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Low-dose intratympanic gentamicin administration for unilateral Meniere's disease using a method based on clinical symptomatology: Preliminary results

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ABSTRACT

Purpose: There are many therapeutic options for Meniere's disease (MD); intratympanic (IT) gentamicin has been proposed for intractable cases although controversy about dosage and method exists. The purpose of this study was to assess the efficacy and safety of low-dose IT gentamicin on vertigo attacks in MD using a clinical symptomatology-based method in which administration was repeated only if vertigo attacks recurred, with a 2-week interval between injections.

Materials and methods: Forty-eight patients with unilateral intractable MD were included in the study. All patients received one to five IT injections with 0.5 ml of 10 mg of gentamicin (80 mg/2 ml) with an interval of 2 weeks between injections. Vertigo attacks were evaluated before and after therapy and categorized into classes A–F according to the 2015 Equilibrium Committee criteria. Audiovestibular assessment with pure tone audiometry, vestibular bed-side examination and video head impulse test was performed.

Results: Before treatment patients had an average of 4.4 vertigo attacks/month; after treatment the average number decreased to 0.52. The majority of patients (77%) reached Class A vertigo control with 5 or less gentamicin injections. VOR gain was unaffected in the healthy side and significantly reduced in the affected side. No hearing deterioration was found in all treated patients.

Conclusions: Low-dose IT gentamicin administration based on clinical symptomatology can produce a satisfactory control of vertigo attacks after treatment; such protocol had an effect mainly on the vestibular function as demonstrated by the significant reduction in VOR gain in the affected side avoiding a cochlear damage.

1. Introduction

Meniere's disease (MD) is an idiopathic inner ear disorder characterized by spontaneous recurrent vertigo, fluctuating sensorineural hearing loss (SNHL), aural fullness and tinnitus [1–5]. The main clinical aspect in MD is the recurrence of sudden and unexpected vertigo attacks that are often debilitating and may severely affect quality of life [4,6–8]. MD diagnosis is based on the criteria of the Barany Society [9].

There are many therapeutic options for MD, but none is considered effective by the scientific community [10]. The first-line treatment commonly includes dietary modification such as restriction of salt, caffeine and alcohol intake; however, there is no evidence from randomized controlled trials that supports the effectiveness of dietary restriction in MD [11,12]. Several drugs have been proposed for the treatment of MD both for acute attacks (dimenhydrinate, benzodiazepines), and as a prophylactic therapy (betahistine, βblockers, diuretics),

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although evidence of their efficacy is lacking [3].

When first-line treatment does not offer a satisfactory symptom control, especially for vertigo, intratympanic (IT) administration of corticosteroids or gentamicin is recommended [13]. Invasive procedures such as vestibular nerve section or labyrinthectomy may be suggested in case of treatment failure. Corticosteroids have been shown to have a lower risk of hearing damage [14,15] but less efficacy in vertigo attack control compared to gentamicin [16,17]. Gentamicin, administered in different doses and timing, has been proven as an effective treatment for vertigo in MD with a potential risk of hearing loss [18–21].

Although IT gentamicin is widely used, controversy remains about the dosage and method used. Some physicians favor the use of low-dose gentamicin in which the drug is injected once and further treatments are only performed in cases of recurrent vertigo attacks; other authors prefer high-dose gentamicin, titration or continuous administration in which the drug is injected until vestibular weakness is reached [22–30]. However, hearing loss and healthy-side vestibular hypofunction after IT gentamicin administration still represent potential risks of this treatment due to its ablative nature and ototoxicity [18,20,31].

The aim of this study was to assess the efficacy and safety of low-dose IT gentamicin on vertigo attacks in MD using a clinical symptomatology-based method, in which gentamicin administration was repeated up to five times only if vertigo attacks recurred respecting in all cases a 2-week interval between injections.

2. Materials and methods

This study was conducted on 48 patients presenting at the Audiology Unit of the University of Salerno, Italy between February 2015 and March 2017. Patients signed a written informed consent; the procedures performed were in accordance with the standards of the ethics committee on human experimentation of the University of Salerno, that specifically approved this study, and with the Helsinki Declaration.

Inclusion criteria were adult age ($\geq$18 years), a clinical diagnosis of unilateral MD according to the Barany Society criteria [9] and a minimum follow-up of 2 years. Exclusion criteria were patients with a clinical diagnosis of bilateral MD, ipsilateral or contralateral middle ear pathology, previous treatment with IT steroids, contralateral SNHL (Pure Tone Audiometry - PTA bone threshold $\geq$35 dB HL), retrocochlear pathology, previous ear surgery. All patients included in the study had been previously treated for a minimum of 6 months with conservative treatment with dietary restrictions and diuretics drug administration.

2.1. Audiovestibular assessment

All patients underwent audiovestibular evaluation before and after each gentamicin IT treatment. Audiological evaluation included PTA (Piano Clinical Audiometer Inventis, Padua, Italy) and acoustic immittance test (AT 235 Tympanometer Interacoustics, Denmark).

PTA was measured at frequencies of 125, 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz; data from the frequencies 500, 1000, 2000 and 3000 Hz were used in the study. Hearing was considered symmetrical if thresholds for each ear occurred within 10 dB of each other.

Vestibular and oculomotor examination included eye movement evaluation with and without fixation by Videonystagmoscopy and Video Head Impulse Test (vHIT). vHIT (GN Otometrics, Taastrup, Denmark) was performed on the horizontal plane to accurately detect lateral semicircular canal (LSC) gain. Corrective saccades were identified as delayed eye movements occurring during (covert saccade) or after (overt saccade) head movements (10 impulses for side). The VOR gain for each semicircular canal was the ratio of peak slow phase eye velocity to peak head velocity. It was considered abnormal if LSC gain was below < 0.8.

