) (0.5, 1, 2, 3 kHz) along with SDS were compared. A change of more than 10 dB in PTA or >15% in SDS was considered significant. If patient developed any hearing loss, that was informed to the patient and further dosing was left to the choice of the patient.

All the patients were followed up for a period of 3 months after their primary schedule. All the data was collected and transferred to MS excel sheet. The statistical software used was SPSS 20.0. The results were considered significant at a two-tailed level of 0.05.

**RESULTS**

This was a prospective study conducted on 44 adults of either sex in the age range between 30-60 years. Three groups were made according to age i.e. Group A included 11 (25%), Group B, 15 (34.09%) and Group C had 18 (40.09%) patients. According to the findings as shown in Table 1, female predominance was higher i.e. M: F ratio was found to be 2:3. Group C i.e. 51-60 year age group had highest number of patients. All these findings were described in Table 1.

All the patients with known Meniere’s disease, few common symptoms of Meniere’s disease were observed prior to the treatment. All 44 (100%) patients had vertigo, 41 (93.18%) patients had Hearing loss, 40 (90.9%) patients had Tinnitus. 36 (81.81%) patients observed Headache, 32 (72.72%) patients had Feeling of fullness in ears, 27 (61.36%)

patients had Abdominal cramps, 30 (68.18%) patients had nausea, 21 (47.72%) patients had diarrhoea.

Follow up period was evaluated on 4<sup>th</sup> week, 8<sup>th</sup> week and 12<sup>th</sup> week. Out of 44 patients, 32 (72.72%) subjects had vertigo on 4<sup>th</sup> week, 09 (20.45%) subjects had vertigo on 12<sup>th</sup> week. Hearing loss was observed in 35 (85.36%) subjects on 4<sup>th</sup> week and 10 (24.39%) subjects on 12<sup>th</sup> week. The fullness and tinnitus became significantly less intense after the therapy. Tinnitus was observed in 32 (80.0%) subjects on 4<sup>th</sup> week, 12 (30.0%) subjects had Tinnitus on 12<sup>th</sup> week. 25 (69.44%) subjects had headache on 4<sup>th</sup> week, 8 (22.22%) subjects had headache on 12<sup>th</sup> week.

Feeling of fullness in ears was observed in 28 (87.5%) subjects on 4<sup>th</sup> week and 12 (37.5%) had Feeling of fullness in ears on 12<sup>th</sup> week. Abdominal cramp was observed in 20 (74.07%) subjects on 4<sup>th</sup> week, 10 (24.39%) subjects had Hearing loss on 12<sup>th</sup> week.

Nausea was observed in 21 (70.0%) subjects on 4<sup>th</sup> week, 5 (16.16%) subjects on 12<sup>th</sup> week. Diarrhoea was found in 15 (71.42%) patients on 4<sup>th</sup> week and only 1(4.76%) on 12<sup>th</sup> week. All the findings were statistically significant and less than 0.01. vertigo, hearing loss and tinnitus were more commonly observed symptoms and diarrhea was found to be more relieved symptom after three weeks in all group patients than any other symptoms i.e. 1 (4.76%) patients. All the findings were described as shown in Table 2.

**Table 1: demographic variables**

	Subgroup	Number	%
<b>Gender</b>	Male	20	40.00
	Female	24	60.00
<b>Age in years</b>	Group A (30-40)	11	25.00
	Group B (41-50)	15	34.09
	Group C (51-60)	18	40.09

