Evaluation of the effect of intratympanic injection of gentamicin for resistant cases of Meniere's disease on hearing and vestibular functions

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Objectives
This study was performed to investigate the effect of a single minimal dose of intratympanic injection (IT) gentamicin on hearing and otolithic function, mainly on the utricle and saccule independently.

Patients and methods
Our study was performed on 10 patients with definite Meniere's disease diagnosed according to AAO-HNS criteria and who had been showing resistance to medical treatment for more than 6 months with persistent vertigo affecting their lifestyle.
IT of gentamicin was given under local anesthesia through direct perfusion in a single dose of 12 mg (0.3 ml of 40 mg/ml) unilaterally on the lesion side.
Preinjection evaluation included history, otoscopy, formal pure tone audiometry (PTA), and tympanometry. In addition, cervical vestibular-evoked myogenic potential (cVEMP) and oVEMP were tested. One month after injection, PTA and both VEMP tests were again carried out. Data before and after injection were analyzed and correlated.

Results
No overall significant effect on hearing was found. IT gentamicin had significant effect on cVEMPs with 100% abolition, as well as a statistically significant effect on oVEMP with 70% abolition and distortion of the remaining 30%. In these remaining 30% latencies and amplitudes, there was no significant difference in values before and after injection.

Conclusion
A 12 mg single dose of gentamicin can abolish otolithic function without affecting hearing.

Keywords:
cervical vestibular-evoked myogenic potential, gentamicin, intratympanic injection, Meniere's disease, ocular vestibular-evoked myogenic potential, otolith

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Introduction

Meniere's disease or endolymphatic hydrops of the inner ear is a disease of unknown etiology. Many theories have been proposed for the etiology of Meniere's. However, the pathophysiology continues to be idiopathic. Most patients have symptoms of vertigo, sensorineural hearing loss, tinnitus, and aural fullness. The course of the disease is progressive. A similar incidence is found in both sexes and it mostly occurs in the fourth to sixth decades of life. However, the most disruptive symptom affecting daily functional life is vertigo that can last hours [1].

The majority of patients respond to medical treatments [2]. However, 10–20% of Meniere's patients do not respond. Such failure of medical treatment has continued to be a challenge, and surgical destruction of the inner ear has been the definitive method [3].

Chemical ablation is another alternative method standing between the oral medical and destructive surgical treatments. In 1957 Schuknecht [4] reported injecting streptomycin into the tympanum of eight patients; he found that vertigo was controlled in five patients but all had profound hearing loss. This made the method unpopular, until Lange in 1989 reported good control of vertigo by using gentamicin instead of streptomycin injected intratympanically [5].

Gentamicin acts on neurosensory cells, particularly type I hair cells, as it does on the dark cells located in the crista ampullaris of the semicircular canals, the posterior wall of the utricle, and the lateral wall of the crus communes [6]. The action on type I hair cells is thought to reduce vertigo. The damage to the dark cells, which reduces endolymphatic production, decreases episodes of hydrops and consequently causes less damage to the hair cells [7].

One of the disadvantages of intratympanic gentamicin injection observed in some studies is hearing loss in almost half of the patients [8]. Further, although gentamicin is applied in the middle ear, great differences exist in the method of application, the

number of applications, and the amount of gentamicin used [9].

Other studies, however, concluded that a fixed low dose of intratympanic gentamicin treatment was an effective treatment option for patients with disabling or intractable Meniere's disease, with a low incidence of hearing deterioration [10].

Schuknecht *et al.* [11] showed that the most frequently involved sites by endolymphatic hydrops are the cochlea, followed by the saccule and the utriculus [12]. Therefore, elimination of saccular and utricular function may prevent vertiginous attacks [13].

Unilateral testing of otolith function has become practicable in recent years. Measurement of cervical vestibular-evoked myogenic potential (cVEMP) has become established as a unilateral test of saccular function [14]. Recently, ocular vestibular-evoked myogenic potential (oVEMP) was used to assess the function of the utricule and the utriculo-ocular pathways [15].

In 2002, De Waele *et al.* showed that 92% of the patients submitted to intratympanic injection (IT) of gentamicin did not respond in cVEMP testing, indicating loss of saccular function in 1 month, which persisted for 1 year after treatment [16].

However, Helling *et al.* [14] conluded in another study that cVEMP response cannot be considered a reliable indicator of the success of treatment.

The aim of our study was to test the effect of gentamicin on otolithic function, mainly on the utricle and saccule independently, aiming to preserve hearing and improve patients' outcome.

Patients

This is a prospective study that was carried out on 10 patients of either sex who were referred to Alexandria University Hospital over a period of time starting from 1 March 2013 with the following strict selection criteria:

(1) Presence of unilateral definite Meniere's disease according to the guidelines of the 'Committee on Hearing and Equilibrium Guidelines for diagnosis and evaluation of therapy in Meniere's disease (1995)' [17].
(2) Age not more than 60 years.
(3) No specific sex.
(4) Have showed no improvement on medical treatment for at least 6 months and those symptoms have significantly affected their normal daily activities.

