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Intratympanic Gentamicin for Intractable Meniere's Disease

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Objective: **The study aimed to analyze the results of the intratympanic injection of gentamicin as a treatment option for patients with unilateral Meniere's disease who were refractory to medical treatment.** ***Study Design:*** **Prospective study in the setting of a tertiary care medical center.** ***Methods:*** **Seventy-one patients with unilateral Meniere's disease according to 1995 American Academy of Otolaryngology—Head and Neck Surgery 1995 guidelines who had been unresponsive to medical therapy for at least 1 year were studied. Intratympanic injections of a prepared concentration of 27 mg/mL gentamicin were performed at weekly intervals until the development of symptoms and signs indicative of vestibular hypofunction in the treated ear. As the main outcome measure, the 1995 American Academy of Otolaryngology—Head and Neck Surgery criteria for reporting treatment outcome in Meniere's disease were used. The results of treatment were expressed in terms of control of vertigo, disability status (functional level and degree of overall impairment evaluated by the Dizziness Handicap Inventory and the University of California Los Angeles Dizziness Questionnaire), hearing level, and quantitative measurement of vestibular function.** ***Results:*** **Vertigo was controlled in 83.1% of the 71 patients. Recurrence of vertigo spells after initially complete control was noted in 17 patients. In 13 of these patients, this was cured by another course of intratympanic injections of gentamicin. Functional level and measures of self-reported handicap were significantly and promptly lowered after treatment in the patients who attained control of vertigo. Hearing level as pure-tone average was unchanged 2 years after treatment, but hearing loss as a result of gentamicin injections occurred in 23 patients at the end of treatment and in 9 and 11 patients at 3 months and 2 years after the treatment, respectively. Vestibular function was kept normal or reduced in 49.3% of the patients, whereas in the rest of the patients vestibular areflexia was observed. Control of vertigo did not depend on the amount of vestibular damage.** ***Conclusions:*** **Ending weekly intratympanic injections when clinical signs of vestibular deafferentation appear can control vertigo in the majority of patients, and it is a useful alternative, together with other surgical options, for the treatment of patients with Meniere's disease who do not respond to medical treatment.** ***Key Words:*** **Gentamicin, Meniere's disease, vertigo, head-shaking nystagmus, head-thrust sign, caloric test, rotary chair test, dynamic posturography, quality of life.**

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INTRODUCTION

Meniere's disease (MD) is a disorder characterized by episodic vertigo, aural fullness, tinnitus, and fluctuating hearing loss. Medical management of MD is based on the symptomatic treatment of the dizzy spells and prophylactic treatment with a salt-restricted diet and diuretics. For medically intractable MD, ablative surgery such as labyrinthectomy or vestibular nerve section has been recommended. Both techniques generate a complete vestibular function loss in the side treated surgically. However, standard labyrinthectomy techniques are always associated with deafness in the treated ear, and vestibular neurectomy requires a craniotomy, with the life-threatening complications that this entails.

In an attempt to control vertigo while minimizing the morbidity associated with other procedures, many investigators have developed the ototoxicity of aminoglycoside antibiotics in a procedure known as "chemical vestibular ablation."[1] Over the last 15 years, a large number of authors have revisited this procedure using intratympanic gentamicin.[2]

Fowler[3] was the first to prescribe systemic streptomycin to treat patients with bilateral MD, and Schuknecht[4] was the first to describe intratympanic injections of aminoglycoside. Control of vertigo was excellent, but a profound hearing loss was seen in the majority of their patients. Since then, a great number of different protocols of intratympanic gentamicin administration have been developed, mainly based on the policy of determining the complete or incomplete ablation of vestibular function. Beck and Schmidt[5] concluded in their series that ablation of the vestibular function was not necessary to obtain a complete control of vertigo, and that this policy

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could result in a greater incidence of hearing loss as a result of the treatment. In 1995, Toth and Parnes[6] made a comparison between a daily and a weekly protocol. No differences in the control of vertigo were observed, but there was a greater incidence of hearing loss in the group to whom a daily protocol was administered. Minor[7] has recently developed a titration protocol based on weekly intervals up to the observance of any end-of-treatment sign, with good control of vertigo and a low incidence of sensorineural hearing loss. Surprisingly, Hirsch and Kamerer,[8] when using a weekly protocol, reported hearing deficits that were comparable with several of the daily protocols. Nevertheless, recent reports on intratympanic gentamicin in unilateral MD have used longer intervals in the application of the antibiotic than those used before the study of Toth and Parnes.[6]

