

## Intratympanic Gentamicin Injection for Treatment of Vertigo in Intractable Meniere's Disease

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### ABSTRACT

**Background:** Vertigo is being treated by Intratympanic Gentamicin (ITG) among Ménière's Disease (MD) patients, but its effectiveness and safety remain controversial.

**Objective:** To know the optimal dose and duration of intratympanic gentamicin needed to cease vertigo attacks in Ménière's disease.

**Patients and Methods:** At Oto-Rhino-Laryngology, and Head and Neck Surgery Departments of Zagazig University hospital, eighteen consecutive patients with disabling unilateral Ménière's disease were included in this randomized controlled trial. The patients were divided randomly into 2 groups; Group A: 9 patients were injected with 20mg/ ml every 3 days for 6 injections, until vertigo completely controlled or presence of complications & Group B: 9 patients were injected with 40mg/ ml every 1 month for 4 injections, until vertigo completely controlled or presence of complications.

**Results:** Twenty mg/ml ITG every 3 days in group A & 40mg/ml ITG every 1month in group B; Both doses can control vertigo, Group A: there was no significant hearing impairment but need repeated rounds of injections, Group B: there was significant hearing impairment and need less rounds of injections.

**Conclusion:** Considering the results of using 20mg/ml ITG every 3 days in group A & 40mg/ml ITG every 1month in group B; Both doses can control vertigo. Group A: there was no significant hearing impairment but need repeated rounds of injections. Group B: there was significant hearing impairment and need less rounds of injections. Using 20mg/ml ITG every 3 days is better and safer than using 40mg/ml ITG every 1 month.

**Keywords:** Intratympanic Gentamicin, Vertigo, Meniere's Disease.

### INTRODUCTION

The symptoms of Ménière's disease (MD) include vertigo attacks, hearing loss in the affected ear that fluctuates at low frequencies, tinnitus, and a fullness in the ear. Issues like stumbling and toppling over are possible side effects. Comorbidities in Ménière's disease include autoimmune diseases and migraine<sup>(1)</sup>. Dilation of the membranous labyrinth is a closely connected result on postmortem examinations, but the exact cause of Ménière's disease is still unknown<sup>(2)</sup>.

Patients with Ménière's disease should take advantage of the various available treatment choices and tailor their care to their own needs. A patient should also be treated for any coexisting conditions they may have, such as allergies, migraines, or autoimmune arthritis<sup>(1)</sup>. Clinicians might recommend a wide variety of treatments, including dietary changes, pharmacological management with diuretics, steroids, or betahistine, and operations like decompression of the endolymphatic sac<sup>(2)</sup>.

Medication and avoiding triggers like too much salt or coffee may not be enough to control vertigo attacks in some people with Ménière's disease. Since the last two decades, intratympanic treatment has gained a lot of popularity due to the fact that it is easy to administer even in an office setting and has a high rate of patient acceptance. The cochleotoxic and vestibulotoxic effects of aminoglycoside medicines have been studied extensively<sup>(3)</sup>. The aminoglycoside antibiotic gentamicin is more harmful to the vestibular system than the auditory system. The neuroepithelium

and type 1 vestibular cells are particularly vulnerable to its effects and are wasting away<sup>(1)</sup>.

With intratympanic gentamicin, there is no agreed-upon standard for dosing, concentration, time between injections, or length of treatment (ITG)<sup>(4)</sup>.

Using ITG to treat vertigo in MD is controversial due to disagreements regarding optimal dosage and administration technique. Some doctors favour high-dose intratympanic gentamicin (HD-ITG), also known as titration or continuous administration, in which the drug is injected at increasingly higher doses until vestibular weakness is achieved, while others favour low-dose intratympanic gentamicin (LD-ITG), in which the drug is injected once and further injections are performed only if vertigo attacks recur<sup>(3)</sup>.

Clinical symptomatology was used to evaluate the effectiveness and safety of LD-ITG for treating vertigo attacks in MD; in this trial, ITG was administered up to five times, with a 2-week gap between injections, and only if the vertigo attacks returned<sup>(3)</sup>.

In their study, **Patel et al.**<sup>(5)</sup> used 40 mg/ml at a frequency of 2 weeks. Patients of **Kaplan et al.**<sup>(6)</sup> were injected thrice daily for four days. Patients were injected with 0.4 ml of 26.7 mg/ml by **Carey et al.**<sup>(7)</sup> once weekly.

