Intratympanic injection in Meniere's disease; symptomatic and audiovestibular; comparative, prospective randomized 1-year control study

Yasser Fawzi ElBeltagy[a], Amr Gouda Shafik[a], Ahmed Maher Mahmoud[a] and Nagwa Mohammed Hazaa[b]

Departments of [a]ENT and [b]Audiology, Ain Shams University, Cairo, Egypt

Correspondence to Amr Gouda Shafik, 4-Elsherka Elwatania, Hosny Othman St, El-Sefarat Area, Nasr City, Cairo, Egypt
Tel: +002 012 2241 6594;
e-mail: amrgouda@hotmail.com

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Objective

The aim of this work is to compare the effectiveness of intratympanic therapy of gentamicin versus steroids in the treatment of Meniere's disease in terms of symptomatic control and audiovestibular changes.

Patients and methods

Thirty patients with intractable unilateral Meniere's disease were included in our study. They were divided into two groups. The first group was administered intratympanic (IT) gentamicin and the second group was administered IT dexamethasone. We followed our patients with respect to three main symptoms including vertigo, which was determined by the number and duration of attacks, and the class according to AA-HNS 1995 guidelines. We also assessed tinnitus and aural fullness in addition to the Dizziness Handicap Inventory. These parameters were followed up after 6 months and 1 year. Audiological assessment included pure tone audiometry, the speech reception threshold, and the speech discrimination score. Vestibular assessment included the caloric test, rotatory chair stimulation, and vestibular evoked myogenic potential. These parameters were checked at 1 week, 6 months, and 1 year after injection.

Results

Our results showed complete control of vertigo in 76.9% of patients in group I and 30.8% in group II, which was found to be statistically significant. Both groups showed 80–86% satisfactory control of vertigo by 6 months of follow-up, which increased to 100% by 1 year. We found an improvement in tinnitus in 30.8% of the patients in group I and in 38.4% of the patients in group II; the difference between the two groups was nonsignificant. In terms of aural fullness, both groups showed a significant improvement in aural fullness (76.9% in group I and 61.5% in group II). Patients in group I had a 15.4% rate of significant hearing loss and those in group II had 7.7%. Also, we found a significant difference in the rate of hearing loss between both the groups in the high frequencies as gentamicin produced more deterioration in the hearing threshold than dexamethasone. However, the dexamethasone group showed a significant improvement in hearing at low frequencies much more than the gentamicin group. In terms of vestibular testing, we found that gentamicin significantly affected the phase parameter in the rotatory chair test and it also increased the canal paresis in caloric testing. Both effects were absent in the dexamethasone group. We did not find any significant correlation between control of vertigo and any of the vestibular tests.

Conclusion

IT therapy, whether gentamicin or dexamethasone, is an effective way to treat intractable Meniere's disease, with very little side effects. When considering complete control of vertigo, IT gentamicin produces better results than dexamethasone. IT dexamethasone leads to greater improvement in tinnitus than gentamicin, but not significantly. Both drugs significantly improve aural fullness. IT gentamicin produces more hearing loss than dexamethasone at high frequencies. No benefit can be gained from vestibular testing in the follow-up of therapy.

Keywords:

intratympanic gentamicin, intratympanic steroids,, Meniere's diesease, vertigo, vestibular tests

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Introduction

Meniere's disease is an inner-ear disorder characterized by sudden attacks of vertigo associated with tinnitus, fluctuant hearing loss, and pressure in the affected ear [1]. A wide variety of conservative approaches have become established for the initial treatment of Meniere's disease. These include medical therapies in the form of low-salt diet and administration of diuretics, steroids, calcium channel blockers, and vasodilators, and they are useful in regulating the symptoms in 50–70% of patients. For medically intractable Meniere's disease, various surgical techniques have been developed. They have been criticized because of their poor results with respect to the long-term control of vertigo, the definite hearing damage that may be induced, and the morbidity associated with the procedure [2]. Recently, the use of local intratympanic delivery of aminoglycosides or corticosteroids has been recommended in an attempt to minimize the complications and risks involved in the surgical procedures [3]. The sensorineural hearing loss in Meniere's disease is typically fluctuating and progressive. A pattern of low-frequency fluctuating loss and a coincident nonchanging, high-frequency loss has been reported, as a 'peaked' or a 'tent-like' audiogram. This peak classically occurs at 2 kHz. Over time, the hearing loss flattens and becomes less variable [4].

Video nystagmographic recording of eye movements after caloric and rotational stimulation represents the most reliable method for the assessment of vestibular function. Vestibular-evoked myogenic potential (VEMP) testing is a relatively noninvasive method to assess patients with vestibular disorders. VEMPs are believed to be a good indicator of saccular and inferior vestibular nerve function in clinical evaluations. Thus, VEMPs indirectly measure vestibular function through a vestibulocollic reflex [5].

Aim of the work

The aim of this work is to compare the effectiveness of intratympanic therapy of gentamicin versus steroids in the treatment of Meniere's disease in terms of symptomatic control and audiovestibular changes.

Patients and methods

This study was a prospective, randomized study, carried out in the Department of Otolaryngology, head and neck surgery, in Ain-Shams University. Thirty patients with definite Meniere's disease, according to the AAO-HNS criteria [6], were selected from the outpatient clinic of Ain-Shams University Hospital. They were divided into two groups:

(1) Group I included 15 patients and they were treated with an intratympanic injection of 0.4 ml gentamycin 40 mg/ml that was buffered with sodium bicarbonate to pH 6.4 to reach a final concentration of 26.7 mg/ml. This was done on a weekly basis until the appearance of signs of unilateral vestibular hypoactivity, which was assessed by bedside tests (appearance of spontaneous nystagmus, head shake nystagmus, or head thrust sign), and the patient was subjected to three injections as a maximum.
(2) Group II included 15 patients and they were treated with an intratympanic injection of 0.4 ml dexamethasone 4 mg/ml every day for 5 consecutive days as a single cycle.

In both groups, the inclusion criteria were unilateral definite Meniere's disease with serviceable hearing (pure tone threshold < 60 dB and speech discrimination score better than 50%) and vestibular function in the unaffected ear, intractable attacks not responding to medical treatment in the form of moduretic 5–50 (amiloride 5 mg and hydrochlorothiazide 50 mg) once daily + betaserc (betahistine 16 mg) three times daily for 6 months, and absence of any associated neurological disorders. A detailed explanation of the procedure including the risks and possible benefits was provided, and a written informed consent was obtained. Patients with sudden sensorineural hearing loss, middle ear pathology, only hearing ear, or those treated with oral steroids in the previous 6 months were excluded from the study..

A signed informed consent was obtained from all patients of both groups, and the study protocol was approved by the Ain-Shams University Ethics Committee. Assessment of symptoms included the number of attacks of vertigo according to AAO-HNS CoHE [6], presence or absence of tinnitus, aural fullness, and Dizziness Handicap Inventory (DHI) before the administration of an intratympanic injection and at 6 months and 1 year after injection. In DHI, the scoring system included no response (0), sometimes (2), or yes (4), with a score 0–25 indicating a mild handicap, a score of 26–50 indicating a moderate handicap, a score of 56–75 indicating a moderately severe handicap, and a score of 76–100 indicating a severe handicap.