To ascertain the benefits of a particular method of treatment so as to determine its indication in patients with MD, a careful analysis of results must be carried out. In the specific case of intratympanic gentamicin for patients with MD who are unresponsive to medical treatment, the dosage in each injection, the periodicity of the injections, and their number are all relevant factors. Other aspects such as hearing outcome and vestibular function are of importance, especially when considering that the drug in use has well-documented cochlear and vestibular toxic effects and that the methodology in use intends to drive it into the perilymphatic space of the inner ear. As in other chronic diseases, to describe nonfatal health outcomes in MD, two models or conceptual frameworks can be followed: the assessment of impairment, disability, and handicap and the evaluation of health-related quality of life.[9] The impact of MD has been analyzed in several works; Kinney et al.[10] found that the disease may cause more emotional than physical disability. Taking this into account, the functional level scale developed and included in the 1995 version of the guidelines of the American Academy of Otolaryngology—Head and Neck Surgery (AAO–HNS) for reporting the results of treatment in MD is a tool with great potential for the assessment of results.[11] Nonetheless, little evidence is available of the specific social, professional, and personal problems caused by vestibular disorders, although this information would be useful not only for public health planning but also for treatment planning for individual patients.[12] Other questionnaires such as the Dizziness Handicap Inventory (DHI)[13] and the University of California Los Angeles Dizziness Questionnaire (UCLA-DQ)[14] are the most common instruments used to address functional performance in this population. In the end, control of vertigo, the aim of the treatment, can be seen in a much broader sense.

The goal of the present study was to assess the effect of intratympanic gentamicin injections on the control of vertigo and the hearing results in patients with MD who did not respond to medical treatment. In the same way, we intended to provide a description of MD, using several general health measures, and to evaluate changes in the self-perceived quality of life after treatment with intratympanic gentamicin.

PATIENTS AND METHODS

Patients

The subjects in the present study were patients with MD who were seen at the University Hospital of the University of Navarra (Navarra, Spain) from 1996 to 2001. In that period, 574 patients with MD were seen. The intratympanic gentamicin treatment was proposed to 151, and 110 patients in all were included in the protocol. Of these, 71 patients could be followed up by means of regular controls for 2 years and therefore are the subject of the present study. Informed consent was obtained from each patient. Criteria for inclusion in the protocol were as follows: 1) "definite" MD according to the criteria described in the 1995 AAO–HNS guidelines for reporting results in the treatment of MD, 2) lack of response to medical therapy after 1 year, 3) no evidence of MD in the contralateral ear, 4) serviceable hearing in the nonaffected ear, 5) normal caloric test response in the contralateral ear, and 6) no symptoms or signs to suggest central nervous system involvement. Criteria for exclusion were as follows: 1) nonfulfillment of the recommendations of the AAO–HNS guidelines for reporting results in the treatment of MD and 2) noncompletion of the intratympanic gentamicin treatment.

Methods

Pretreatment evaluation. Patients underwent a complete neurotological examination, audiogram, caloric testing, and rotatory chair testing before beginning the protocol. Patients were asked about the presence of vertigo spells, tinnitus and Tumarkin attacks. A functional level score was determined for each patient according to the six-point scale proposed by the AAO–HNS. Furthermore, two self-report measures for functional impairment were used for every patient, the DHI and UCLA-DQ, correctly adapted and validated for Spanish patients.[9]

Treatment protocol. We followed the protocol of weekly injections according to Minor.[7] A concentration of 40 mg/mL gentamicin sulfate was buffered with sodium bicarbonate to pH 6.4 to reach a final concentration of 26.7 mg/mL. Gentamicin injections were performed in an office setting, using a microscope. The patient was placed in a supine position with the head turned toward the uninvolved ear. Topical anesthesia was provided with a phenol solution applied in a small area of the mid posterior aspect of the tympanic membrane. A radial myringotomy incision was made where the anesthesia was applied. Through the myringotomy, an endoscopic assessment of the status of the round window was performed. Any fibrosis or mucous doubling that was present was carefully excised. Once the round window was localized, the buffered gentamicin was injected through a 27-gauge needle to fill the middle ear. The patient remained in the Trendelenburg position for 30 minutes and was instructed not to swallow.

Patients returned for weekly follow-up examinations during the course of the treatment protocol. An audiogram and bedside tests were performed during each follow-up examination. The following bedside tests were performed to find any sign of unilateral vestibular hypofunction: 1) observation for spontaneous nystagmus, 2) head-shaking test, and 3) head-thrust test. The treatment was considered to be completed when any of the bedside test results were positive after the weekly injection. In the case of any of the three bedside test results being positive before beginning the treatment, the injections were administered until a test result that had been negative became positive. If pure-tone average (PTA) in the treated ear increased by more than 10 dB or if the speech discrimination score (SDS) fell by more than 15 percentage points, the patient was informed about the risks of hearing loss if further injections were administered.

Post-treatment Evaluation

Patients were monitored for 3 months after the completion of the therapy and at intervals of 12 months thereafter. Every patient was monitored for at least 2 years. Audiometric, caloric, and rotatory testing was performed in every follow-up examination, in addition to the neurotological examination. The number of vertigo spells, functional level score, DHI and UCLA-DQ scores, and assessment of the severity of tinnitus and Tumarkin attacks were reported in every follow-up period. The Sensory Organization Test of dynamic posturography was performed at the 2-year follow-up examination. Recurrence of the disease was defined if two definitive episodes of vertigo lasting 20 minutes or longer with hearing deterioration and tinnitus took place in a short time period (less than 3 mo).

