On-Demand and Low Dose Intratympanic Gentamicin for Meniere's Disease: A Customized Approach

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Objective: To evaluate the efficacy of on demand and low dose intratympanic gentamicin (ITG) in patients with intractable Meniere's disease (MD).
Study Design: Clinical chart review.
Setting: Secondary care center.
Patients: Subjects with MD who failed conventional treatment and underwent on demand ITG infiltration from June 2013 to December 2018.
Intervention: 0.4 to 0.5 ml of buffered gentamicin were administered through an intratympanic route. A total of 5 mg in case of low dose and 20 mg as a standard dose.
Main Outcome Measures: Vertigo control, Meniere's Disease Functional Level Scale (MDFLS), Dizziness Handicap Inventory (DHI), and pure tone audiometry pre and posttreatment.
Results: Thirty-one patients, 16 women and 15 men with a mean age of 52.81 (22–79) years were included. The number of ITG injections ranged from 1 to 7, with a mean of 2.52 applications per patient. Mean interval between doses was 212.15 (21–1442) days. Average follow-up was 24.03 months. An improvement on MDFLS was seen on 77.4% (n = 24) patients. DHI score improved after gentamicin treatment (mean 55.23 versus 24.06, $p \leq 0.001$). Thirty patients (96.8%) reached complete or substantial vertigo control. Only one patient did not achieve control. Hearing was preserved in 43.5% (n = 10) of analyzed audiograms, whereas 17.4% (n = 4) developed hearing loss greater than 20 dB, which was not statistically significant ($p = 0.099$).
Conclusions: In our study, on demand and low dose ITG was effective for vertigo control in patients with intractable MD. Individualized therapy is recommended in all patients to minimize vestibular and cochlear toxicity.
Key Words: Gentamicin—Intratympanic injection—Meniere's disease.

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Meniere's disease (MD) is an inner ear disorder characterized by vertigo, fluctuating hearing loss, tinnitus, and aural fullness. Incidence is estimated to be 15.3 per 100,000 (1) and a prevalence of 0.12 to 0.5% (2).

Treatment of MD has been improved by the use of gentamicin. This medication is predominantly vestibulotoxic; although it exerts certain cochleotoxicity, is among the aminoglycosides that causes less cochlear damage. This also depends on the dose and the frequency of administration (3–5). The use of intratympanic gentamicin (ITG) has been proven to be effective in controlling MD's vertigo in several reviews and meta-analyses (3–6). The frequency of gentamicin applications described in the literature is: multiple daily, weekly, continuous, low dose, and titration (5). Unfortunately, the heterogeneity in the design of the studies, the different doses and the frequency of applications used, leave the clinician with no guidance on the election of the gentamicin protocol. Ideally, gentamicin applications would have an effective vertigo control with the least of side effects. Moreover, the lack of standardization of studies, has led to different recommendations by the existing literature (3–6).

On demand or low dose ITG is defined as one to two injections with repeat treatment only for recurrent vertigo (5). There are a number of studies that support its use (7–17). On demand ITG could represent a minimal invasive form to deliver gentamicin with minimum side effects. We aim to evaluate the efficacy of on demand

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and low dose ITG in patients with intractable MD (18) and to determine the number of ITG doses required for vertigo control.

MATERIALS AND METHODS

Study Design

A clinical chart review was performed to identify all patients diagnosed with definite MD as defined by the Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in MD (19), from June 2013 to December 2018 at our secondary care center. Institutional Review Board approval was obtained with number 332 (CIDOCS).

Inclusion Criteria

Patients older than 18 years with unilateral MD, who failed conventional treatment (low-salt diet, diuretics, betahistine, or intratympanic steroids) and therefore received one or more ITG injections under an on demand protocol were included. As strict inclusion criteria, only patients with pretreatment and posttreatment Meniere's Disease Functional Level Scale (MDFLS) (19) and Dizziness Handicap Inventory (DHI) (20) were included to measure outcomes as subjectively perceived by patients.