**Table 2: symptoms of before and follow up time.**

Symptoms	Before treatment n(%)	Follow up n(%)			
		4 <sup>th</sup> week	8 <sup>th</sup> week	12 <sup>th</sup> week	p-value
<b>Vertigo</b>	44 (100)	32 (72.72)	24 (54.54)	09 (20.45)	0.01
<b>Hearing loss</b>	41 (93.18)	35 (85.36)	22 (53.65)	10 (24.39)	0.02
<b>Tinnitus</b>	40 (90.9)	32 (80.0)	21 (52.5)	12 (30.0)	0.05
<b>Headache</b>	36 (81.81)	25 (69.44)	16 (44.44)	8 (22.22)	0.01
<b>Feeling of fullness in ears</b>	32 (72.72)	28 (87.5)	20 (62.5)	12 (37.5)	0.01
<b>Abdominal cramps</b>	27 (61.36)	20 (74.07)	15 (55.55)	10 (37.03)	0.02
<b>Nausea</b>	30 (68.18)	21 (70.0)	10 (33.33)	5 (16.16)	0.005
<b>Diarrhea</b>	21 (47.72)	15 (71.42)	6 (28.57)	1 (4.76)	0.001

## DISCUSSION

The difficulty in the treatment of the patients with disabling MD led many researchers to find alternative therapeutic strategies to the traditional medical or surgical therapy, which were able to control vertigo attacks with minimum side effects. The rationale of the use of aminoglycosides, and in particular of the intratympanic gentamicin, arises from the mechanism of action of these drugs.

This was a prospective study conducted on 44 adults of either sex in the age range between 30-60 years. Three groups were made according to age i.e. Group A included 11 (25%), Group B, 15 (34.09%) and Group C had 18 (40.09%) patients. According to the findings as shown in Table 1, female predominance was higher i.e. M: F ratio was found to be 2:3. All these findings were described in Table 1. Similar findings were described by Kaplan DM et al<sup>10</sup> in 2002, Harner SG et al in<sup>11</sup> 1998, Minor LB et al<sup>12</sup> in 1999, Moffat DA et al<sup>13</sup> in 1997 showed same female predominance in their studies. Other studies conducted by Berryhill WE et al<sup>16</sup> in 2002 and Bauer PW et al<sup>19</sup> in 2001 showed opposite results i.e. male predominance.

All the patients with known Meniere's disease, Few common symptoms of Meniere's disease were observed prior to the treatment. All 44 (100%) patients had vertigo, 41 (93.18%) patients had Hearing loss, 40 (90.9%) patients had Tinnitus. Berryhill WE et al<sup>16</sup> in 2002, Bauer PW et al<sup>19</sup> in 2001 also showed similar triad of symptoms in their study. Other least common symptoms were found like Headache, Feeling of fullness in ears, abdominal cramps, nausea and diarrhoea. In our study, 36 (81.81%) patients observed Headache, 32 (72.72%) patients had Feeling of fullness in ears, 27 (61.36%) patients had abdominal cramps, 30 (68.18%) patients had nausea, 21 (47.72%) patients had diarrhoea. These results were also similar to the study conducted by Daneshi A et al<sup>20</sup> in 2014 and Banerjee AS et al<sup>21</sup> in 2006.

Follow up period was evaluated on 4<sup>th</sup> week, 8<sup>th</sup> week and 12<sup>th</sup> week. Out of 44 patients, 32 (72.72%) subjects had vertigo on 4<sup>th</sup> week, 09 (20.45%) subjects had vertigo on 12<sup>th</sup> week. Hearing loss was observed in 35 (85.36%) subjects on 4<sup>th</sup> week and 10 (24.39%) subjects on 12<sup>th</sup> week. Parnes et al<sup>6</sup> 1993, in 12 patients, 3 times titration daily for 4 days showed hearing loss in 5 (41.7%) patients and vertigo control

in 12 (100%) patients. Murofushi et al<sup>7</sup> in 1997, in 18 patients, 3–5 days injection showed hearing loss in 6 (30%) patients and vertigo control 14 (77.8%) patients. Corsten et al<sup>8</sup> in 1997, in 21 patients 3 times titration daily for 4 days showed hearing loss in 12 (57%) patients and vertigo control in 17 (80.9%) patients. Rauch et al<sup>9</sup> in 1997, in 21 patients Twice daily–twice weekly showed hearing loss in 5 (24%) patients and vertigo control in 20 (95%) patients. Kaplan et al<sup>10</sup> in 2002, in 90 patients 3 times titration daily for 4 days showed hearing loss in 22 (25.6%) patients and vertigo control in 84 (93.4%) patients. In the study of Ardiç et al<sup>28</sup> in 2017, there was no correlation of the number of injections with hearing loss or caloric weakness in the IT gentamicin group. Demarco RC et al<sup>5</sup> in 2011, reported that application of gentamicin to oval window caused more vestibulotoxicity and hearing loss in Guinea pigs. This was supposed to be due to more absorption of gentamicin through the oval window.