Audiometry and Vestibular Testing

Findings on audiometry were reported in terms of PTA, which was computed by determining the average of the four frequencies (0.5, 1, 2, and 3 kHz) and SDS. Vestibular responses were obtained using conventional bithermal caloric testing (30°C and 44°C) and 10-second ice-water caloric tests when indicated. A video-based system was used (Ulmer VNG, version 1.4, Synapsis, Marseille, France) for the attainment and analysis of eye response. Maximum velocity of the slow-phase components of nystagmus evoked by each ear was analyzed for unilateral weakness and directional preponderance, as determined by the Jongkees formula. If the asymmetry found between the responses for the left and right ears was greater than 20%, the result was considered as a unilateral vestibular weakness.

When applying rotary stimulation (CHARTR RVT system, ICS Medical Corporation, Schaumburg, IL), the following principal tests were carried out: 1) the impulse rotational test, described in terms of "time constant," which is the time at which eye velocity has decreased to 37% of its initial value, and 2) the sinusoidal rotational test, described in terms of "gain," which is the ratio of maximum horizontal velocity of the slow-phase components of the nystagmus divided by the stimulus velocity. In the impulse rotational test, the patient is subjected to velocity steps to the right and left. For a leftward velocity step the patient undergoes an angular acceleration of $100°/s^{-2}$ lasting for 1 s. At the end of the acceleration, the patient continues to rotate at a constant velocity of $100°/s^{-1}$ to the left; this is maintained for 60 s. After this time, the patient is decelerated to $0°/s^{-1}$ within a 1-s time period. The procedure just described is repeated for a rightward step. In the sinusoidal rotational test, the patient is subjected to 0.32-Hz sinusoidal oscillations, with a peak angular velocity of $250°/s^{-1}$, with at least seven completed cycles.[15] Results were analyzed according to rotations to the side of the lesion (ipsilateral time constant and gain) and to the normal side (contralateral time constant and gain). Sensory organization test of dynamic posturography (Smart Equitest, version 7.0, Neurocom International, Inc., Clackamas, OR) was performed by patients at the 2-year follow-up.

Statistical Analysis

When studying the PTA and rotary chair test results, a repeated-measures analysis of variance (ANOVA) was performed, with posterior application of the Dunnet test. When studying the caloric test and DHI and UCLA-DQ results, a Friedman test was applied with a Wilcoxon test after Bonferroni's adjustment. When comparisons were made before and after the treatment with functional level results, χ^2 tests were performed. When comparisons were made between the groups with and without recurrences, t tests were applied as parametric tests, and Kruskall-Wallis and χ^2 tests as nonparametric tests.

RESULTS

Of the 71 patients included, 35 patients were women and 36 were men, with a mean age of 53.6 years (95% confidence interval [CI], 50.75–56.37). The right ear was affected in 38 patients, and the left in 33. The duration of disease before patients entered our protocol was 6.9 years (95% CI, 5.51–8.36). Three patients had previous surgical treatment (two cases of sac surgery and one vestibular neurectomy). The number of vertigo spells in the 6 months before gentamicin application was 16.8 (95% CI, 14.10–19.48). Every patient had documented follow-up of at least 2 years (range, 24–48 mo).

Protocol

Fifty-four (76.1%) patients needed only one course of injections to control their vertigo, and their mean number of injections was 3.1 (95% CI, 2.8–3.6). The rest of the patients (17 patients [023.9%]) had recurrence of their vertigo, and another course of treatment was required, with a mean number of injections of 2.5 (95% CI, 1.9–3.1). The vertigo recurred 12.6 months after the end of the first course of treatment. Patients were given the option of observation and medical therapy or additional intratympanic gentamicin. The number of injections received in each course of treatment is shown in Figure 1.

Vestibular Signs Defining End of Treatment

The therapeutic ototoxic effect appeared in most patients 4 or 5 days after the last injection of gentamicin. Forty-seven patients (66%) developed a clinical course of acute unilateral vestibular hypofunction consisting of vertigo, nausea, vomiting, and unsteadiness. The rest of the patients experienced unsteadiness and disequilibrium.

New signs found in the weekly bedside examination indicating onset or progression of unilateral vestibular hypofunction as a result of the gentamicin were spontaneous nystagmus alone in 19 patients (26.8%), head-shaking nystagmus alone in 6 (8.5%), head-thrust sign alone in 2 (2.9%), spontaneous and head-shaking–induced nystagmus in 10 (14.1%), spontaneous and head-thrust sign in 2 (2.9%), and the three signs together in 13 (18.3%). When a patient already had the three oculomotor signs before the gentamicin application, we considered the end of the treatment to be when the patient related congruent symptomatology, and this was the case in 16 patients (22.5%).

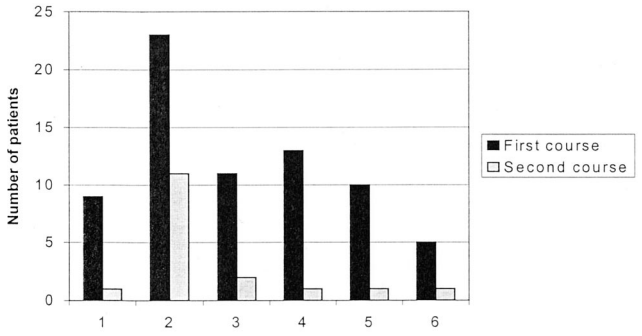

Fig. 1. Number of injections received in each course of treatment.