The purpose of this research was to determine the best dosage and treatment schedule for intratympanic gentamicin in patients with Ménière's disease suffering from vertigo attacks.

## SUBJECTS AND METHODS

### Patients:

At Oto-Rhino-Laryngology, and Head and Neck Surgery Departments of Zagazig University Hospital, this randomized controlled experiment included eighteen consecutive individuals with debilitating unilateral Ménière's illness. Using the AAO-HNS<sup>(8)</sup> criteria, all of these patients had unilateral definite MD; At least 6 months of medical therapy including "diuretics, betahistine, steroid, salt-restricted diet and lifestyle adjustment" was completed before any patient was accepted to ITG treatment.

### Ethical consent:

After receiving written agreement from each participant, the Zagazig University Research Ethics Board (ZU-IRB#5960-7-4-2020) approved the study. The World Medical Association's Helsinki Declaration established standards for the treatment of patients who participated in medical trials.

### Inclusion criteria:

Unilateral Ménière's disease, adult patients ( $\geq 18$  years), the middle ear is working normally, and patient cooperation is crucial for a smooth and efficient administration.

### Exclusion criteria:

Patients with vertigo of other causes, response to treatment in patients with Ménière's illness or other systemic diseases, people with untreatable Ménière's disease who have previously received an intratympanic steroid or gentamicin, bilateral Ménière's disease, pathology of the middle ear can occur on either side of the head, and the loss of hearing in the affected ear is sensorineural (SNHL).

### This is what all of the participants in this research had to go through:

1. A thorough review of the patient's medical history.
2. Complete ENT examination.

**Pre-operative examination:** (1) Otoloscopic examination was performed to evaluate the tympanic membrane. (2) Tuning fork tests. (3) Cranial nerves examination. (4) Neck examination.

**Pre-operative investigation:** (1) Pure tone audiometry (PTA). (2) Electronystagmography (ENG).

**Two groups of patients were selected at random:** **Group A:** 9 patients were injected with 20mg/ ml every 3 days for 6 injections, until vertigo completely controlled or presence of complications, and **Group B:** 9 patients were injected with 40mg/ ml every 1 month for 4 injections, until vertigo completely controlled or presence of complications.

### Preparation:

Topical anesthetic (Xylocaine 10 mg/dose spray) was applied to the tympanic membrane for 15-30 minutes. Patients were urged to have someone drive them home because they could feel dizzy after the operation. 1ml of distilled water was mixed with 1ml of 40mg/mL gentamicin then in one group (every three days), "group A," 1 ml of this combination was drawn into a 1 cc tuberculin syringe. Group B received 1 ml of the 40 mg/ml gentamicin solution once a month. A spinal needle of size 25 guage was attached to the syringe. We were able to place the spinal needle without the syringe getting in the way because to the needles bending design.

### Procedure:

A secondary perforation "borehole, vent-hole" injection of gentamicin relieves pressure in the middle ear and prevents barotrauma to the round window by inserting the needle in the anterosuperior quadrant of the tympanic membrane<sup>(9)</sup>. Needle damage to the middle and inner ear structures can be avoided with a steady hand and the ability to react in real time to patient movement<sup>(10)</sup>, The middle ear space was filled by injecting 1cc of gentamicin through the anteroinferior quadrant of the tympanic membrane until the vent-hole was completely clogged with air bubbles and the medial ear canal was flooded with gentamicin solution<sup>(11)</sup>. Following administration, the patient remained supine with injected ear up and avoids swallowing, yawning, or speaking for 20 to 30 minutes to prevent any opening of the eustachian tube and leakage of gentamicin through it and to facilitate gentamicin passage across the round window membrane and annular ligament of the stapes into the inner ear<sup>(11)</sup>.

**Post-operative investigation:** (1) Pure tone audiometry (PTA). (2) Electronystagmography.

**Follow-up:** All patients underwent follow up by PTA and ENG after 1 month, 3 months and 6 months after the last injection.

### Statistical analysis

In order to analyze the data acquired, Statistical Package of Social Sciences (SPSS) version 20 was used to execute it on a computer. In order to convey the findings, tables and graphs were employed. The quantitative data was presented in the form of the mean, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t test (T) was used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (X<sup>2</sup>) were used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

**RESULTS**

Two groups were studied using a randomized controlled trial.: Group A, received ITG 20mg/ml every 3 days, while Group B, received ITG 40mg/ml every 1 month and injections was repeated until vertigo attacks were controlled.