For all patients in both the groups, in addition to careful history taking, basic audiological and vestibular assessments were carried out. Basic audiological assessment was in the form of pure tone audiometry (PTA) and the speech discrimination score (SDS). Vestibular assessment included caloric testing, sinusoidal harmonic acceleration testing (rotary chair), and cervical VEMP (cVEMP). Before testing, patients were instructed to stop any medication that may influence their balance for a period of 48 h. The monothermal warm caloric test was carried out, where the patient was placed in the supine position with his head elevated 30°. The irrigation time was 30 s with 200 cm^3 of water at a temperature of 30°C. The patient was asked to perform a mental task while recording the nystagmus for 30 s (60–90 s) from the onset of irrigation. Then, the patient was asked to open his eyes and fixate on a stationary target directly above his head. The presence of caloric weakness is considered if there is greater than 20% difference in the peak slow phase velocity between both ears.

In sinusoidal harmonic acceleration testing (rotary chair), the patient was seated in a computer-driven rotary chair placed in a dark enclosure. The patient's head was tilted 30° forward so that rotation occurred in the plane of horizontal semicircular canals. The patient's head was held stationary by applying a head band mounted to the back of the chair. Horizontal eye movements were recorded with electrodes mounted on the outer canthi of each eye, with an additional ground electrode on the forehead. An infrared video camera was used to allow visual monitoring of a patient's eyes during testing.

Calibration was performed at the beginning of the test by asking the patient to follow a laser target. The sinusoidal harmonic acceleration test was performed at frequencies of 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, and 0.64 Hz. The chair was rotated with a fixed velocity of 60°/second at each test frequency. The sequence of testing was from the lowest to the highest frequencies. Patients were engaged in conversation and/or counting tasks to maintain an alert state during testing. Three parameters of vestibulo-ocular reflex were recorded: gain, phase, and symmetry.

In cVEMP, the patients were instructed to rotate their heads to the opposite side of the stimulated ear as much as possible. Surface electrodes were placed on symmetrical sites over the midpoints of each sternomastoid muscle with the reference electrode over the upper sternum. A ground electrode was placed on the forehead. The stimulus was rarefactive square waves 0.1 ms clicks at a 100 dBnHL intensity. The click repetition rate was presented at 5/s. The electromyography response from each side was amplified and bandpass filtered (10–1000 Hz). At least two consecutive averages were recorded from each side to verify reproducibility. The average of two runs was taken for the amplitude and latencies. For latency, the peak latencies of p13 (the first positive peak) and n23 (the first negative peak) were measured. The normal values of latency in our lab are p13 (11.2–14.8 ms) and n23 (20.2–25.0 ms). For the evaluation of the amplitude of waves, the evoked amplitude ratio was calculated as 100[(Au–Aa/Au + Aa)], where Au is the p13–n23 amplitude on the unaffected side and Aa is the p13–n23 amplitude on the affected side. The normal range for the evoked amplitude ratio in our lab is (3–10.4).

The treatment protocol was applied for both groups and after treatment, audiological and vestibular assessments were carried out 1 week, 6 months, and 1 year after the injection. The data were coded, entered, and processed on an IBM-PC compatible computer. SPSS statistical software package, version 13, Echosoft Corp., USA, 2002, was used for data analysis.

Results

The 30 patients of our study ranged in age between 29 and 57 years (mean 42 years). Eleven patients (36.7%) were women and 19 patients (63.3%) were men. Eleven patients had Meniere's disease in the left ear and 19 patients in the right ear. The duration of the disease ranged from 1 year to 17 years (mean ± SD = 4 ± 4.9 years). Before treatment, the number of definitive attacks of vertigo in the last 6 months ranged from 6 to 360 attacks (mean ± SD = 43.8 ± 63.8), whereas the duration of the attacks ranged from 30 min to 10 h (mean ± SD = 126 ± 126 min). All patients complained of unilateral tinnitus (100%) and 73.3% of patients complained of unilateral aural fullness during the attacks of vertigo, whereas 26.7% did not complain of fullness. In terms of DHI, 13.3% of patients had a mild handicap, 23.3% of patients had a moderate handicap, and 63.3% had a moderately severe handicap. No patients had a severe handicap.

Table 1 Number and percent of different classes of vertigo control at the 6-month follow-up

	N (%)	
Class	Group I	Group II
A	9 (60%)	4 (26.7%)
B	3 (20%)	9 (60%)
C	2 (13.3%)	2 (13.3%)
E	1 (6.7%)	–

After treatment, both groups were followed up after 6 months and 1 year. According to AAO-HNS CoHE [6], the control of vertigo after 6 months was determined in classes, where in group I, nine patients (60%) achieved class A (complete control of their vertiginous attacks) whereas in group II, only four patients (26.7%) achieved class A (Table 1).

On comparing both groups in terms of the complete control of vertigo (class A), the χ^2-test yielded $\chi^2 = 3.394$, P value = 0.065, which was statistically nonsignificant. Class (A + B), which is considered as effective control of vertigo, was found in 12 patients (80%) in group I and in 13 patients (86%) in group II.

In group I, the two patients who achieved class C and the patient who achieved class E were reinjected with another cycle of gentamycin. In group II, the two patients who achieved class C were reinjected with another cycle of dexamethasone.

After 1 year, only 26 patients continued the follow-up, 13 patients in each group.

In group I, 10 patients achieved class A (76.9%) and three patients achieved class B (23.1%) and the three patients who were reinjected at the 6-month follow-up achieved complete control of their vertiginous attacks and were among the 10 patients of class A. The two patients who did not come for follow-up were among class A in the 6-month follow-up.

In group II, the same patients who achieved class A in the 6-month follow-up continued to maintain complete control of their vertiginous attacks and were still classified as class A (30.8%). Nine patients were classified as class B (69.2%), including the two patients who were reinjected at the 6-month follow-up. The two patients who did not come for follow-up were in the class B group at the 6-month follow-up.

On comparing both groups in terms of complete control (class A), the χ^2-test yielded $\chi^2 = 5.571$, P value = 0.018, which was statistically significant, indicating the better effect of gentamicin when compared with dexamethasone in terms of the complete control of vertiginous attacks. The appearance of statistical significance at 1 year can be attributed to the fact that the patients who were reinjected at 6 months were classified as class A at 1 year in group I, whereas those in group II were classified as class B. On considering class A + B, both groups achieved 100% effective control of vertigo (Table 2).

In terms of the number of attacks of vertigo and the duration of attack, at the 6-month follow-up, both groups achieved a significant reduction in the number of attacks of vertigo ($P<0.05$) and a highly significant reduction in the duration of attacks ($P<0.01$). On comparing both groups, a nonsignificant difference was found in their effects on those two parameters ($P>0.05$) (Table 3).

At the 1-year follow-up, the same results were obtained; both groups showed a significant reduction in the number of attacks of vertigo ($P<0.05$) and a highly significant reduction in the duration of attacks ($P<0.01$). On comparing both groups, a nonsignificant difference was found in their effects on those two parameters ($P>0.05$) (Table 4).

In terms of the number of weekly injections of gentamicin (group I) required to control vertigo, only two patients were injected once, nine patients were injected twice, and four patients were injected three times.

In terms of tinnitus, after 6 months of follow-up, two patients (13.3%) in group I reported the disappearance of tinnitus, two patients (13.3%) reported improvement in their tinnitus, whereas six patients (40%) had the same intensity and five patients (33.3%) reported worsening of their symptom. In group II, two patients (13.3%), four patients (26.7%), and nine patients (60%) reported the disappearance of tinnitus, improvement in tinnitus, and no change in tinnitus, respectively, with no single case of worsening of tinnitus (Table 5).