When we compared the vestibular signs that defined completion of therapy between the group of patients who had a recurrence and the group of patients who did not, we found no differences in the distribution of these signs between the two groups (χ^2 test, >0.05). We found no relationship between the number of injections and the vestibular signs that developed after the treatment ($P > .05$), nor did we find any association between the end-of-treatment signs and the control of vertigo or the post-treatment caloric test results.

Control of Vertigo

The index required by the AAO–HNS is based on the number of episodes of vertigo per month for 6 months before the therapy and the number of episodes of vertigo per month for the most recent 6 months in the 18- to 24-month period after ending the treatment. In addition to the index, any patient who undergoes a surgical procedure is classified as "F." Following this index, complete control of vertigo (class A) was obtained in 49 (69.0%) patients and substantial control (class B) in 10 (14.1%). Nine patients (12.7%) underwent a surgical procedure (class F), because of the lack of control of vertigo, and the technique performed was a transmastoid labyrinthectomy. There was one patient for each remaining category (classes C, D, and E).

Complete or substantial control of vertigo was significantly less likely to be obtained in patients who had a recurrence in their vertigo than in those who did not (χ^2 test, <0.001). The vertigo indexes in the group of patients who had a recurrence and in the group who did not are shown in Table I.

Functional Outcome

The results of the DHI and UCLA-DQ, as well as the functional level recommended in the 1995 AAO–HNS criteria, are presented in Table II. In every measurement determined to obtain functional outcome, a decrease in self-reported handicap was observed ($P < .05$), as represented in Figures 2–4.

Audiometric Results

Table III shows the results of baseline and 2-year follow-up testing for PTA and SDS and the audiometric stages in both time periods, as defined by the criteria of the 1995 AAO–HNS guidelines. Pure-tone average before treatment (taken from the poorest audiogram within 6 mo of beginning the protocol) was 67.25 dB (95% CI, 62.65–71.84). Speech discrimination score for the same period was 68.57% (95% CI, 62.70–74.41).

Although no statistically significant differences were observed for mean baseline, 3-month, 1-year, and 2-year follow-up data ($P > .05$), individual subject data were analyzed to determine whether a clinically significant change in hearing status existed. The definition of change in audition was based on the recommendations of the Committee on Hearing and Equilibrium. Taking these considerations into account, hearing loss as a result of gentamicin injection occurred in 23 (32.4%), 9 (12.7%), and 11 patients (15.5%) at the end of treatment, 3 months after the treatment, and 2 years after the treatment, respectively.

TABLE I.
Vertigo Index in the Group of Patients Who Recurred and in the Group Who Did Not.

Class*	No Recurrence	Recurrence
A	39	10
B	7	3
C	0	1
D	1	0
E	1	0
F	6	3
Total	54	17

Class obtained from the following formula: (X/Y) × 100, rounded to the nearest whole number, where X is the average number of definite spells per month for 18 to 24 months after therapy and Y is the average number of definite spells per month for the 6 months before therapy.

Vestibular Function Results

Caloric test responses were obtained in every patient before administration of gentamicin. Function was considered normal in 29 (40.9%) patients. Unilateral weakness was identified in 36 (50.7%) patients, and no response to ice-water testing was detected in 6 (8.4%) patients. Caloric test results at 2 years or more after the completion of therapy were obtained in 68 patients. Normal function was found in 3 patient (4.22%), unilateral weakness in 32 patients (45.1%), and no response to ice-water testing in 28 patients (39.4%). The evolution in time of the caloric test responses is represented in Figure 5. When both groups were compared, statistical differences (χ^2 test, <0.001) were found. We found no relationship between the post-treatment caloric test responses and the number of injections ($P > .05$), nor did we find any association between the post-treatment caloric test responses and control of vertigo. However, we did find lower canal paresis ($P < .005$) in the group of patients who required the surgical option to control their symptoms (class F). The baseline value for canal paresis in the group of patients who had a recurrence and subsequently required a second course of injections was significantly higher ($P < .001$) than the baseline value for canal paresis obtained in the group without a recurrence.

Rotary Chair Testing

Time constants and gain for rotary chair testing were obtained in 47 patients before the beginning of the treatment, in 69 patients 3 months after the end of the injections, and in 63 patients 2 years after termination of the protocol. The time constant and gain values through these time periods are shown in Figures 6 and 7. The baseline value for ipsilateral and contralateral gain was 0.8 (95% CI, 0.7–0.7). The initial time constant values were 12.3 s (95% CI, 10.9–13.7) for ipsilateral direction and 14.6 s (95% CI, 12.7–16.6) for contralateral direction of rotation.

There was a significant decrease ($P < .05$) in the ipsilateral and contralateral gain values determined at the 3-month follow-up. The values obtained at the 2-year follow-up showed a slight ($P < .05$) recovery in the contralateral gain values. Significant differences for ipsilat-

TABLE II.
Functional Data.