Exclusion Criteria

Patients without MDFLS or DHI before or after treatment and patients with a total follow up lesser than 1 month were excluded.

Outcome Measures

Vertigo control, MDFLS, DHI, and pure tone audiometry before and after treatment were the outcome measures.

Vertigo Control

Since vertigo is the most remarkable symptom of MD, clinical outcomes were measured by a method proposed by the American Academy of Otolaryngology, Head and Neck Surgery (AAO-HNS) (19), which gives a numerical value to vertigo episodes as shown: numerical value $= (X/Y) \times 100$, rounded to the nearest whole number, where X is the average number of definitive spells per month for the 6 months 18 to 24 months after therapy and Y is the average number of definitive spells per month for the 6 months before therapy. This value is then converted into Meniere Class. For the purposes of this study, Meniere Class A and B were considered as successful treatment, meaning complete and substantial vertigo control, respectively (8).

MDFLS

Regarding to functional level scale, it was implemented as suggested by the 1995 Committee on Hearing and Equilibrium guidelines (19) as improved, unchanged, or worsened for each patient.

DHI

DHI is a 25-item questionnaire that assesses the self-perceived handicapping effects caused by vestibular disease, independently from the total of vertigo spells experimented. Items are subgrouped into functional, emotional, and physical aspects (20). Overall score was analyzed. DHI score goes from 0 on asymptomatic patients to 100 representing significant impairment. Any improvement on DHI score posttreatment was considered. DHI scores were categorized as well into mild (0–30 points), moderate (31–60 points), and severe (61–100 points) handicap (21).

Audiometry

Pure-tone average (PTA) of frequencies 0.5, 1, 2, and 4 kHz was used to quantify hearing loss. A change of 10 dB or more was considered clinically significant as defined by the Committee (19). Any increase on PTA was categorized as satisfactory.

Electronystagmography (ENG)

Because some patients did not undergo ENG, this was not included as an outcome measure. Clinically, head impulse test is performed to post-infiltrated patients in every visit and a partial vestibular ablation is expected.

Intervention

ITG was delivered by direct instillation of medication through the tympanic membrane. Gentamicin sulphate (10–40 mg/ml) was buffered with one-third of sodium bicarbonate. Previous, the auditory canal was anesthetized with topical tetracaine for 20 minutes. Later, under microscopic vision, gentamicin was injected to the middle ear through the inferior quadrants of the tympanic membrane. An insulin syringe with a 22-gauge needle was used to do the procedure. Application of 0.4 to 0.5 ml of the buffered solution with an average concentration of 5 to 20 mg of gentamicin was undertaken in all patients. After the injection the patient remained supine for 45 minutes with head positioned to the contralateral side; swallowing or talking was prohibited. All interventions were performed with informed consent.

On Demand and Low Dose Protocol

On demand and low dose ITG protocol followed at our center consists on injecting gentamicin on a dose–response basis. After the first ITG infiltration is performed, patients are re-evaluated and after 3 weeks, if one or more vertigo spells present with otological symptoms, a second ITG injection is suggested. A vertigo spell is expected from 0 to 20 days after the intratympanic application due to vestibulotoxic properties of gentamicin, this vertigo spell is not considered as part of MD.

Patients are assigned with the minimum possible dose of gentamicin according to their symptoms, from 5 mg to a maximum of 20 mg. Some variables are considered to select the infiltration dose. Regarding to the patient's age; the elderly, preferably, are infiltrated with the lowest possible dose (5 mg) as with aging it is more difficult to compensate for a vestibular loss following ablation. The number of spells, its duration, MDFLS, as well as patient's degree of disability is taken into consideration. All patients follow a standard protocol of vestibular rehabilitation with emphasis on the vestibulo-ocular reflex (VOR). Regularly, patients are scheduled at the clinic 2 weeks after infiltration and every month for 3 consecutive months. Once asymptomatic, follow-up appointments are every 3 to 4 months.