Regarding demographics no significant differences were found between both groups (Table 1).

**Table (1): Demographic data:**

Parameter	Group		Test	
	Group A N=9 (%)	Group B N=9 (%)	$\chi^2/t$	p
<b>Gender:</b>				
<b>Male</b>	3 (33.3%)	4 (44.4%)	Fisher	>0.999
<b>Female</b>	6 (66.7%)	5 (55.6%)		
<b>Age (year)</b>	49.22±	44.22		
<b>Mean ± SD</b>	10.81	±11.23	0.962	0.351

Neither group significantly differs from the other in terms of injection site. About 67% and 44% of those within group A and B had been injected in right ears respectively (Table 2).

**Table (2): Side of injections:**

Parameter	Group		Test	
	Group A N=9 (%)	Group B N=9 (%)	$\chi^2$	p
<b>Side:</b>				
<b>Left</b>	3 (33.3%)	5 (55.6%)	Fisher	0.637
<b>Right</b>	6 (66.7%)	4 (44.4%)		

Among the groups examined, there is a statistically significant distinction in how long it takes for vertigo to disappear. About 56% and 33% with groups B and group A had received two injections respectively. After 3 ITG injections, 55.5% of group A while 100% of group B controlled vertigo (Table 3).

**Table (3): Number of injections to control vertigo:**

Parameter	Group		Test	
	Group A N=9 (%)	Group B N=9 (%)	$\chi^2/t$	p
<b>Number:</b>				
<b>One injection</b>	0 (0%)	1 (11.1%)		
<b>Two injections</b>	3 (33.3%)	5 (55.6%)		
<b>Three injections</b>	2 (22.2%)	3 (33.3%)	4.474	0.034*
<b>Four injections</b>	2 (22.2%)	0 (0%)		
<b>Five injections</b>	2 (22.2%)	0 (0%)		

After injection, there was no statistically significant difference in hearing loss severity between the study groups. No change at all was detected in group A while within group B, two patients with moderate HL progressed to moderate to severe HL, one patient with moderate HL progressed to severe HL, and the other three with pre-injection moderate HL still had

moderate HL after injections. Those with pre-injection mild HL still had mild HL after injection (Table 4).

**Table (4): Severity of hearing loss before and after injections:**

Parameter	Group		Test	
	Group A N=9 (%)	Group B N=9 (%)	$\chi^2$	p
<b>Severity before</b>				
<b>None</b>	1 (11.1%)	0 (0%)		
<b>Mild</b>	0 (0%)	2 (22.2%)		
<b>Moderate</b>	0 (0%)	6 (66.7%)	2.28	0.131
<b>Moderate to severe</b>	5 (55.6%)	0 (0%)		
<b>Severe</b>	3 (33.3%)	0 (0%)		
<b>Profound</b>	0 (0%)	1 (11.1%)		
<b>Severity after</b>				
<b>None</b>	1 (11.1%)	0 (0%)		
<b>Mild</b>	0 (0%)	2 (22.2%)		
<b>Moderate</b>	0 (0%)	3(33.3%)	1.30	0.253
<b>Moderate to severe</b>	5 (55.6%)	2 (22.2%)		
<b>Severe</b>	3 (33.3%)	1 (11.1%)		
<b>Profound</b>	0 (0%)	1 (11.1%)		
<b>P (Wx)</b>	>0.999	0.157		

Comparison of VNG before and after injections reveals no statistically significant change between the groups studied. All patients had abnormal VNG before injections which turned into normal after ITG (Table 5).

**Table (5): Comparison between the studied groups regarding VNG before and after injections:**

Parameter	Group		Test	
	Group A N=9 (%)	Group B N=9 (%)	$\chi^2$	p
<b>Before:</b>				
<b>Normal</b>	0 (0%)	0 (0%)	0	>0.999
<b>Abnormal</b>	9 (100%)	9 (100%)		
<b>After:</b>				
<b>Normal</b>	9 (100%)	9 (100%)	0	>0.999
<b>Abnormal</b>	0 (0%)	0 (0%)		

There was no statistically significant difference in the rate of complications between the two groups. Four patients within group A versus three ones within group B passed uncomplicated.

Posture vertigo and tongue numbness occurred in only one patient, also unsteadiness occurred in another patient within group B versus 0% within group A. Burning sensation in the injection site occurred in two patients within group B versus 0% within group A. Combined ear fullness and tinnitus occurred in two patients, and one patient had headache within group A versus 0% within group B. Ear fullness was reported in two patients with each group (Table 6).