Table 2 Number and percent of different classes of vertigo control at the 1-year follow-up

	Group I	Group II
Class A	10 (76.9%)	4 (30.8%)
Class B	3 (23.1%)	9 (69.2%)

When comparing the two groups, there was a nonsignificant difference ($\chi^2 = 6.267$, $P = 0.099$) between the two drugs in their effect on tinnitus.

After 1 year of follow-up, in group I, of the 13 patients who continued follow-up, two patients (15.4%), two patients (15.4%), five patients (38.5%), and four patients (30.7%) reported disappearance, improvement, persistence, and worsening of their tinnitus, respectively. One of the two patients who did not attend follow-up was classified as having worse tinnitus in the 6-month follow-up and the other patients reported no change in tinnitus. In group II, one patient (7.7%), four patients (30.77%), seven patients (53.85%), and one patient (7.7%) reported disappearance, improvement, persistence, and worsening of their tinnitus, respectively (Table 5).

The patient who reported that his tinnitus was worse was among the group of patients in whom the tinnitus remained unchanged at the 6-month follow-up. The two patients who did not continue up to follow-up were classified at 6 months as having a disappeared tinnitus and an unchanged tinnitus, respectively. Also, on comparing the two groups, there was a nonsignificant difference ($\chi^2 = 3.13$, $P = 0.37$) between the effect of the two drugs on tinnitus.

In terms of aural fullness, after 6 months of follow-up for group I, nine patients (60%) had no aural fullness and six patients (40%) had the same degree of fullness. On statistical analysis, $\chi^2 = 6.7$, $P = 0.0157$, indicating a significant improvement in aural fullness by gentamycin. In group II, 11 patients (73.4%) reported improvement in fullness, seven of them (46.7%) had no aural fullness at all, and the other four patients (26.7%) reported improvement in their fullness; four patients (26.7%) reported no change in their symptoms. On statistical analysis, $\chi^2 = 5.21$, $P = 0.03$, indicating a significant effect of corticosteroid on aural fullness (Table 6).

On comparing both groups, both drugs improved aural fullness significantly, but there was a nonsignificant

Table 3 Mean ± SD of number of attacks and duration of a single attack in the two groups at the 6-month follow-up

	Group I				Group II			
	Before treatment	6 months	*t* value	*P* value	Before treatment	6 months	*t* value	*P* value
Number of attacks/6 months	43.8 ± 63.8	14.2 ± 32.6	2.09	0.045	43.8 ± 63.8	2.47 ± 2.33	2.42	0.02
Duration of single attack	126 ± 126 min	16.67 ± 31.5	3.316	0.002	126 ± 126 min	27.33 ± 37.32	3.2	0.002

Table 4 Mean ± SD of number of attacks and duration of a single attack in the two groups at the 1-year follow-up

	Group I				Group II			
	Before treatment	1 year	*t* value	*P* value	Before treatment	1 year	*t* value	*P* value
Number of attacks/6 months	43.8 ± 63.8	11.8 ± 29	2.07	0.049	43.8 ± 63.8	2.9 ± 2.5	2.45	0.02
Duration of single attack	126 ± 126 min	14.5 ± 29.2	3.14	0.004	126 ± 126 min	22.4 ± 32.4	3.31	0.003

difference ($\chi^2 = 4.65$, $P = 0.09$) between the effect of the two drugs on fullness.

After 1 year of follow-up for group I, of the 13 patients who continued follow-up, 10 patients (76.9%) had no aural fullness and the other three patients (23.1%) had the same degree of fullness as before treatment. On statistical analysis, $\chi^2 = 3.93$, $P = 0.047$, indicating a significant improvement in aural fullness. The two patients who did not continue the follow-up were included in the unchanged aural fullness group at the 6-month follow-up. One patient from this group at the 6-month follow-up reported that his aural fullness had disappeared by 1 year. In group II, of the 13 patients who continued follow-up, eight patients (61.5%) had no aural fullness, three patients (23.1%) reported improvement in their fullness, and two patients (15.4%) had the same degree of fullness as before treatment (Table 6).

On statistical analysis, $\chi^2 = 15.58$, P less than 0.0001, indicating a highly significant improvement in aural fullness in this group. The two patients who did not continue the follow-up were included in the unchanged aural fullness group at the 6-month follow-up. One patient who was in the group that reported improved fullness at the 6-month follow-up reported that his aural fullness disappeared by 1 year. On comparing both groups, both drugs improved aural fullness significantly, but there was a nonsignificant difference ($\chi^2 = 4.286$, $P = 0.117$) between the effect of the two drugs on fullness.

No patients ever reported an increase in aural fullness following therapy whether by gentamycin or by steroids. After 6 months of follow-up of DHI results in group I, seven patients (46.7%) were classified as having a mild handicap, another seven patients (46.7%) as having a moderate handicap, and one patient (6.7%) as having a moderately severe handicap. Analysis of the results indicated an improvement in DHI, but $\chi^2 = 3.429$, P value 0.48, indicating a nonsignificant effect (Table 7).

In group II, four patients (26.7%), nine patients (60%), and two patients (13.3%) were classified as having mild, moderate, and moderately severe handicap, respectively. On analysis of these results, a significant improvement in DHI ($\chi^2 = 6.667$, $P = 0.016$) was found following corticosteroids therapy.

After a 1-year follow-up of DHI results in group I, of the 13 patients who continued the follow-up, six patients (46.1%) were classified as having a mild handicap and seven patients (53.9%) as having a moderate handicap. Analysis of the results indicated a significant improvement in DHI ($\chi^2 = 8.33$, $P = 0.015$).

The patient who was in the moderately severe group at the 6-month follow-up improved by 1 year and was included in the mild DHI group, whereas the two patients who did not continue the follow-up were included in the mild DHI group at 6 months.

In group II, of the 13 patients who continued the follow-up, three patients (23.1%) were classified as having a mild handicap, eight patients (61.5%) as having a moderate handicap, and two patients (15.4%) as having a moderately severe handicap. Analysis of the results indicated a highly significant improvement in DHI ($\chi^2 = 10.97$, $P < 0.001$).

One of the two patients who did not continue follow-up was from the mild DHI group and the other one was from the moderate DHI group.

On comparing both groups, a nonsignificant difference was found between the effect of the two drugs on DHI ($\chi^2 = 3.067$, $P = 0.215$) (Table 7).

Pre-treatment and post-treatment ranges of the hearing thresholds of the affected ear at different frequencies are shown in Tables 8 and 9.