The Lowest Possible Dose

To minimize vestibulotoxic effects of gentamicin, older patients ($\geq$60 yr), bedridden patients or with very little physical activity, or those with low DHI were assigned a total dose of 5 mg of ITG injection. Also, patients with vestibulotoxic effects after any injection of gentamicin but with persistent vertigo spells compatible with MD, were assigned the lowest dose (5 mg) in subsequent doses.

On the other hand, if the lowest dose was not effective for vertigo control, a dose of 20 mg was administered. In this manner, a personalized approach is used based on patient's symptoms (definitive MD vertigo spells). Intending to improve vertigo control with the minimal side effects, we customized the doses according to the clinical response of our patients, i.e., what we call variable doses.

Statistical Analysis

Statistical analysis was performed with SPSS version 21.0 for Windows (IBM Corp., NY). Descriptive statistics were used for demographic data. Continuous variables were analyzed by Student's *t* test and categorical variables with χ^2 test. MDFLS was analyzed as categorical and continuous variable. Analysis pretreatment and posttreatment was performed with a paired sample *t* test (MDFLS, DHI, PTA). A p value < 0.05 was considered significant.

RESULTS

On the selected period, 35 patients with MD were classified as intractable. Among these; a total of 31 patients, 16 women and 15 men, met the inclusion criteria. Of the remaining four, one did not have pretreatment DHI and the other three did not have posttreatment DHI. The mean age was 52.81 (±15.43) years. Besides medical treatment, two patients had also received IT steroid previously with poor improvement.

The number of ITG injections ranged from 1 to 7, with a mean of 2.52 (±1.69) applications per patient. Gentamicin sulphate (10–40 mg/ml) was buffered with a third of sodium bicarbonate in all cases. Single doses of gentamicin ranged from 5 to 20 mg. Figure 1 shows the pattern of required doses. Accumulative dose of gentamicin by patient ranged from 5 to 125 mg, with a mean of 35.65 mg. The global average interval between injections was 212.15 days (±145.7), with a minimum interval of 21 days and maximum of 1442 days. Mean periods between single applications are shown on Table 1.

Mean follow-up from first ITG injection to last evaluation (total follow-up) was 24.03 (1–63) months. After last infiltration, patients were followed up for 10.87 months in average.

Vertigo control was achieved in 96.8% (n = 30) at the end of the study. Twenty patients reached Meniere's Class A and 10 patients Class B. One patient did not achieve vertigo control, remaining on Class C. Table 2 shows the detailed doses per patient and their clinical response.

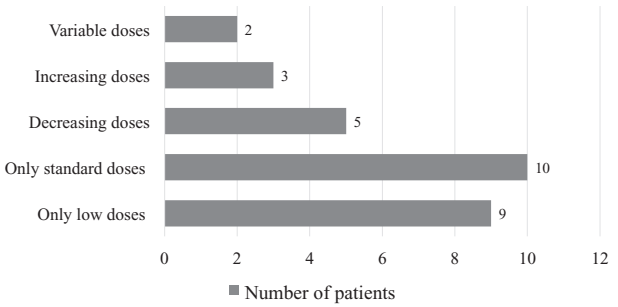

FIG. 1. Customized approach of on-demand intratympanic gentamicin.

TABLE 1. *Interval length between ITG injections*

Interval	Days
Between 1st and 2nd ITG	206 (±152.7)
Between 2nd and 3rd ITG	495 (±489.6)
Between 3rd and 4th ITG	214 (±132.8)
Between 4th and 5th ITG	133 (±63.3)
Between 5th and 6th ITG	112 (±92.5)
Between 6th and 7th ITG	113 (±101.1)

ITG indicates intratympanic gentamicin.

Pretreatment, there were no patients graded level 1 on MDFLS, nine (29%) patients were graded level 2, 12 (38.7%) patients level 3, 7 (22.6%) patients level 4, and 3 (9.7%) patients level 5. Posttreatment, 17 (54.8%) patients were graded level 1 (vertigo has no effect on activities), five (16.1%) patients level 2, seven (22.6%) patients level 3, two (6.5%) patients level 4, and no patients remained on level 5; thus, 24 (77.4%) patients presented some improvement on MDFLS, three (9.7%) patients remained unchanged, and four (12.9%) patients worsened posttreatment. MDFLS mean difference was 3.13 pretreatment versus 1.81 posttreatment ($p \leq 0.001$). MDFLS per patient is reported on Table 2.