DHI			UCLA-DQ*			Functional Level		
Subscale	Initial	2 Years	Item	Initial	2 Years	Level	Initial	2 Years
Total	56.25	29.42	1	3.2	1.98	1	0	37
Functional	18.55	8.31	2	3.6	2.23	2	0	14
Physical	15.52	10.92	3	4.1	2.11	3	13	5
Emotional	18.55	10.64	4	4.1	2.41	4	32	6
			4	4.1	2.41	4	32	6
			5	3.9	2.76	5	16	6
						6	10	3

Mean values.
*Average patient self-report of frequency (1), severity (2), limitation of daily activities (3), general quality of life (4), and fear of dizziness (5) responses.

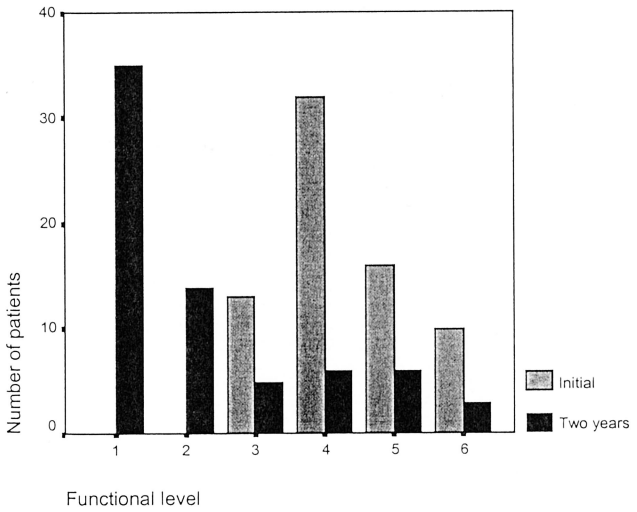

Fig. 2. Functional level score for patients before intratympanic gentamicin and 2 years after the treatment.

eral and contralateral gains were found at the 3-month follow-up evaluation ($P < .05$).

There was a significant decrease ($P < .05$) in the ipsilateral and contralateral time constant values at the 3-month assessment, with no recovery in these values at the 2-year follow-up ($P > .05$). An asymmetry of the time constant was found from baseline testing to the 2-year follow-up.

Tinnitus, Tumarkin Attacks, and Unsteadiness

Tinnitus in the affected ear was experienced by 65 patients before beginning the gentamicin treatment. Two years after completion of the treatment, tinnitus was unchanged in 31 patients (47.7%), and in 34 patients (52.3%) the tinnitus had improved. Tumarkin attacks were present in six patients. Two years after the end of the treatment, Tumarkin attacks were not seen in any patient. However, Tumarkin attacks were present in three patients who had a recurrence and who were surgically treated.

Seventeen patients (22.6%) had slight and moderate unsteadiness 2 years after completion of the intratympanic gentamicin treatment. When differences in age, initial PTA, initial canal paresis, and number of gentamicin injections between groups with and without unsteadiness were studied, no statistical differences were found ($P > .05$).

DISCUSSION

The results obtained in our study support the feasibility of the use of intratympanic gentamicin for patients with Meniere's disease. Since this modality of treatment was initiated in our hospital, it has been indicated in 26% of new patients with MD who were considered, at that point in time or after follow-up, medical failures. It is difficult to compare with other series because these data are unavailable. Before being treated with gentamicin, all the patients were treated using the various methods that were available, and in all cases, they had been following a low-salt diet and taking a diuretic (acetazolamide) for a period of at least 1 year. Other medications taken by the patients during that time period included betahistine (56%), trimetazidine (24%) and others, especially central sedatives (20%); doses varied among patients. However, dizzy spells recurred during treatment, and they generated a significant degree of disability. In this sense, we must conclude that, in our study, intratympanic gentamicin was given to patients with MD when all other medical treatments had failed and patients had an active and severe disease.

The number of dizzy spells and the duration of the disease are data that were usually not presented in other series, but when they were available for comparison, we have found that our patients have shown fewer dizzy spells and similar disease time.[7] Several of the patients at the beginning of the treatment were patients who had previously refused any surgical procedure for their disease, so intratympanic gentamicin was a well-received method of treatment to control their symptoms.

Defining the intractable form of MD is frequently easy, and the criteria shown are in agreement with most reports in the literature. The data obtained from the responses given in scales such as the "functional level scale"