After a 1-week follow-up, at 250 Hz frequency and an average of 500–1000 to 2000–4000 Hz, on comparing both the groups, we found no statistically significant difference between them ($\chi^2 = 0.682$, $P > 0.05$ and $\chi^2 = 2.04$,

Table 5 Effect of treatment on tinnitus at different points of follow-up

	Group I		Group II	
	6 months ($n=15$)	1 year ($n=13$)	6 months ($n=15$)	1 year ($n=13$)
Disappeared	2 (13.3%)	2 (15.4%)	2 (13.3%)	1 (7.7%)
Improved	2 (13.3%)	2 (15.4%)	4 (26.7%)	4 (30.77%)
Same	6 (40%)	5 (38.5%)	9 (60%)	7 (53.85%)
Worse	5 (33.3%	4 (30.7%)	0	1 (7.7%)

Table 6 Effect of treatment on aural fullness at different points of follow-up

	Group I		Group II	
	6 months ($n=15$)	1 year ($n=13$)	6 months ($n=15$)	1 year ($n=13$)
Disappeared	9 (60%)	10 (76.9%)	7 (46.7%)	8 (61.5%)
Improved	0	0	4 (26.7%)	3 (23.1%)
Same	6 (40%)	3 (23.1%)	4 (26.7%)	2 (15.4%)
Worse	0	0	0	0

Table 7 Number of patients with different degrees of handicap following treatment

	Group I			Group II		
	Before	6 months	1 year ($n=13$)	Before	6 months	1 year ($n=13$)
Mild	2 (13.3%)	7 (46.7%)	6 (46.1%)	2 (13.3%)	4 (26.7%)	3 (23.1%)
Moderate	5 (33.3%)	7 (46.7%)	7 (53.9%)	2 (13.3%)	9 (60%)	8 (61.5%)
Moderately severe	8 (53.3%)	1 (6.7%)	0	11 (73.3%)	2 (13.3%)	2 (15.4%)

Table 8 Range, mean, and SD of hearing threshold at different frequencies

	Group I			
	Before	1 week	6 months	1 year
250	60.3 ± 13	58 ± 14.6	62 ± 19.62	59.2 ± 18.6
Average	57.7 ± 10.6	57.192 ± 8.99	58.9 ± 13.77	61.6 ± 9.56
8000	57.3 ± 20.6	66.67 ± 16.76	69.33 ± 19.35	73.2 ± 8.6
SDS	72.9 ± 12	73.8 ± 10.6	67.13 ± 10.78	66.3 ± 7.62
SRT	56.66 ± 11.28	55.72 ± 15.29	59 ± 13.25	57.8 ± 11.6

AVG is the average of 500–1000 to 2000–4000 Hz at different points of follow-up in group I.
SDS, speech discrimination score; SRT, speech reception threshold.

Table 9 Range, mean, and SD of hearing threshold at different frequencies

	Group II			
	Before	1 week	6 months	1 year
250	55 ± 9.26	43.67 ± 16.4	48.3 ± 11.1	42.28 ± 6.8
Average	47.5 ± 8.33	41.2 ± 13.295	45.98 ± 8.34	41.8 ± 12.98
8000	53.3 ± 18.96	49.67 ± 23.7	44.3 ± 20.3	55.29 ± 29.8
SDS	85.66 ± 6	86.6 ± 14.66	81.5 ± 7.3	82.8 ± 7.1
SRT	47 ± 14.7	37.7 ± 16.15	44.3 ± 8.83	40 ± 9.1

AVG is the average of 500–1000 to 2000–4000 Hz at different points of follow-up in group I.
SDS, speech discrimination score; SRT, speech reception threshold.

$P > 0.05$, respectively). However, at 8000 Hz, on comparing both groups, a highly significant difference was found between them ($\chi^2 = 9.579$, $P < 0.01$), which indicates the occurrence of significant hearing loss at 8000 Hz because of gentamicin after 1 week of injection. In terms of speech reception threshold (SRT) and SDS, on comparing the results of both groups, no significant difference ($\chi^2 = 3.33$, $P > 0.05$ and $\chi^2 = 2.154$, $P > 0.05$, respectively) was found between the effects of the two drugs on SRT and SDS.

After 6 months of follow-up, at 250 Hz frequency and an average of 500–1000 to 2000–4000 Hz, on comparing both the groups, we found no statistically significant difference between them ($\chi^2 = 2.40$, $P > 0.05$). However, at 8000 Hz, on comparing both the groups, a highly significant difference was found between them ($\chi^2 = 12.222$, $P < 0.01$), which indicates the occurrence of significant hearing loss at 8000 Hz because of gentamicin after 6 months of injection. In terms of SRT and SDS, on comparing the results of both groups, no significant difference ($\chi^2 = 4.66$, $P > 0.05$ and $\chi^2 = 2.64$, $P > 0.05$, respectively) was found between the effects of the two drugs on SRT and SDS.

After 1 year of follow-up, only 13 patients in each group continued follow-up. At 250 Hz frequency, on comparing both groups, a significant improvement ($\chi^2 = 7.778$, $P < 0.05$) in the hearing threshold was found in group II. On comparing the results of both groups for the average of 500–1000 to 2000–4000 Hz), we found no statistically significant difference between them ($\chi^2 = 7.778$, $P < 0.05$). However, at 8000 Hz, on comparing both the groups, a highly significant difference was found between them ($\chi^2 = 9.529$, $P < 0.01$), indicating the negative effect of gentamicin on high-frequency thresholds after 1 year of injection.

In terms of SRT and SDS, on comparing the results of both groups, no significant difference ($\chi^2 = 1.22$, $P > 0.05$ and $\chi^2 = 2.54$, $P > 0.05$, respectively) was found between the effects of the two drugs on SRT and SDS.

Results of the caloric test after 1 week of follow-up showed that in group I, four patients had a bilateral symmetrical caloric response (26.7%), whereas 11 patients had a unilateral caloric weakness (73.3%); the mean ± SD% of caloric weakness was (42.3 ± 22.89%) ($t = 2.08$, $P = 0.055$), indicating a nonsignificant effect of gentamicin on the caloric response at a 1-week interval following injection. In group II, two patients (14.3%) showed a bilateral symmetrical caloric response, whereas 13 patients (86.7%) showed unilateral caloric weakness, mean ± SD = (38.6 ± 14.58%) ($t = 0.047$, $P = 0.96$).

At the 6-month follow-up, group I showed a mean caloric weakness ± SD of 44 ± 25.3%. There was a highly significant reduction in the caloric response ($t = 3.35$, $P = 0.04$) by gentamicin injection at the 6-month interval and the same effect was observed at the 1-year follow-up; the mean ± SD was 87.6 ± 21.7 ($t = 8.9$, $P < 0.001$). However, in group II, the mean caloric weakness ± SD was 40.9 ± 22.9 ($t = 0.29$, $P = 0.77$) and by 1 year it was 45.6 ± 22.1 ($t = 0.99$, $P = 0.35$), which indicates that corticosteroids had a nonsignificant effect on the caloric response ($P > 0.05$) both at 6 months and at 1 year of follow-up.

It is noteworthy that at the 1-year follow-up, five of eight patients in group I (62.5%) had a completely absent caloric response whereas none of the patients in group II had an absent response. The results are summarized in Table 10.

The results of a rotatory chair before treatment and following treatment at 1 week, 6 months, and 1 year are summarized in Tables 11 and 12. On comparing the results of both groups after 1 week, the gentamicin led to a significant deterioration in the phase parameter ($\chi^2 = 4.773$, $P = 0.029$), whereas steroids exerted a nonsignificant effect on chair parameters. After 6 months of follow-up, gentamicin injection significantly affected gain ($\chi^2 = 4.286$, $P < 0.05$) and phase ($\chi^2 = 4.773$, $P < 0.05$), whereas corticosteroids had a nonsignificant effect on the rotatory chair parameters. After 1 year, the results were similar to those after 6 months.