**Table (6): Postoperative complications:**

Parameter	Group		Test	
	Group A N=9 (%)	Group B N=9 (%)	$\chi^2$	p
<b>Complications:</b>				
No	4 (44.4%)	3 (33.3%)		
Burning sensation in inj. site	0 (0%)	2 (22.2%)		
Ear fullness	2 (22.2%)	2 (22.2%)	MC	>0.999
Ear fullness and tinnitus	2 (22.2%)	0 (0%)		
Headache	1 (11.1%)	0 (0%)		
Posture vertigo& numbness	0 (0%)	1 (11.1%)		
Unsteadiness	0 (0%)	1 (11.1%)		

There was statistically non-significant relation between severity of hearing loss after injections and number of injections.

**Table (7): Relation between severity of hearing loss after injection and number of injections in group B:**

Severity of HL after	Median	Range	KW	p
Mild	2.5	2 – 3		
Moderate	2.5	2 – 3	4	0.261
Moderate to severe	2	2 – 2		
Profound	1			

At 6 months follow-up, there was no statistically significant difference between the groups in terms of the percentage of patients who had achieved full control of their vertigo and the percentage who reported a recurrence of their vertigo (Table 8).

**Table (8): Comparison between the studied groups regarding 6 months follow-up:**

Parameter	Group		Test	
	Group A N=9 (%)	Group B N=9 (%)	$\chi^2$	p
<b>Follow up 6 months</b>	9	9	0	>0.999
<b>Complete control</b>	(100%)	(100%)		
<b>Recurrence no</b>	9 (100%)	9 (100%)	0	>0.999

**DISCUSSION**

The most promising feature of gentamicin is its vestibular toxicity, which causes damage to the vestibular hair cells while sparing the cochlear hair cells, and may act on the cells responsible for endolymph production, thereby reducing endolymph pressure. This is the central mechanism in the pathogenesis of Ménière's disease (12).

In their review of MD therapies, **Ward et al.**(2) found that intratympanic gentamicin reduced both vertigo bouts and missed work more than any other

medication. Patients generally rank vertigo as their worst symptom, making it the primary focus of treatment in clinical trials; patients' fear over the unpredictability of vertigo attacks also causes them to withdraw from social situations and hold them back professionally. Fortunately, investigations of Meniere's illness have shown that vertigo is the symptom most likely to improve following ITG (2).

Clinical data of 18 unilateral MD patients were analyzed in our study with age range (24-62years), and duration of illness range (8-30 years): 9 patients were treated in group A by ITG 20mg every 3 days (2-5 injections). The Mean age  $\pm$  SD was  $49.22 \pm 10.81$  years, and the Mean illness duration  $\pm$  SD was  $17.33 \pm 7.78$  years, and there were 66.7% female, and 33.3% male. 9 patients were treated in group B by ITG 40mg every 1month (1-3 injections). The Mean age  $\pm$  SD was  $44.22 \pm 11.23$  years, and the Mean illness duration  $\pm$  SD was  $18.22 \pm 6.26$  years, and there were 55.6% female, and 44.4% male. Our results are in concordance with those reported by **Pietro et al.** (13) in their study who reported also female predominance. **Fawzi et al.** (12) reported on a male predominance, with 11 women (36.7% of the total) and 19 men (63.3%), spanning an age range of 29-57 years (mean 42 years).

In our study, there is statistically non-significant difference between the studied groups regarding the side of injections. In group A, 3 patients (33.3%) were injected in left ears and 6 patients (66.7%) were injected in right ears, while in group B, 5 patients (55.6%) were injected in left ears and 4 patients (44.4%) were injected in right ears.

These results are in accordance with **Wegmann et al.** (14) study that reported that about 57% and 63% of those within group 1 (single dose) and group 2 (need a subsequent or more ITG) had been injected in right ears respectively and about 43% and 37% of those within group 1 and group 2 had been injected in left ears respectively, and in accordance with **Guan et al.** (15) study that reported that 49% had been injected in right ears and 51% had been injected in left ears.

The number of injections required to treat vertigo varies significantly amongst the groups examined; About 56% and 33% had vertigo control after two injections within groups B and A respectively. About 33% and 22% had vertigo control after 3 injections within groups B and A respectively. About 22% and 0% had vertigo control after 4- 5 injections within groups A and B respectively.