The fullness and tinnitus became significantly less intense after the therapy. Tinnitus was observed in 32 (80.0%) subjects on 4<sup>th</sup> week, 12 (30.0%) subjects had Tinnitus on 12<sup>th</sup> week. 25 (69.44%) subjects had headache on 4<sup>th</sup> week, 8 (22.22%) subjects had headache on 12<sup>th</sup> week. Berryhill WE et al<sup>16</sup> in 2002, Bauer PW et al<sup>19</sup> in 2001 in their review studies observed the similar results as our study.

Feeling of fullness in ears was observed in 28 (87.5%) subjects on 4<sup>th</sup> week and 12 (37.5%) had Feeling of fullness in ears on 12<sup>th</sup> week. Abdominal cramp was observed in 20 (74.07%) subjects on 4<sup>th</sup> week, 10 (24.39%) subjects had Hearing loss on 12<sup>th</sup> week. These findings were correlated to the findings confirmed by Berryhill WE et al<sup>16</sup> in 2002, Bauer PW et al<sup>19</sup> in 2001 and Corsten M et al<sup>8</sup> in 1997.

Nausea was observed in 21 (70.0%) subjects on 4<sup>th</sup> week, 5 (16.16%) subjects on 12<sup>th</sup> week. Diarrhoea was found in 15 (71.42%) patients on 4<sup>th</sup> week and only 1 (4.76%) on 12<sup>th</sup> week. All the findings were statistically significant and less than 0.01. vertigo, hearing loss and tinnitus were more commonly observed symptoms and diarrhea was found to be more relieved symptom after three weeks in all group patients than any other symptoms i.e. 1 (4.76%) patients.

Vestibulotoxicity of gentamicin is the most interesting characteristic because it allows damaging of the vestibular hair cells and a certain degree of sparing of

the cochlear ones. Salt AN et al<sup>22</sup> in 2008, Helling K et al<sup>23</sup> in 2007, performed a comparative effectiveness trial of intratympanic methylprednisolone versus gentamicin in patients with refractory unilateral MD. Patients were randomly assigned (1:1) to two intratympanic methylprednisolone (62.5 mg/ml) or gentamicin (40 mg/ml) injections given 2 weeks apart, and were followed up for 2 years. The study showed no significant difference between the methylprednisolone and gentamicin for the control of vertigo, total number of injections, number of patients with relapsing vertigo, or the amount of pain from injection but better speech discrimination after methylprednisolone. Based on the above prospective, double-blind, randomized controlled clinical trials, intratympanic gentamicin, as a medically ablative method, seems to be the most effective non-surgical treatment to eradicate vertigo in intractable MD, but with a potential risk of hearing loss. However, there is no consensus on the treatment protocol of ITG, especially for the concentration of gentamicin, dosage in each application, number of injection, and the time interval between two doses.

## CONCLUSION

One-shot low-dosage gentamicin is completely effective on controlling vertigo attacks in Meniere's disease and has useful effects on the aural fullness and tinnitus of patients as well. However, even doses as low as 20 mg gentamicin can cause hearing loss. Intratympanic injection of gentamicin is probably the most effective nonsurgical treatment to eradicate vertigo in MD. But it is also an ablative method that carries a non-negligible risk of hearing loss. However, based on the combination of current clinical practice, basic science models, and results from clinical trials, low drug dose and long intervals between injections are reasonably recommended. In comparison with surgery, the vertigo control is comparable, the overall cost is reduced, and complications are limited. ITG in treating intractable MD has gradually become a prevalent therapy during the past decades.

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