DHI

DHI score pretreatment was 55.23 points in average, with 13 (41.9%) patients classified as severely handicapped (61–100 points), 12 (38.7%) patients as moderately handicapped (31–60 points), and 6 (19.4%) patients as mildly handicapped. After treatment, mild handicap was found in 19 (61.3%) patients, moderate handicap in 7 (22.6% patients), and severe handicap in 5 (16.1%) patients; with a DHI score average of 24.06 points. Categorically, 19 (61.3%) patients changed to a lower handicap degree (e.g., from moderate to mild), 8 (25.8%) patients remained in the same category, and 4 (12.9%) patients worsened their handicap. On overall DHI score, 25 (80.6%) patients improved their result ($p \leq 0.001$) and six (19.4%) patients worsened on the test (eight points in average). DHI per patient on Table 2. DHI components are reported on Table 3.

All 31 patients underwent pure tone audiometry pretreatment; however, only 27 audiograms were found on medical records. Fourteen patients underwent audiometry at the end of the treatment, 10 patients at some point of the treatment and seven patients had pending follow-up audiogram. As a result, only 23 patients were analyzed with both pre and posttreatment audiogram. Mean PTA pretreatment on the affected ear was 43.20 dB, after treatment PTA was 49.67 dB ($p = 0.099$). Thirteen (56.5%) patients developed hearing loss from 1.25 to 57.5 dB, with an average of 17.59 dB. Of these, eight (34.8%) were clinically significant losses (>10 dB) and one patient had a very significant drop on audition