The results for VEMP before treatment, 1 week, 6 months, and 1 year after treatment are summarized in Tables 13 and 14. Statistical analysis indicated a nonsignificant effect of either gentamicin or dexamethasone on the different parameters of VEMP. Statistical analysis was carried out in a trial to correlate between the success of therapy represented in the form of complete control of vertiginous attacks, which is represented by the class, and the different vestibular tests (VEMP, rotatory chair, and caloric test), but all indicated a nonsignificant

Table 10 Caloric response in both groups at 1 week, 6 months, and 1-year follow-up

	1 week		6 months		1 year	
	Group I (*N*=15)	Group II (*N*=15)	Group I (*N*=15)	Group II (*N*=15)	Group I (*N*=8)	Group II (*N*=7)
SR	4 (26.7%)	2 (14.3%)	2 (14.3%)	2 (14.3%)	0	1 (14.2%)
UW	11 (73.3%)	13 (86.7%)	13 (86.7%)	13 (86.7%)	8 (100%)	6 (85.8%)
Mean ± SD	42.3 ± 22.9	38.6 ± 14.6	44 ± 25.3	40.9 ± 22.9	87.6 ± 21.7	45.6 ± 22.1

SR, symmetrical response; UW, unilateral weakness.

Table 11 Chair parameters before and after treatment in group I

Group I	Before (*N*=15)	1 week (*N*=15)	6 months (*N*=15)	1 year (*N*=8)
Gain				
Normal	14 (93.3%)	15 (100%)	12 (80%)	6 (75%)
Abnormal	1 (6.7%)	0	3 (20%)	2 (25%)
Phase				
Normal	11 (73.3%)	7 (46.7%)	7 (46.7%)	2 (25%)
Abnormal	4 (26.7%)	8 (53.3%)	8 (53.3%)	6 (75%)
Symmetry				
Normal	11 (73.3%)	9 (60%)	11 (73.3%)	6 (75%)
Abnormal	4 (26.7%)	6 (40%)	4 (26.7%)	2 (25%)

Table 12 Chair parameters before and after treatment in group II

Group II	Before (*N*=15)	1 week (*N*=15)	6 months (*N*=15)	1 year (*N*=7)
Gain				
Normal	11 (73.3%)	13 (86.7%)	11 (73.3%)	5 (71.4%)
Abnormal	4 (26.7%)	2 (13.3%)	4 (26.7%)	2 (28.6%)
Phase				
Normal	9 (60%)	8 (53.3%)	8 (53.3%)	2 (28.6%)
Abnormal	6 (40%)	7 (46.7%)	7 (46.7%)	5 (71.4%)
Symmetry				
Normal	11 (73.3%)	13 (86.7%)	11 (73.3%)	5 (71.4%)
Abnormal	4 (26.7%)	2 (13.3%)	4 (26.7%)	2 (28.6%)

Table 13 Effect of treatment on different vestibular-evoked myogenic potential parameters in group I

	N (%)			
Group I	Normal response	Absent response	Delayed latency	Reduced amplitude
Before	6 (40)	2 (13.3)	1 (7.7)	7 (53.8)
1 week	3 (20)	3 (20)	4 (33.3)	6 (50)
6 months	6 (40)	4 (26.7)	1 (9.1)	5 (45.5)
1 year	5 (62.5)	3 (37.5)	1 (20)	2 (40)

Table 14 Effect of treatment on different vestibular-evoked myogenic potential parameters in group II

	N (%)			
Group II	Normal response	Absent response	Delayed latency	Reduced amplitude
Before	4 (26.67)	4 (26.7)	5 (45.5)	4 (40)
1 week	4 (26.67)	4 (26.7)	5 (45.5)	4 (36.4)
6 months	2 (13.3)	8 (53.3)	4 (57.1)	2 (28.6)
1 year	5 (71.4%)	2 (28.6)	3 (60%)	0 (0)

correlation between the patient's class and the results of these tests at each follow-up point. This indicates the failure of these tests to predict the response of the patient or to follow up their therapy.

Discussion

The difficulty in the treatment of the patients with disabling Meniere's disease led many researchers to find alternative therapeutic strategies to the traditional medical or surgical therapy. The most popular of these are intratympanic steroids and intratympanic gentamicin. Oral and intravenous treatment of steroids, although very easy to use, has well-known long-term side effects. Therefore, they must be used with caution and only when there is absolute necessity. This shows the importance of local steroid administration [7].

Vestibulotoxicity of gentamicin is the most interesting characteristic because it leads to damage of the vestibular hair cells and a certain degree of sparing of the cochlear ones. Moreover, it seems to act on the cells responsible for endolymph production, decreasing the endolymph pressure, which is the cornerstone in the pathogenesis of Meniere's disease [8]. Therefore, we compared the results of the local application of dexamethasone and gentamicin.

In our study, the patients ranged in age between 29 and 57 years (mean 42 years). Da Costa *et al.* [1] studied the epidemiology of Meniere's disease in patients who ranged in age from 40 to 60 years; he found no sex predilection, whereas our study showed a slightly more male predominance, with 11 women (36.7%) and 19 men (63.3%).

As vertiginous attacks are the major symptom in Meniere's disease patients, it is the main target of treatment in most trials. There are different protocols of intratympanic gentamycin injection (low dose, weekly, multiple daily, continuous, and titration protocol) [9]. We adopted the titration protocol in (group I) our study and at 1 year, complete control of vertigo (class A) was achieved in 10 (76.9%) patients and substantial control (class B) in three (23.1%) patients, which means that 13 patients (100%) had satisfactory relief of vertigo. There have been slightly different reports on the rate of control. Bertino *et al.* [8] studied 71 patients with unilateral Meniere's disease for a mean follow-up period of 20 months (range: 3–48 months), using the titration protocol, and obtained almost similar rates of vertigo control as ours class A 65% and class B 35%, yielding an

overall 100% satisfactory control of vertigo. Similarly, in the present study, the three patients who were classified as class C and E at the 6-month follow-up were reinjected with another cycle of gentamicin and they were upgraded to class A by the 1-year follow-up; this led to an improvement in the control of vertigo to 100% by the 1-year follow-up. The same results were reported by Wu and Minor [10], as they injected 34 patients with unilateral Meniere's disease with gentamicin using the titration method and followed them up for 24 months; they obtained slightly higher control rates of vertigo in class A as they had 88% of their patients in this class, only 9% in class B, and 3% in class C (partial control). Twenty-nine percent of their patients (10 patients) experienced recurrence of symptoms after achieving full control, but their symptoms were significantly less severe in terms of the number and duration of attacks than before the initial treatment and they attributed this recurrence to the persistence of some discharging vestibular nerve afferents following intratympanic gentamicin therapy that are capable of transmitting abnormal impulses that trigger an episode of vertigo. These patients were reinjected with a second course of gentamicin; eight of them were reclassified into class A. Martin and Perez [2] used the titration method on 71 patients; after 2 years, 69% of patients were found to be grouped into class A, 14.1% into class B and 12.7% into class F (those who required other forms of therapy because of failure of the injection). Picciotti *et al.* [11] injected their patients twice with gentamicin 20 mg/ml) 7 days apart. After a mean follow-up period of 12 months (6–28 months), 11 of 12 patients were in class A and one patient was in class D (insignificant control). Flanagan *et al.* [12] used a tympanomeatal flap and placed gel foam next to a round window membrane and inserted a T-tube into the tympanic membrane and injected 56 patients through the T-tube with gentamicin. After a mean follow-up period of 16 months (range: 2–40 months), 81.3% of patients achieved significant improvement in vertigo, 8.3% of patients had nonsignificant improvement in their symptoms, and 6.3% had progression of their symptoms. However, Helling *et al.* [13] used another protocol of injection in 19 patients; they used a fixed dose of 12 mg of gentamicin and followed their patients after 4 weeks. Overall, 68% reported completely absent vertiginous attacks and 26% received a second dose of either 12 or 6 mg according to their response to caloric stimulation; finally, they achieved 100% control of vertigo after 12 months of follow-up.