Patients seen to fulfill the following exclusion criteria were excluded from the study:

(1) Presence of otitis media.
(2) Having a PTA average better than 40 dB.
(3) Allergy to aminoglycoside or having other risks with the use of aminoglycosides for example renal problems.
(4) Affected ear is the only hearing ear.
(5) Presence of bilateral Meniere's disease.
(6) Having conductive hearing loss.
(7) Having known disease affecting the cervical vertebrae or spinal cord.

Patients and methods

Written consent was obtained from all patients or first-degree relatives before the study and the study was approved by the local ethics committee. All VEMPs were carried out at the audiology unit of Alexandria Petrol Hospital (Egypt).

All patients in the study group were subjected to full history taking, otoscopic examination, PTA, measurement of cervical and oVEMPs before and 1 month after the IT of gentamicin.

IT of gentamicin was performed under local anesthesia induced by applying EMLA cream to the EAC and TM of the lesion ear and waiting for 30 min. Direct perfusion of a single dose of 12 mg (0.3 ml of 40 mg/ml) was carried out using a 14-G spinal needle [14]. The injected ear was kept in the uppermost position for 30 min. This position would facilitate gentamicin diffusion to the inner ear through oval and round windows.

Protocol for cervical VEMP: the patient is made to sit with tonic contraction of ipsilateral sternocleidomastoid (SCM) muscle to the stimulated ear by looking or moving the head against resistance. Electrode montage: the ground is on the forehead, the positive electrode is placed on the middle third of the ipsilateral (SCM), and the negative electrode is placed on the ipsilateral sternoclavicular joint. The stimulus given is tone burst of 500 Hz in Blackman shape (2-1-2), intensity of 95 dB in HL delivered by AC (insert phone), 5/s, at 150 tone bursts. The filter used is of 10–1000 Hz. This is analyzed for P13 and N23, latency and amplitude.

Protocol for oVEMP: the patient is made to sit with tonic contraction of the contralateral inferior oblique muscle by looking upward in midline. Electrode

montage: The ground is placed on the forehead, the positive electrode is placed 1 cm below the lower eyelid of the contralateral eye to the stimulated ear, and the negative electrode is placed 1 cm below the positive one. The rest of the parameters are the same as those for cVEMPs except that the analysis is for N10, latency and amplitude.

Results

This study was performed on 10 patients with intractable Meniere's disease. Sixty percent of the patients were male. The mean age was 36.50 years with a SD of 9.48. Fifty percent of the patients were injected in the right ear and 50% were injected in the left ear (Table 1).

The morphology of VEMPs categorically rated as present, absent, or distorted showed that there was a significant change in morphology before and after injection. Before the injection 10 and 0% of patients had absent waves in the oVEMP and cVEMP tests, respectively; after injection this percentage increased significantly to 70 and 100%, respectively. The level of significance was remarkable with an oVEMP *P* value of 0.002. The significance for cVEMPs was *P* less than 0.001, with our level of significance set at *P* 0.05 or less (Table 2).

For those with preserved reflexes, further comparison was carried out on the preinjection and postinjection latencies and interpeak amplitudes. With regard to VEMPs before injection, the mean N1 latency was 12.0 ± 0.35 ms, whereas the mean P1 latency was 15.68 ± 1.17 ms. The mean N1P1 amplitude was 3.05 ± 1.92 micro Volts (μV. For the three patients with preserved reflexes after injection, the mean N1 latency was 12.26 ± 0.29 ms, whereas the mean P1 latency was 15.10 ± 1.14 ms. The mean N1P1 amplitude was 1.41 ± 0.53 μV. The *P* value for N1 latency was 0.204, that for P1 latency was 0.662, and that for N1P1 amplitude was 0.226. Consequently, no significant effect of IT injection of gentamicin was found in these patients, as *P* level was set at *P* less than or equal to 0.05.

With regard to cVEMPs before injection, the mean P13 latency was 15.96 ± 1.13 ms, whereas the mean N23 latency was 23.52 ± 0.36 ms. The mean P13N23 amplitude was 23.85 ± 10.40 μV. Postinjection correlation was not possible as all patients has lost their cVEMPs (Table 3).

The effect of injection of gentamicin on hearing in our patients was also analyzed. The mean threshold for hearing at each of the tested frequencies for all patients was analyzed and compared before and after injection. Overall analysis showed no significant difference in hearing levels before and after injection in all six tested frequencies of PTA. *P* values were 1 for 250 Hz, 0.882 for 500 Hz, 0.221 for 1000 Hz, 0.081for 2000 Hz, 0.158 for 4000 Hz, and 0.907 for 8000 Hz. Level of significance was set at *P* less than or equal to 0.05 (Table 4).