About 11% and 0% had vertigo control after one injection within groups B and A respectively Group A had 55.5 percent of patients with vertigo under control after 3 ITG injections, while Group B had 100 percent. Patients, especially those in group A, should be warned about the prospect of recurrent rounds of treatment until complete vertigo control has been achieved because LD-ITG (group A) required more frequent injections to be effective than HD-ITG (group B).

These findings are consistent with those of **Guan et al.**<sup>(15)</sup> (using 40mg/ml of ITG), who found that 33.3% of their patients received just one injection, 32.6% received two, and 34.1% received three to ten injections. Study results by **Stefano et al.**<sup>(16)</sup> found that ITG (40mg) was effective in 60% of patients when vertigo persisted after a single cycle.

These results are in different from **Wegmann et al.**<sup>(14)</sup> who used low-dose ITG (26.7 mg/ml) and reported that Group 1 consisted of 28 patients who only had a single ITG injection (59.6% of treated patients), while Group 2 consisted of 19 patients who received multiple ITG injections. Twelve patients required two injections, one required three, five required four, and one required five.

There is statistically non-significant difference between the studied groups regarding severity of hearing loss before and after injection. In each group, there is statistically non-significant change in severity of hearing loss.

There was no change at all was detected in group A. Within group B, two (22.2%) patients with moderate HL progressed to moderate to severe HL, one (11.1%) patient with moderate HL progressed to severe HL, and the other three (33.3%) patients with pre-injection moderate HL still had moderate HL after injections. Those with pre-injection mild HL (22.2%) still had mild HL after injection. One (11.1%) patient had profound HL.

In contrast to the findings of **Guan et al.**<sup>(15)</sup>, these ones are different. Before ITG, 3 out of 244 patients (1.2%) had normal hearing, 26 (10.7%) had mild HL, 109 (44.7%) had moderate HL, 103 (42.2%) had severe HL, and 3 (1.2%) had profound HL. ITG was performed on 144 individuals, and the results showed that 5% had no hearing loss, 7% had mild HL, 43% had moderate HL, 43% had severe HL, and 2% had profound HL.

Comparison of VNG before and after injections reveals no statistically significant change between the groups studied. All patients had abnormal VNG, with weakness in caloric stimulation in the diseased ear, before injection which turned into normal VNG after injection, with symmetrical nystagmus in caloric stimulation.

Our results are in different from those reported in **Carey et al.**<sup>(7)</sup> study that reported that gentamicin caused a marked reduction or ablation of the caloric responses even in a single injection. Before ITG, caloric responses from the diseased ears were reduced in 13 of 17 patients and absent in 2 patients compared with the contralateral ear. After ITG, caloric responses in the treated ear were absent in 9 of 15 patients (60%). They concluded that there wasn't any link between control of vertigo and reduction in vestibular function. **Hone et al.**<sup>(17)</sup> reported that 62% of patients had an absent caloric response, 17% had a reduced caloric response, and 18% of patients had no significant reducing caloric function after ITG. They concluded

that ITG wasn't uniformly successful in reducing caloric response<sup>(17)</sup>.

Regarding post-operative complications in our study; Posture vertigo and tongue numbness occurred in only one patient (11.1%), also unsteadiness occurred in another patient (11.1%) within group B versus 0% within group A.

Consistent with the findings of **Pietro et al.**<sup>(13)</sup>, six patients in the high-dose group experienced persistent imbalance that impeded their everyday lives after therapy, while no such cases were observed in the low-dose group.

Our study at 6-months follow-up, complete control of vertigo (class A) was achieved in 18 (100%) patients (both group A, and B), and all had satisfactory relief of vertigo and none of them reported recurrence of vertigo. The low-dose and high-dose groups do not differ from one another statistically.

Our findings are consistent with those of **Fawzi et al.**<sup>(12)</sup>, who found that all 13 patients in their research experienced complete or near-complete resolution of their vertigo. At a 1-year follow-up, **Fawzi et al.**<sup>(12)</sup> found that 10 patients (76.9%) had obtained total control (class A) of their vertigo, while three patients (23.1%) had acquired substantial control (class B).

## CONCLUSION

Considering the results of using 20mg/ml ITG every 3 days in group A & 40mg/ml ITG every 1month in group B; Both doses can control vertigo. Group A: there is no significant hearing impairment but need repeated rounds of injections. Group B: there is significant hearing impairment and need less rounds of injections. Using 20mg/ml ITG every 3 days is better and safer than using 40mg/ml ITG every 1 month.

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