TABLE 2. *Gentamicin protocol and clinical evolution*

Patient	Sex	Age	No. ITG	Dose Applied	Functional Class Pre ITG	Functional Class Post ITG	Score of Vertigo Control	Class of Vertigo Control	DHI pre ITG	DHI post ITG	Mean Increase in PTA	Follow-up from Last ITG (mo.)	Total Follow-up (mo.)	Clinical Follow-up
1	F	44	2	10 mg/10 mg	4	1	0	A	96	4	−17.5 dB	28	39	No vertigo
2	F	78	3	20 mg/5 mg/5 mg	3	4	0	A	78	62	18.75 dB	0.7	33	No vertigo/unsteadiness
3	F	51	2	5 mg/20 mg	3	1	0	A	50	0	−8.75 dB	49	52	No vertigo/unsteadiness
4	F	52	3	5 mg/20 mg/20 mg	5	3	0	A	76	80	5.0 dB	0.6	54	No vertigo
5	M	43	4	20 mg/20 mg/20 mg/ 20 mg	3	2	0	A	68	62	13.75 dB	31	44	No vertigo
6	M	36	3	20 mg/20 mg/20 mg	3	3	0	A	60	62	−5.0 dB	8	63	No vertigo
7	M	61	4	5 mg/5 mg/20 mg/20 mg	4	1	0.69	B	54	0	−2.5 dB	24	35	Two vertigo spells/unsteadiness
8	M	33	2	5 mg/5 mg	2	3	4.00	B	22	36	−5.0 dB	15	35	Four vertigo spells
9	M	39	1	5 mg	2	3	0	A	16	34	−13.75 dB	14	14	No vertigo
10	M	74	3	5 mg/5 mg/5 mg	4	1	0	A	30	0	−8.75 dB	7	35	No vertigo
11	F	48	4	20 mg/5 mg/5 mg/5 mg	5	1	10	B	82	32	12.5 dB	10	31	One vertigo spell/unsteadiness
12	F	48	6	20 mg/20 mg/20 mg/ 20 mg/20 mg/20 mg	2	1	4	B	60	12	23.75 dB	15	29	No vertigo
13	F	71	3	20 mg/5 mg/5 mg	4	3	0	A	46	28	15 dB	4	32	No vertigo/unsteadiness
14	M	60	7	5 mg/20 mg/20 mg/20 mg/ 20 mg/20 mg /20 mg/ 20 mg	4	3	0	A	28	14	6.25 dB	10	48	No vertigo/unsteadiness
15	F	56	2	5 mg/5 mg	2	1	0	A	62	0	5.0 dB	3	6	No vertigo
16	M	44	7	20 mg/20 mg/5 mg/20 mg/ 20 mg/20 mg/20 mg	5	1	1	B	64	0	30 dB	21	43	Two vertigo spells
17	F	57	2	5 mg/20 mg	3	2	0	A	30	10	−12.5 dB	14	25	No vertigo
18	M	58	1	20 mg	3	1	0	A	32	6	n/a	1	1	No vertigo/unsteadiness
19	M	50	1	20 mg	3	1	0	A	68	8	n/a	6	6	No vertigo/unsteadiness
20	F	61	3	20 mg/5 mg/20 mg	3	2	8.33	B	84	44	57.5 dB	8	23	Two vertigo spells/unsteadiness
21	F	59	2	20 mg/5 mg	4	1	0	A	84	26	−2.5 dB	8	19	No vertigo/unsteadiness
22	M	37	1	20 mg	2	1	3.85	B	36	0	37.5 dB	26	26	One vertigo spell
23	F	45	2	20 mg/20 mg	2	2	0	A	74	40	−3.75 dB	0.2	11	No vertigo
24	M	79	2	5 mg/5 mg	2	1	0	A	12	n/a	n/a	6	9	No vertigo
25	M	22	2	20 mg/20 mg	3	1	1.14	B	40	6	n/a	8	11	One vertigo spell/unsteadiness
26	F	33	1	20 mg	4	2	56	C	88	50	1.25 dB	3	3	10 vertigo spells/unsteadiness
27	M	71	1	5 mg	2	1	2	B	58	4	n/a	2	2	One vertigo spell
28	F	76	1	5 mg	2	1	0	A	46	6	n/a	2	2	No vertigo
29	F	61	1	5 mg	3	3	4	B	58	62	n/a	4	4	One vertigo spell/unsteadiness
30	M	66	1	20 mg	3	4	13	B	48	54	2.5 dB	9	9	Five vertigo spells/unsteadiness/ pending injection
31	M	24	1	20 mg	3	1	0	A	52	4	n/a	1	1	No vertigo/unsteadiness

dB indicates decibels; DHI, Dizziness Handicap Inventory; F, female; ITG, intratympanic gentamicin; M, male; mo., months; PTA, pure-tone average.

TABLE 3. *DHI components*

DHI Scale	Pretreatment	Posttreatment	*p*
Total	55.23	24.06	<0.001
Emotional	18.45	8.32	<0.001
Functional	20.71	7.87	<0.001
Physical	16.06	7.87	<0.001

DHI indicates Dizziness Handicap Inventory.

(57.5 dB). Ten patients were found to gain hearing from 2.5 to 17.5 dB, 8 dB in average.

Among treatment side effects, 15 (48.4%) patients developed chronic dizziness or unsteadiness. Other complications were minor tympanic perforation which latter resolved (n = 1), aural fullness (n = 1) and tinnitus (n = 1).

DISCUSSION

Gentamicin treatment has been used more frequently to control MD, it is a procedure that is simple and cost-effective. Ward et al. (22) reported that ITG was the best treatment for MD, providing the greatest results on reduction of vertigo episodes and work-place absenteeism, compared with other therapies. Nonetheless, multiple dose regimens and applications have been used and no standard protocol exists to this day (7–16). Meta-analyses have recommended different application strategies, such as low dose (4), titration (5), weekly or on demand (3), and another author states effectiveness regardless of the protocol used (6).

As clinicians, it is desirable to have a protocol known to be effective and with minimum side effects. Low dose gentamicin could be a good alternative in the management of MD patients. Effectiveness in vertigo control has been documented from 86.6% (5) to 100% (17). However, complete vertigo control has a lower result (66.7%) (5).