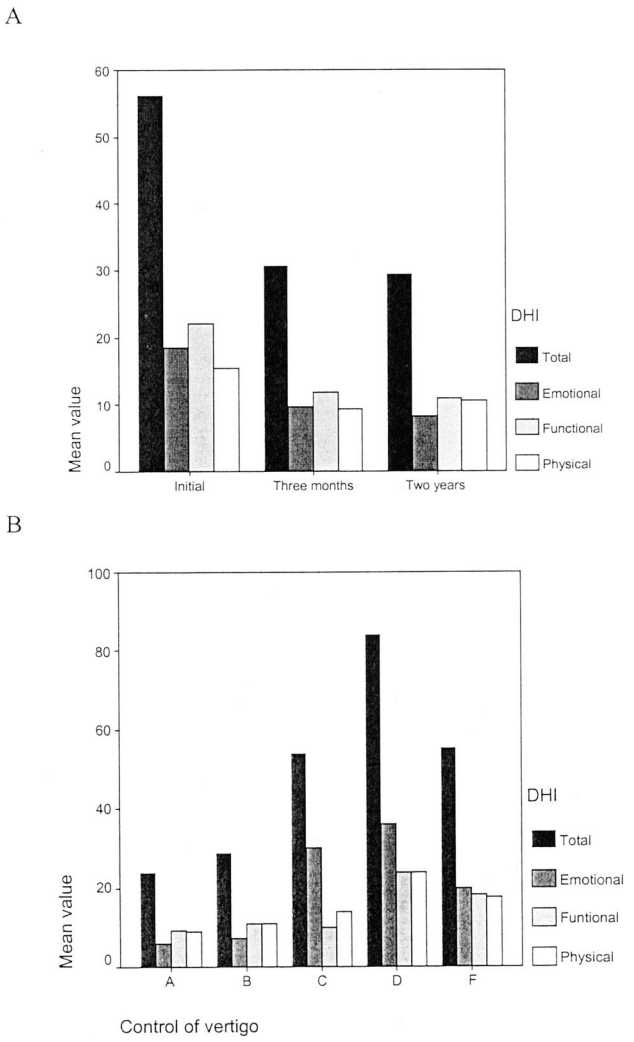

Fig. 3. Dizziness Handicap Inventory values. (**A**) Before the beginning of the treatment and at 3 months and at 2 years after completion of the therapy in all the patients. (**B**) According to control of vertigo.

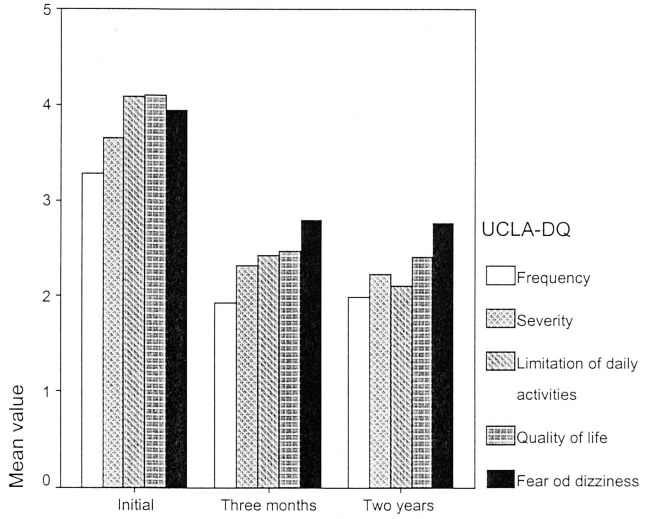

Fig. 4. University of California Los Angeles Dizziness Questionnaire values before the beginning of the treatment and at 3 months and 2 years after completion of the therapy.

TABLE III.
Audiometric Data.

Characteristic	Pretreatment (n = 71)	Most Recent (n = 71)
Pure tone average*	67.25 (CI: 62.65–71.84)	68.37 (CI: 62.32–74.42)
Speech discrimination score	68.57 (CI: 62.72–74.41)	71.73 (CI: 65.27–78.20)
Stage†		
1 (PTA < 25 dB)	1	5
2 (PTA 26–40 dB)	5	5
3 (PTA 41–70 dB)	35	25
4 (PTA > 70 dB)	30	35

*PTA based on the four-tone average of the pure tone thresholds at 0.5, 1, 2, and 3 kHz.
†Staging based on the four-tone average of the PTA (AAO-HNS).

(AAO–HNS, 1995) and the DHI and UCLA-DQ provided a better insight into the disability and handicap of the patients. Before treatment, their positioning in the functional scale and the answers given to the different items in the DHI and UCLA-DQ were helpful in distinguishing an intractable form of the disease from another form not yet treated medically. Discussing the results with the patient after completion of the written questionnaire led us to a more in-depth evaluation of their disease than that obtained from a mere description of the number of dizzy spells. This is a good method to indirectly assess the severity of the clinical situation of the patient and allows the "vertigo index" to be calculated. This enables us to classify the patients according to results, following AAO–HNS criteria. This is the framework in which data from different series using similar or different therapeutic methods can be compared, and it was strictly followed throughout the present study. When comparing our results on the functional level scale and the DHI and UCLA-DQ with those obtained by other authors, there were no differences in the first scale[7,16,17] or in the UCLA-DQ[14]; however, the score on the DHI was higher in our patients.[18] To document and evaluate the results of any treatment in diseases such as MD, disability and handicap assessment is one of the best methods to allow results to be compared almost item by item. It is also a good complement to the criteria defined by the AAO–HNS.[19] Taking all of this into consideration, we found that the population to be treated had a long-standing disease and was particularly disabled.