In another trial by Sennaroglu *et al.* [7], in which they compared intratympanic gentamicin with intratympanic dexamethasone and endolymphatic sac surgery, Grommet tubes were inserted in 16 patients and gentamicin ear drops were instilled. After 18 months, 50% of their patients were classified as class A and 23% as class B.

In group II (dexamethasone 4 mg/ml group), at the 1-year follow-up, we had a considerably lower rate of complete control of vertigo (class A), in only four patients (30.8%), but there were nine patients in class B (69.2%), which yielded an overall satisfactory control rate of vertigo of 100%. The two patients who were classified as class C, at the 6-month follow-up, were reinjected with another cycle and were reclassified into class B by the 1-year follow-up, making A + B by the end of 1 year 100%. Slightly lower results were obtained by Barss [14]; he followed 34 patients for 2 years using a dexamethasone concentration of 10 mg/ml. He had only eight patients (24%) in class A and another 24% in class B. Of the 26 patients who had a recurrence of vertigo during the 2-year observation period, eight patients achieved control of vertigo with additional injections, usually administered every 1–3 months. The combination of the initial injection and the repeat injections led to control of vertigo in about one half of the 34 patients (47%). However, in an earlier study by Barss *et al.* [15], on 21 patients, a lower concentration of dexamethasone (4 mg/ml) was used. They administered five injections, two in successive days and once weekly for 3 weeks, and they reported complete control of vertigo in 11 patients (52%) for 3 months and in nine patients (43%) for 6 months, which made them conclude that the concentration of dexamethasone might not be a factor in determining the response to therapy. This is in contrast to Hamid's [16] reports, who used dexamethasone at a concentration of 24 mg/ml and followed his patients for 24 months; this high concentration facilitated complete vertigo control in 90% of his patients. Also, in 17 patients, Hirvonen *et al.* [17] started treatment with an initial intramuscular injection of dexamethasone 15 mg, and then used a combination of three 0.2–0.4 ml intratympanic injections of dexamethasone, 16 mg/ml each, in 1 week. At the 1-year follow-up, 76% achieved sufficient control of vertigo.

However, Garduno-Anaya *et al.* [18], in a double-blind, randomized, placebo-controlled trial, reported high control rates of vertigo similar to those reported by Hamid [16], despite using 4 mg/ml dexamethasone for 5 successive days, and had 82% of patients in class A and 18% in class B, reaching up to 100% satisfactory control of vertigo after 2 years of follow-up.

In earlier studies, the rates of vertigo control reported cannot be compared with the recent ones as they were not carried out according to AAO-HNS [4], but they indicate the efficacy of IT dexamethasone. Itoh and Sakata [19] reported an improvement in vertigo in 80% of MD patients, whereas Shea and Ge [20] reported 96.4% control which dropped to 63% at 2 years; they carried out an exploratory tympanotomy and evaluated the round window and removed any obstruction if present. They also used systemic dexamethasone with the local one. On comparing the vertigo control rates between both groups in our study, we found that gentamicin produced a higher percentage of class A 76.9 versus 30.8% in the dexamethasone group, which was statistically significant. When we compared both groups in terms of satisfactory control of vertigo (class A + B), both of them yielded almost the same results at the 6-month follow-up (80% group I vs. 86% group II) and improved to 100% by 1 year; this is in agreement with the results of the study carried out by Sennaroglu *et al.* [7], in which they found 73% improvement in the gentamicin group versus 72% in the

dexamethasone group. When considering the effect of therapy on the number of attacks of vertigo and the duration of each attack, both groups showed a significant reduction in both parameters, but the difference was not significant ($P > 0.05$). Finally, it can be stated that gentamicin achieved better control of vertigo than dexamethasone 4 mg/ml when considering complete control of vertiginous attacks, but when considering satisfactory control of vertigo, both drugs had the same effect.

In terms of tinnitus, after 1 year of follow-up, in group I, four patients (30.8%) reported improvement in their tinnitus (in two patients, it disappeared completely and in two, it improved) and four patients reported worsening of tinnitus (30.7%). This was also reported by Flanagan *et al.* [12]; they reported that 32% of their 56 patients had improvement in tinnitus. Also, Yetiser and Kertmen [21] found, in their trial on 25 patients with MD, after a 1-year follow-up, that 16% of the patients (four patients) had improvement in tinnitus and in 12% (three patients), it disappeared completely; thus, overall 28% of their patients reported better tinnitus sensation. They concluded that gentamicin exerted a nonsignificant effect on tinnitus. Sennaroglu *et al.* [7] reported, in the gentamicin group of patients, a 21% improvement in tinnitus, with the rest having the same degree of tinnitus. They did not report any case of worsening of tinnitus. In our study, it was found that the patients who reported worsening in their tinnitus were among the group of patients who had hearing loss in the 8 kHz frequency. However, in a 2-year follow-up study, Smith *et al.* [22] reported much worse results as only one patient out of 20 who had tinnitus before treatment improved after gentamicin injection. In group II, we obtained slightly better results than group I, where five patients (38.4%) reported improvement or disappearance of tinnitus following therapy, and these patients were among those who had improvement in their hearing threshold at 250 Hz at 1 year; there was only one case of worsening, which was very close to that reported by Sennaroglu *et al.* [7] in their dexamethasone group. 50% of their patients reported improvement in their tinnitus and the other 50% had the same degree of tinnitus as before treatment. Also, Garduno-Anaya *et al.* [18] reported 48% improvement of tinnitus in their patients. The same was reported by Hirvonen *et al.* [17]; six of 15 patients (40%) reported improvement in tinnitus, which they considered a nonsignificant effect. Good results were also reported by Shea and Ge [20]; 82% of their patients experienced a decrease in tinnitus. These results, however, are confounded because all patients also received intravenous dexamethasone at the time of the intratympanic treatment, followed by oral dexamethasone.

Therefore, in our study, dexamethasone produced an improvement in tinnitus more than gentamicin, but the difference between them did not reach statistical significance.

In terms of aural fullness, at the 1-year follow-up, in group I, 67.9% had no aural fullness following therapy, which indicates a significant effect ($P < 0.05$) of gentamicin on aural fullness. This was also reported by Bertino *et al.* [8]; they reported significant improvement in aural fullness in their study. They classified fullness as absent (53%), mild (32%), and moderate (15%), without any case of severe fullness. Sennaroglu *et al.* [7] reported that 50% of their patients (the gentamicin group) showed benefit from the treatment. Slightly lower results were reported by Flanagan *et al.* [12]; 45% of their 56 patients showed improved aural fullness.