Our experience shows that an average of 212 days is required for a new gentamicin application. Adequate vertigo control was achieved in 96.8% of our patients, whereas 64.5% accomplished a vertigo control class A, without any definitely vertigo spells posttreatment. Only one patient (3.22%) did not achieve vertigo control, abiding in class C.

Unfortunately, response to gentamicin treatment is highly unpredictable, as mentioned by other authors (7). No relation has been found with demographic or audiometric parameters (7). Nevertheless, Manrique-Huarte et al. (11) found a better response in patients with shorter disease duration.

Gentamicin ototoxicity is caused by the generation of iron-aminoglycoside complexes that increase the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that generate mitochondrial damage, and consequently, activates several pathways that cause apoptosis of vestibular cells and cochlear hair cells. The severity of toxicity is related to dose and the duration of the treatment (23). This theory is one of the main reasons that support the role of on demand and low dose ITG protocols.

Based on our results and those reported throughout the literature, more gentamicin applications could be expected in patients with longer follow up (16). Subsequent ITG injections should be undertaken every time a definitive vertigo spell is reported by a patient. Vestibular function recovery can occur not only from actual hair cell regeneration (24), but also from the loss of calcium channel competitive inhibition at the level of the hair cell membrane as well through metabolism of the aminoglycoside molecule.

Casani et al. (16) found that although low dose regimen patients required, more likely, repeated rounds of gentamicin; high dose patients developed a refractory response to gentamicin treatment in up to 40% of patients in the long term. This data supports the importance of establishing the right dose of gentamicin at the beginning of therapy.

In our study, MDFLS and DHI showed a significant improvement in the posttreatment evaluation. Seventeen of our patients reached MDFLS 1 and 19 improved their DHI score to a lower handicap degree. Mean DHI posttreatment was 24.06; nonetheless, five patients remained in severe handicap score at the end of follow up. In spite of the high DHI scores reported, all of the severe handicapped patients had a vertigo control class A. Interestingly, the only patient who did not achieved vertigo control (class C) has a moderate handicap score on DHI.

Pullens et al. (3) in their meta-analysis found only two studies that were randomized double blind trials with placebo control; among these, Stokroos and Kingma (17) followed an on demand ITG protocol with complete vertigo control. However, the use of placebo in MD is controversial (6,11,16).

The goal of this study besides vertigo control, was to maintain hearing through a partial vestibular ablation. One meta-analysis found no statistical significance between complete vestibular ablation versus partial vestibular ablation and vertigo control (5). Although, there was a higher chance of preserving hearing with partial ablation (5).

Interestingly, hearing gain was observed in 10 patients, with an average improvement of 8 dB. Gentamicin and hearing gain or minimum hearing impairment has been found also in other studies (25–27).

Chronic dizziness or unsteadiness is one of the complications of ITG treatment. Unfortunately, 15 patients in this study developed unsteadiness. Although nine of those patients denied definite vertigo spells, five of them were in control class B, and the only patient without vertigo control had also unsteadiness. Zhang et al. (28) reported in their meta-analysis 10 articles with postural instability without vertigo spells after ITG injection. Other authors have also pointed out the unsteadiness after gentamicin treatment in class ''A'' patients (29). One possible explanation is that patients could develop a lower tolerance to vertigo and unsteadiness, since control of vertigo spells is achieved in each gentamicin

application, this has been mentioned also by other authors (7,30). However, further research on unsteadiness after gentamicin treatment needs to be addressed by future studies (29).