Table 1 Distribution of the studied cases according to demographic data

Demographics	*N* (%)
Sex	
Male	6 (60)
Female	4 (40)
Age	36.50 ± 9.48
Side	
Left	5 (50)
Right	5 (50)

Table 2 Distribution of the studied cases according to occular vestibular-evoked myogenic potential and cervical vestibular-evoked myogenic potential

VEMPs	Preinjection [*N* (%)]	Postinjection [*N* (%)]	*P*
oVEMPs			
Absent	1 (10)	7 (70)	0.002*
Present	8 (80)	0 (0)	
Distorted	1 (10)	3 (30)	
cVEMPs			
Absent	0 (0)	10 (100)	<0.001*
Present	7 (70)	0 (0)	
Distorted	3 (30)	0 (0)	

cVEMP; cervical vestibular-evoked myogenic potential; oVEMP; occular vestibular-evoked myogenic potential; *Statistically significant at $P \leq 0.05$.

Table 3 Distribution of the studied cases according to occular vestibular-evoked myogenic potential and cervical vestibular-evoked myogenic potential

VEMPs	Preinjection	Postinjection	*P*
oVEMPs	(*n* = 9)	(*n* = 3)	
P1 latency	15.68 ± 1.17	15.10 ± 1.14	0.662
N1 latency	12.0 ± 0.35	12.26 ± 0.29	0.204
Interpeak amplitude	3.05 ± 1.92	1.41 ± 0.53	0.226
cVEMPs	(*n* = 10)	(*n* = 0)	
P13 latency	15.96 ± 1.13	–	–
N23 latency	23.52 ± 0.36	–	–
Interpeak amplitude	23.85 ± 10.40	–	–

cVEMP, cervical vestibular-evoked myogenic potential; oVEMP; occular vestibular-evoked myogenic potential; *Statistically significant at $P \leq 0.05$.

Discussion

Controversies remain, despite the fact that the identification of Meniere's disease goes back to more

Table 4 Distribution of the studied cases according to patients/frequency (Hz)

Frequency (Hz)	Preinjection hearing thresholds	Postinjection hearing thresholds	*P*
Patients/frequency (Hz)			
250	65.50 ± 4.38	65.50 ± 11.65	1.000
500	65.0 ± 6.24	65.50 ± 10.92	0.882
1000	61.0 ± 3.94	66.0 ± 10.75	0.221
2000	49.0 ± 6.58	53.50 ± 4.74	0.081
4000	47.0 ± 10.33	52.0 ± 16.53	0.158
8000	62.0 ± 23.0	61.0 ± 23.31	0.907

*Statistically significant at $P \leq 0.05$.

than 150 years. IT injection of aminoglycosides introduced by Schuknecht is considered a breakthrough, even though the exact effect of gentamicin on the inner ear is still not 100% clear.

Our patients showed no statistically significant effect of IT gentamicin on hearing considering the overall results, which is in accordance with those of Kasemsuwan *et al.* [1] This suggests that IT gentamicin will have better results in patients with intractable Meniere's disease who have better hearing.

Some studies showed hearing improvement after IT gentamicin; for example, 16% of patients showed improvement in a study by Sala *et al.* [18] This is mostly because these patients were in the early stage of the disease at which decrease in hydrops gives a chance for cells in earlier stage of damage to heal. This was not the case in our study, in which only one patient (10%) showed improvement; this is mostly because of our strict selection of patients who already had a hearing loss of at least 40 dB.

With regard to the effect of Meniere's disease on cVEMP, only 30% of our patients had distorted cVEMPs before injection and the remaining 70% had present cVEMP, which means that none of the cases had absent cVEMP before injection. Even though a study by Welgampola *et al.* reported the absence of waves in 35% of patients [19], we suggest that the 30% of the distorted figures in the present study would later disappear in case of delay of treatment of the disease. We think it represents early affection of the disease of the saccule.

In our study 100% of our patients lost their cVEMP after IT gentamicin, similar to that reported by Helling *et al.* [14] in whose study also 100% of patients lost their cVEMPs. Thus, we can conclude in agreement with this study's suggestion that cVEMP can be used to assess the adequacy of vestibular ablation of gentamicin on saccular function.

Literature on oVEMP and Meniere's disease is scarce. In our study, oVEMPs were found to be absent in 10% of patients and distorted in another 10%, which is in accordance with the study in which Schuknecht concluded that utricle was less affected by Meniere's disease than was saccule [11].

Studies on the effect of gentamicin on oVEMP are deficient in the literature. Only guinea pig studies could be found where '70%' of animals lost their reflexes after being injected with 2 mg of IT gentamicin. These authors concluded that incomplete abolition was either due to incomplete cell death or due to uncrossed fibers of the vestibulo-ocular reflex pathway [19]. In our study, the effect of gentamicin was similar; 70% of our patients lost their oVEMPs after injection. The remaining 30% had distorted waves. None of our patients preserved their reflexes completely after injection.

Latencies were almost similar in the remaining three patients in relation to their own preoperative results. Amplitudes when compared with preoperative preserved reflexs were diminished but this was statistically insignificant. Our results were in accordance with those of other authors such as Helling *et al.* [14] where the utricle was also less affected by IT gentamicin than was the saccule. They suggested that it was due to different patterns of absorption by different parts of the inner ear.

Conclusion

We can thus conclude that our single low-dose injection can have significant effect on the otolithic function, predominantly on the saccule, with no significant effect on hearing.

Acknowledgements

Conflicts of interest

None declared.

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