In group II, the results obtained were slightly better than those in group I. Eleven patients (83.6%) had improved aural fullness, eight (61.5%) had no fullness at all, and three (23.1%) had better sense of fullness. The same results were reported by Sennaroglu *et al.* [7]; 75% of the patients in the dexamethasone group showed benefit from treatment (50% reported improvement in fullness and 25% reported complete disappearance). Slightly lower results were obtained by Garduno-Anaya *et al.* [18]; they reported a 48% improvement in fullness in their 11 patients. In the study by Hirvonen *et al.* [17], although they had eight patients of 15 who reported better fullness (decreased: six patients, absent: two), in their conclusion, they considered that dexamethasone had a nonsignificant effect on aural fullness. However, very high and promising results were reported by Hamid [16] with a high concentration of dexamethasone 24 mg/ml as he reported a 90% decrease in aural pressure.

Finally, we found that both drugs, gentamicin and dexamethasone 4 mg/ml, significantly improved aural fullness, although the results with steroid were better, but on comparing their effects, a nonsignificant ($P > 0.05$) difference was found between them. Also, we did not have any patient who reported worsening of fullness. This was also in agreement with the result of Sennaroglu *et al.* [7], as they obtained a nonsignificant difference between gentamicin and steroid groups and also no increase in aural fullness was reported by any of their patients. Gentamicin did not affect the frequencies crucial for speech discrimination significantly. The very high-frequency sensorineural hearing loss (8 kHz) can be attributed to the distribution of the drug following an intratympanic injection, as it was found in animal studies that that there is a concentration gradient of intratympanic gentamicin between the base of the cochlea and its apex, where gentamicin was found to be much more concentrated at the base and not reaching the apex. This gradient is because of the fact that the concentration of the drug in the endolymph depends on the concentration gradient across the round window and the clearance force that clears the drug and prevents its spread to the cochlear apex, resulting in this gradient across the cochlea [23]. Because of this higher basal concentration, the toxic effect of gentamicin is observed mainly in the high frequencies.

In terms of SDS, patients in group II had better results than those in group I, with no single case of deterioration of the score at the 6-month and the 1-year follow-up. However, the difference between the two groups was not statistically significant. This confirms the previous results

as both drugs had no significant effect on the average frequencies, which are closely related to speech discrimination. Finally, gentamicin caused a significant hearing loss at high frequencies and it did not affect the average frequencies more than dexamethasone. Significant hearing improvement at low frequencies occurred at the 1-year follow-up in the dexamethasone group. We had no patients with total hearing loss. Sennaroglu *et al.* [7] reported in their results that 38% of their patients in the steroid group had significant hearing loss (> 10 dB), along with 35% in the gentamicin group, which included 14% with total hearing loss. This result in the gentamicin group could have been because of the insertion of a grommet tube and instruction of patients to instill gentamicin drops in their ears, which might be the reason for the entry of large amounts of gentamicin. The hearing loss in the steroid group was attributed to the natural progression of the disease. They had 16% significant hearing improvement, which is comparable with our results of hearing improvement (15.4 vs.23.1%, group I vs. group II).

There are several reports in the literature on hearing loss following a gentamicin injection compared with a fewer number of reports following an injection of steroids. In the steroid trials, there were studies that reported results close to ours in terms of hearing improvement; Garduno-Anay *et al.* [18] reported 9%, Hirvonen *et al.* [17] reported 17%, and Barss [14] reported a much lower rate (one patient of 34 patients), but it is noteworthy that in these three studies, the percentage of patients who showed hearing improvement was exactly the same as the percentage who had hearing loss, which was found in our study at the 6-month follow-up. However, earlier reports have shown better results for hearing improvement. Shea and Ge [20] reported 68% improvement in hearing loss in their 28 patients, which later decreased to 35% at the 2-year follow-up. Silverstein *et al.* [24] reported 43% improvement in hearing. It is difficult to compare the results with those two studies because all our patients had intractable vertigo, which was not the case in those studies. Hamid [16], reported 90% improved speech discrimination with 24 mg/ml dexamethasone. Also, Hillman *et al.* [25] administered one to three weekly IT injections of dexamethasone, 16 mg/ml, to evaluate significant hearing improvement. After 2 years, of 50 patients with MD, hearing improved in 20 (40%), remained stable in 28 (56%), and worsened in two (4%). In the gentamicin trials, in the previous studies that were using a high dose of gentamicin or frequent injections as daily or multiple daily doses or even a continuous infusion, all of them had very high rates of hearing loss, with a high incidence of dead ear. However, recent studies with the low-dose protocol or the titration protocol have reported a lower incidence of hearing loss. Wu and Minor [10] studied 34 patients and used the titration protocol; they compared the mean PTA before and after gentamicin injection at 24 months of follow-up and a nonsignificant change was observed, $P = 0.8$, and this was the case even in the 8 kHz frequency. They found that 17% of their patients had significant hearing loss (> 10 dB), only 3% had profound hearing loss, and 15% experienced significant improvement in hearing. Their results were very similar to ours, except that none of our patients had profound hearing loss in the average thresholds. They reported that these rates do not differ from those in patients on medical treatment for MD. This explains why we had almost the same rate of hearing loss in both the gentamicin and the steroid groups as this coincides with the natural course of the disease. If we considered the 3% profound hearing loss that occurred in their trial, we find that the rates of sensorineural hearing loss that are reported in a hearing-preserving operation such as vestibular neurectomy is higher (5–6%) [26]. Harner *et al.* [27] reported the same results; 14% of their patients had hearing loss following gentamicin treatment and 11% had an improved hearing threshold. They reported 40% deterioration in SDS, which is slightly higher than that of our SDS results. Similar results have been reported by Martin and Perez [2] in their study on 71 patients. They adopted the titration protocol and reported a significant decrease PTA after 1 week of treatment in 32.4% of their patients, but observed recovery of PTA at 3 months and only 15.5% hearing loss after 2 years of follow-up. Slightly higher results of hearing loss have been reported by others. Flanagan *et al.* [12] reported that 26% of their 56 patients had hearing loss; this may have been because of their protocol of raising a tympanomeatal flap and inserting a piece of gel foam soaked in gentamicin near the round window, which might have led to a slight increase in the amount of drug delivered through the round window. Smith *et al.* [22] reported 33% hearing loss and three patients of 29 had profound hearing loss. This also can be attributed to their protocol as they continued injecting gentamicin weekly until the complete absence of a caloric response, although control of vertigo can be achieved before complete loss of caloric response, indicating that extra injections were administered in this protocol. Also, Bertino *et al.* [8] reported 26% hearing loss.

A number of theories have been proposed to explain the observed variability in sensitivity to gentamicin. Walsted suggested that this was because of the decreased patency of communication routes between the inner ear and the cerebrospinal fluid, primarily the cochlear aqueduct, making the clearance of gentamicin slower, resulting in a higher concentration in the inner ear fluids. In-vitro studies have also shown a variation in the round window membrane's permeability to gentamicin [28]. Others have suggested that there is a variation in the vestibulocochlear hair cells, perhaps because of genetic variability. Identification of the gene(s) responsible could lead to pretreatment testing to identify those patients requiring a reduced dose of gentamicin [22].

In terms of the vestibular testing, before treatment, 76.7% of our patients had unilateral caloric weakness. Following treatment with gentamicin, no significant effect was found at the 1-week follow-up but at 6 months, a significant reduction in the mean percentage of caloric weakness was found that was maintained at the 1-year follow-up, with no recovery of vestibular function.