As a result of the treatment, there was a marked reduction in the vertigo index, reflected in the number of patients in classes A and B (69% and 14.1%, respectively). There was a prompt and sustained reduction in disability and level of handicap due to the disease, as well as an increase in overall functional perception. Interestingly, fear of dizziness is an item that remains present and becomes more important after the treatment than before, when the perception of a deteriorated quality of life and

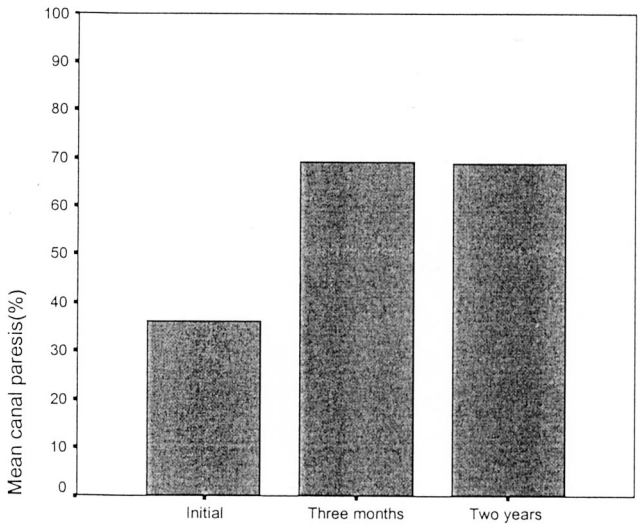

Fig. 5. Canal paresis obtained before the beginning of the treatment and at 3 months and 2 years after completion of the therapy.

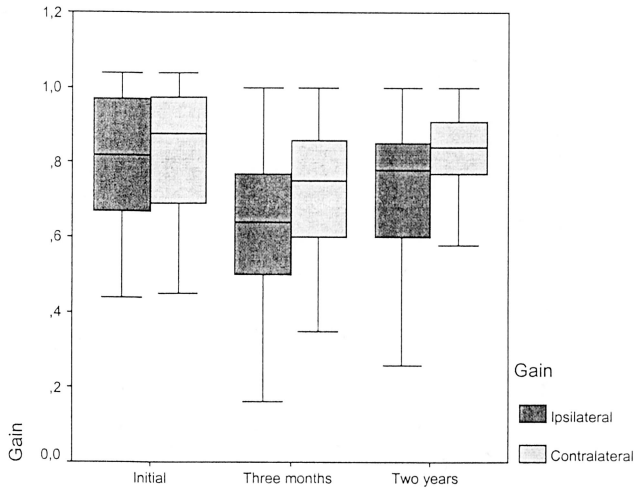

Fig. 6. Ipsilateral and contralateral gain values through time.

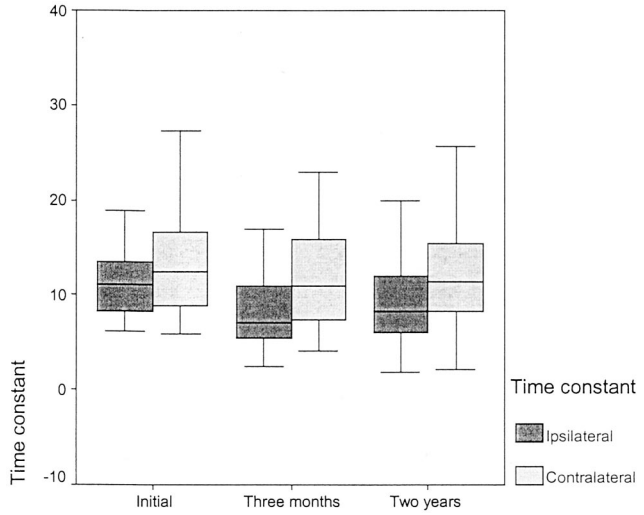

Fig. 7. Ipsilateral and contralateral time constant values before the beginning of the treatment and at 3 months and 2 years after completion of the therapy.

reduced performance of daily activities are more relevant. This is reflected in the follow-up, when even patients in classes A and B observe that dizzy spells after the treatment have not reappeared for a long time, which they have not previously experienced, but still question the duration of this effect. The reason for this is connected to the repetition of the dizzy spells and their consequences for the subject, which prevail even when there are no more attacks (class A) or the reduction is significantly high (class B). As such, fear as an emotional response to vertigo itself can be traced to specific restrictions in lifestyle that every patient has experienced.[20]

Although using a common method to evaluate and report the results, when dealing with intratympanic gentamicin, great care must be taken when analyzing different methods of instillation. When comparing results with those obtained by Minor,[7] whose protocol we have used, we found that control of vertigo is lower in our study, with fewer patients in class A and more in class B. These differences can be caused by variations in the methodology or longer follow-up of our patients. With regard to the first point, the symptoms and clinical signs defining the end of treatment are subtle and, at times, difficult to pursue; this could favor less treatment than required and probably incomplete therapy. This is not the case, as is evident from the results in caloric testing, in which a higher proportion of vestibular areflexia and stronger asymmetry in the rotary chair parameters are seen in our patients. With regard to follow-up, all of our patients were seen at least 2 years after ending the treatment (or retreatment in cases where it was needed). However, in Minor's study,[7] 9 of the 34 patients were followed for a period longer than 2 years, and 12 for a period of less than 1 year. This is especially relevant when we consider that recurrences took place in 23.9% of the patients in a mean period of 12.6 months after ending the treatment. If follow-up does not include this time period, this phenomenon will be ignored. However, 2 years must still be considered insufficient, and a longer time period must be analyzed. In this sense, preliminary results in the first 20 patients who were monitored for more than 4 years show no changes after the 2-year period. Still, this is an observation that has not been validated in a broader group and to which statistical assessment was not applied.