Vertigo score posttreatment was standardized by the Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in MD. This scale requires 18 to 24 months after therapy to evaluate the efficacy of MD treatment (19). Nevertheless, the repeated nature of this treatment, being on demand, makes it difficult to proceed rigorously with this evaluation. Quaglieri et al. (7) have also stated this drawback. In our study, we calculated the vertigo score at the end of follow up, although 26 patients did not fulfill 24 months of follow-up since the last ITG injection. Despite the majority of the patients had a long total follow up, not enough time has passed to fulfill the AAO-HNS scale posttreatment in all of our patients since our work resides on multiple ITG doses and our time to follow up is restarted after every ITG. Even though, we recommend the use of this scale after every on demand gentamicin application; yet, this has to be defined by the Committee on Hearing and Equilibrium. This matter has become a problem for on demand regimens, that is why some investigators are already migrating to Kaplan–Meier analysis for the interpretation of the results instead (7,11).

ENG was not performed in all patients in our study, instead the cephalic impulse test was applied as a clinical test to evaluate the response to ITG and the compensation of the horizontal VOR due to the partial chemical ablation. A long follow-up study of 132 patients showed that the absence of caloric response is not related to vertigo control; on the other hand, a correlation was proved between the decrease of DHI and the long-term vertigo free control (31).

Limitations of this study are the low sample of patients, the limited time of follow-up in 26 patients, and the lack of ENG control. Additionally, a longer follow-up could have improved our knowledge on the long-term gentamicin response in our patients.

A characteristic of our study that must be considered is the selection of gentamicin doses. The patients admitted to the on demand protocol have very different clinical characteristics. To achieve vertigo control, the gentamicin doses have to be individualized in each patient. We understand this undermines the study's reproducibility, but instead improves vertigo control with minimal toxicity.

Some factors can cause a predisposition to vestibular toxicity such as history of use of other ototoxic drugs, previous therapy with gentamicin and age over 65 years old.

At the beginning of the study, gentamicin doses were fixed at 20 mg; nevertheless, patients showed significant vestibular disability, especially the elderly. Lower doses were then implemented. The importance of a personalized approach is that medical personnel can be intimidated by these adverse events, precluding the use of gentamicin. MD treatment could find its ideal in the personalized approach.

Currently, the doses proposed for the on demand and low dose protocol, depends on the degree of disability showed by MDFLS and DHI. For patients with significant disability, the initial dose recommended is 20 mg, whereas patients with lower grade of disability should be infiltrated with 5 mg.

In addition, patients' age is an important issue; vestibular toxicity is a factor directly proportional to the age of the patient, meaning that generally, older patients have greater vestibular toxicity. Younger patients tend to compensate earlier, therefore, higher doses can be used. On the other hand, in this study, a few patients with lower disability and older age, low doses were indicated, nevertheless a change to standard dose (20 mg) occurred due to the lack of response to treatment (Fig. 1).

This study recommends the use of the minimum possible dose at the start of any treatment with gentamicin and re-evaluating the patient every month. In patients with a lack of response to treatment or relapse, a new infiltration can be indicated after 21 days. Subsequent doses are calculated based on the number of vertigo attacks and the disability caused.

A highlight of this study is the effective vertigo control in our small sample, reaching statistical significance. We added also the subjective measurements of DHI, as well as the MDFLS, which are both infrequently reported in previous studies (7–17). This could expand our knowledge in the correlation between subjective symptoms and more objective measurements, such as the number of vertigo spells per month. There are patients with total DHI as high as 80, but with no vertigo attacks. Rehabilitation of these patients is the key to surpass this dizziness handicap. Also, a previous study (29) has drawn attention to this issue, and more studies on gentamicin treatment should add these evaluations in their patients.

This study adds evidence to the literature about a controversial topic, the dose of gentamicin needed to reach Meniere control. Several studies have proven the efficacy of gentamicin compared with other treatments, such as steroids and placebo (32,33). The effectiveness of on demand ITG on MD's vertigo control has been corroborated in multiple studies as well (3,4,7–17,34,35). Nonetheless, further research is required to corroborate our results. A personalized approach is recommended.

CONCLUSION

On demand and customized low dose ITG was effective and achieved vertigo control in patients with MD. Vertigo recurrence post-ITG should be treated with subsequent on demand and low dose ITG applications. More long-term studies are needed to corroborate effectiveness of a personalized approach in patients with intractable MD.

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