It is noteworthy that almost all patients who achieved complete absence of a caloric response were in class A control of vertigo, but vice versa was not true, meaning that there were patients who achieved class A without the complete absence of caloric response. This indicates that complete vestibular ablation is not a necessity to achieve full vertigo control. Smith *et al.* [22] reported results that were in agreement with ours in that although all patients developed symptoms and signs of vestibular hypofunction after 1 week of gentamicin injection, this was not correlated with caloric testing results. They reported the incidence of recovery of a caloric response in one of their patients that was associated with recurrence of vertigo. This finding was not obtained in our study.

Bertino *et al.* [8] reported that 67% of their patients showed an absent caloric response after a gentamicin injection and 32.4% showed caloric weakness. They also concluded that vertigo control does not seem to be linked to vestibular ablation and explained this by 'a depressed but still active vestibular receptor can stop producing vertigo spells', and they also assumed that this may be because of the direct effect of gentamicin on the dark cells. The same was found by De Waele *et al.* [29], who reported more than 80% canal paresis in 76% of their patients 1 month after treatment, which increased to 86% after 6 months. Picciotti *et al.* [11] found a total loss of caloric response in 50% of their patients. Martin and Perez [2] reported weak response in 45% of patients and complete absence in 39.4%. Helling *et al.* [13] reported total loss of caloric response in 84% and a weak response in 10% of their patients (a higher dose of gentamicin was administered), and they reached the same conclusion. This indicates that some protocols depended on the injection of gentamicin until complete loss of caloric response, for example in Smith *et al.* [22], and this is not necessary according to our results and other studies. This explains the higher rates of hearing loss in the Smith *et al.*'s study.

In group II, there was no detectable effect of dexamethasone on the caloric response. This was also reported by Garduno-Anaya *et al.* [18]; they found no significant difference in caloric response following an intratympanic dexamethasone injection. The mean canal weakness, at the start of treatment, was 40.8%, which is comparable with ours (42.3%), and also there were no significant differences between the treated group and the placebo group. The same results have been reported by Silverstein *et al.* [30], in a prospective, randomized, and double-blind crossover study, in which they found no significant change in the caloric response following dexamethasone injection. An abnormal phase parameter of the rotatory chair test was the most frequent finding in our patients before treatment (33.3%). Palomar Asenjo *et al.* [31] also reported the same finding; they had an abnormal phase in 23% of their patients and it was also the most frequent finding. Following therapy, we found that gentamicin significantly affected the phase parameter as early as 1 week and continued throughout the study and also affected the gain significantly, but this effect was slower as it appeared at the 6-month follow-up.

In our study, 10 patients (33.3%) showed a normal VEMP response; an absent response was found in six patients (20%), delayed latency in six patients (25%), and reduced amplitude in 11 patients (45.8%). Reports in the literature are conflicting with respect to VEMP results in Meniere's disease. Akkuzu *et al.* [32] reported that 20% of their 20 patients had an absent VEMP response and 30% had delayed latency. Murofushi *et al.* [33] reported different results as they had a 34% absent response and only 2.3% delayed latency and 16% reduced amplitude. In another study carried out by El-Gohary *et al.* [34], they had 40% absent VEMP, 35% reduced amplitude, and 15% delayed latency. Timmer *et al.* [35] reported only 13% absent VEMP response. Picciotti *et al.* [11] reported only one patient out of their 12 patients with absent VEMP, whereas the rest of their patients had a detectable VEMP response; when they compared the (p13, N23) mean latencies with the other unaffected ear and with the control group, a nonsignificant difference was found that was also the same for the amplitude. Following therapy with gentamicin, the number of patients with an absent response was doubled, from 13.3% before treatment to 26.7% at the 6-month follow-up. However, statistically, we found no significant difference in the VEMP Parameters in both groups of our study in the different follow-up periods. This was in contrast to the very few studies in the literature studying the effect of gentamicin on VEMP results as Helling *et al.* [13] reported that the VEMP response was absent in all of their patients following intratympanic gentamicin injection. This can be attributed to the higher dose of gentamicin they administered to their patients as they injected them with gentamicin until they observed an increase in the canal paresis as detected by the caloric response and they used this as a parameter to stop the injections. In another study by De Waele *et al.* [29], 92% of their patients had an absent response following therapy with IT gentamicin, but they used 'a shot gun' protocol for three of 22 of their patients, as those patients received three injections per day for 4 consecutive days (12 doses). The rest of their patients were treated by a titration protocol, although they continued injecting their patients weekly for 6 weeks and what interrupted the treatment was the appearance of ocular nystagmus, ataxia, and diplopia, which are not the same parameters as that used to detect vestibular hypofunction (spontaneous nystagmus, positive head thrust sign, or positive post head shake nystagmus) in the titration protocol. In the study by Picciotti *et al.* [11], they had absent VEMP in 10 of 12 of their patients. They did not use the titration method; they used a fixed dose protocol, injecting gentamicin only twice. Although this dosage is considered small, their reports as regards VEMP were said to be 'at the last follow-up examination', which was not determined and surely not fixed as they had a duration of follow-up of 6–28 months, which might explain the high incidence of absent VEMP response by the effect of progression of the disease itself. To the best of our knowledge, there is no literature on the effect of intratympanic steroids on either VEMP or rotatory chair parameters. At the end of the statistical analysis of our results, we attempted to

correlate between the different vestibular tests and the control of vertigo to find markers or predictors of success of therapy, but we did not find any significant correlation between the vertigo control represented in the class of patients and the VEMP, rotatory chair, or caloric test. This indicates that patients should be followed up after an intratympanic injection by a clinical assessment, with no significant benefit from the vestibular testing. The same has been reported by other studies in the literature. Flanagan *et al.* [12] found no reliable links between the results of post treatment caloric testing and either the success of control of vertigo or the recurrence of symptoms. They concluded that the most valuable and practical method of follow-up is symptomatic. Also, Smith *et al.* [22] found that vestibulotoxic symptoms (those that appear when the treatment is stopped in cases of the titration method in IT gentamicin) did not correlate with the results of caloric testing, negating by this finding the importance to do caloric test to define point of stoppage of treatment in the titration method. Bertino *et al.* [8] concluded in their study that the marker of successful IT gentamicin therapy for Meniere's disease is the appearance of signs of vestibular hypofunction in the short term and the disappearance of vertiginous attacks as reported by the patient in the long term. The only study that we found to report a good predictor for recurrence of vertigo after control was that of Wu and Minor [10]; they found that patients who had abolished VEMPg (galvanic current) following therapy had no recurrence of vertigo, which was not measured in our study. Otherwise, no definite test has been reported to be used in the follow-up of patients.

Conclusion

Intratympanic therapy, whether gentamicin or dexamethasone, is an effective treatment for intractable Meniere's disease, with very little side effects. When considering complete control of vertigo, IT gentamicin produces better results than dexamethasone 4 mg/ml. However when considering satisfactory control of vertigo, both groups produced the same results. Intratympanic dexamethasone produces an improvement in tinnitus more than gentamicin, but not significantly. Both drugs significantly improve aural fullness. Intratympanic gentamicin produces more hearing loss than dexamethasone at high frequencies. Vestibular tests are useful in the beginning of therapy as they aid in diagnosis and also in identifying the diseased side. No benefit can be achieved from vestibular testing in the follow-up of therapy. The best way to follow up a patient treated by IT therapy is by clinical assessment.

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Conflicts of interest

There are no conflicts of interest.

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