As found by other authors, vestibular ablation was not needed to achieve control of vertigo.[7,21–23] Although some level of damage is needed, as is evident in the first evaluation after treatment, canal paresis in class F patients is significantly lower than that in patients in classes A and B. However, surprisingly, class F patients also showed significantly higher levels of canal paresis before beginning the treatment than did those who did not show recurrence in vertigo spells. Other measurements of vestibular function were analyzed, but their low number precluded any statistical analysis. Future work will be aimed at determining whether data from vestibular tests could

be used as risk factors for recurrence, thus deciding a change in the protocol (e.g., further "preventive" injections or closer follow-up). An expected but difficult-to-explain finding was that patients maintain normal caloric test response immediately after the treatment.[1,24,25] Of the five patients in our study who maintain normal caloric test response after treatment, three were in class A, one was in class B, and one was in class F. The number is similar to that reported by other authors, and the explanation for this finding is complex. Several hypotheses have been put forward without definite demonstration. The results in vestibular and auditory function rule out any possible placebo effect or even a nonspecific effect, as can be seen from the dramatic change in the clinical profile and results in auditory and vestibular function tests: 1) When the desired gentamicin ototoxic effect appears, symptoms are seen by the patients that are clearly different from any classic dizzy spells of MD, which are well known to them; 2) the clinical bedside examination based on the search for the main signs of unilateral vestibular damage is congruent with the expected unilateral peripheral vestibular damage in all of the patients; and 3) hearing loss is always associated with the first injection, whatever symptoms or signs of vestibular damage appear simultaneously. Two other difficult-to-prove hypotheses refer to recovery of function spontaneously or after hair cell damage and to the possible toxic effect occurring in cells engaged in the production of endolymph to a greater degree than in the hair cells in the ampullae of the semicircular canals.

After reviewing the results of the present study and those from other authors using different techniques, seeking a "subablative" effect in the vestibular system, we conclude that a significant number of patients (81%–93.4%) can obtain control of vertigo after the treatment with intratympanic gentamicin, according to a 2-year follow-up.[23,26] The incidence of hearing loss is, undoubtedly, high at the end of treatment. This is due to several causes. First, some patients decided to proceed with injections when, without having developed the symptomatology or appearance of vestibular signs defining the end of the treatment, hearing loss was observed. These were typically those who rejected any surgical approach for their disease. Second, during the treatment, some patients can have a dizzy spell with its corresponding hearing loss; in these cases, the clinical examination allows any end-of-treatment sign to be excluded and allows the physician to proceed with the next injection. Third, of course, we must consider the case of existence of direct damage to the cochlear system, whether transitory, incomplete, or definitive. All of these possibilities explain both the appearance of 32.4% hearing loss at the end of treatment and also the fact that, 2 years later, this rate is 15.4%, which probably represents the latter possibility of definitive cochlear ototoxic damage. When comparing our results with those obtained by other authors with the same[7] or different[22,23,25] technique, we have obtained a lower incidence of hearing loss.

Unsteadiness is a symptom that is frequently overlooked after any treatment. This is mainly because of its difficult definition and measurement. The number of patients with unsteadiness in our study is similar to[23] or lower than[25] that mentioned by other authors. Reducing assessment to the six possibilities in the functional level study makes it an easy questionnaire to pass but gives little concretion. In this sense, the DHI and UCLA-DQ can indirectly assess this symptom, giving a better insight into the patients' evolution.

The AAO-HNS reporting guidelines are the most widely accepted staging and reporting system for MD, although not every author follows them. Considerations about the AAO–HNS guidelines should be made. First, unsteadiness after the treatment is not contemplated as a unilateral deafferentation symptom, and apart from our experience, many other authors have reported a similar incidence of unsteadiness,[23,25] even in surgical series.[18,27] Second, the AAO–HNS limits itself to creating a class F to categorize patients who had been subjected to a surgical option because of the lack of control with the initial treatment, without offering the possibility of studying this group of patients in more detail. In such a way, we could offer the patient more complete information about the existing possibilities in the case of failure with the gentamicin therapy. Third, the recurrence of the vertigo symptoms is not contemplated either, although many authors have reported a similar incidence of recurrence similar to ours.[7,26,28] A new category of patients with these characteristics would lead us to seek more appropriately predictive factors for recurrence.

CONCLUSION

The treatment of MD with weekly intratympanic gentamicin injections administered until the appearance of an end-of-treatment sign provided substantial or complete control in 83.1% of patients. Recurrence of vertigo episodes was observed in 23.6% of the patients, and similar control of vertigo was obtained with an additional course of treatment. The risk of hearing loss after the gentamicin therapy is comparable to other gentamicin protocols and lower than vestibular neurectomy series. Disability is significantly reduced because dizzy spells do not recur.

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