The number of vertigo attacks were categorized into classes A–F according to the 2015 Equilibrium Committee Amendment to the 1995 AAO-HNS guidelines for the definition of MD [32] as follows: Complete Control (A), Substantial Control (B), Limited Control (C), Insignificant Control (D), Worse Control (E) and Secondary treatment required (F). The following formula was used: average number of attacks per month in the final six months of treatment/average number of vertigo attacks per month for the six months before treatment × 100 where, 0 = Complete Control, 1–40 = Substantial Control, 41–80 Limited Control, 81–120 Insignificant Control and > 120 Worse Control of vertigo.

2.2. Gentamicin administration

All patients received one to five IT injections with 0.5 ml of 10 mg of gentamicin (80 mg/2 ml) buffered with sodium bicarbonate (10 ml − 10 mEq/ml). The IT injections were performed using a 2.5 ml syringe and 25-gauge spinal needle in the posteroinferior region of the eardrum. After each injection, the patient was positioned on the contralateral side for 10 min avoiding talking and swallowing. Subsequent IT administrations were applied after an interval of 2 weeks.

A maximum of 5 gentamicin IT injections were performed in each patient; we stopped when the patient had no > 1 episode of vertigo in a 3-month period. Failure of treatment was considered when after 5 injections of gentamicin no vertigo control was obtained (> 1 episode in 3 months) or when PTA in the treated ear deteriorated by at least 30 dB HL.

2.3. Questionnaires

Before and after each IT gentamicin administration, all subjects were asked to complete the Italian versions of the Dizziness Handicap Inventory (DHI) [33] and of the Tinnitus Handicap Inventory (THI) [34].

2.4. Outcome measures

The primary outcome measure was vertigo control (Class A) with 5 or less IT gentamicin injections. Secondary outcome measures were subjective vertigo and tinnitus evaluation based on self-administered questionnaires, ototoxicity and other adverse events after gentamicin IT administration.

2.5. Statistical analysis

Statistical analyses were performed using Prism GraphPad v7. Descriptive statistics, mean, and standard deviation were calculated for numeric variables; frequency and percentages were calculated for categorical variables. Unpaired *t*-test was used to evaluate differences between timepoints for numeric variables. The *p*-value for assessing statistical significance was an alpha of 0.05.

3. Results

Forty-eight patients were enrolled in the study; 23 were males (47.9%) and 25 were females (52.1%). Mean age was 57 years (range: 39–71 years, SD = 14.1). All patients had single-sided MD; the left ear was affected in 29 patients (60.4%) and the right ear in 19 patients (39.6%). The history of vertigo episodes ranged from 8 months to 15 years. All patients suffered from severe vertigo attacks accompanied by nausea or vomiting.

Vertigo control data is shown in Fig. 1. Forty-two patients (87.5%) had ≤1 episode of vertigo in a 3-month period with 5 or less IT gentamicin injections. Of these, 6 patients received 1 IT gentamicin injection (14.3%), 19 received 2 (45.2%), 13 received 3 (31%), 1 received 4

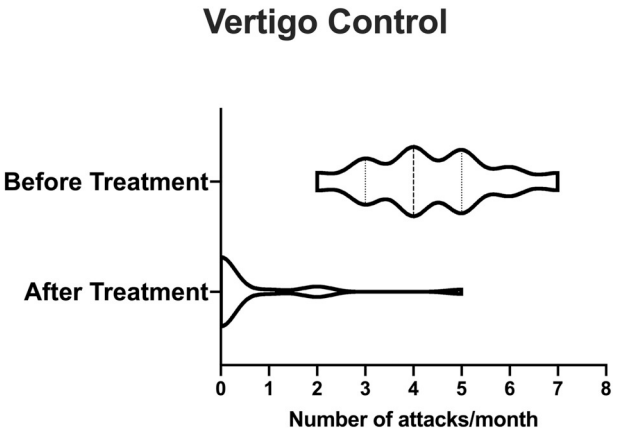

Fig. 1. Vertigo control shown by number of vertigo episodes/month before and after treatment. A significant reduction of vertigo episodes was seen after treatment compared to before treatment.

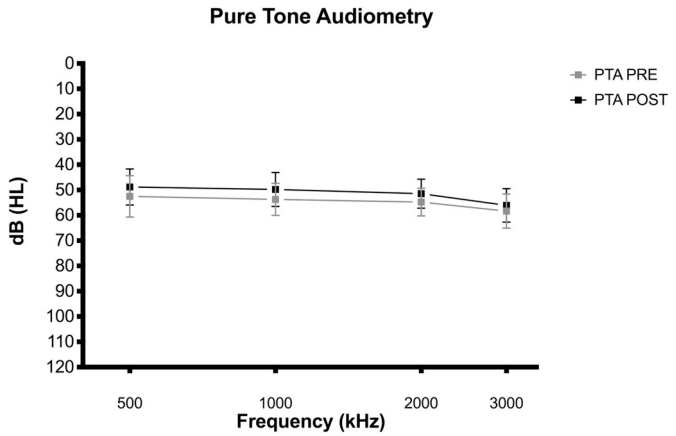

Fig. 3. Average Pure Tone Audiometry thresholds before and after treatment. Changes were not statistically significant ($p = 0.1573$).

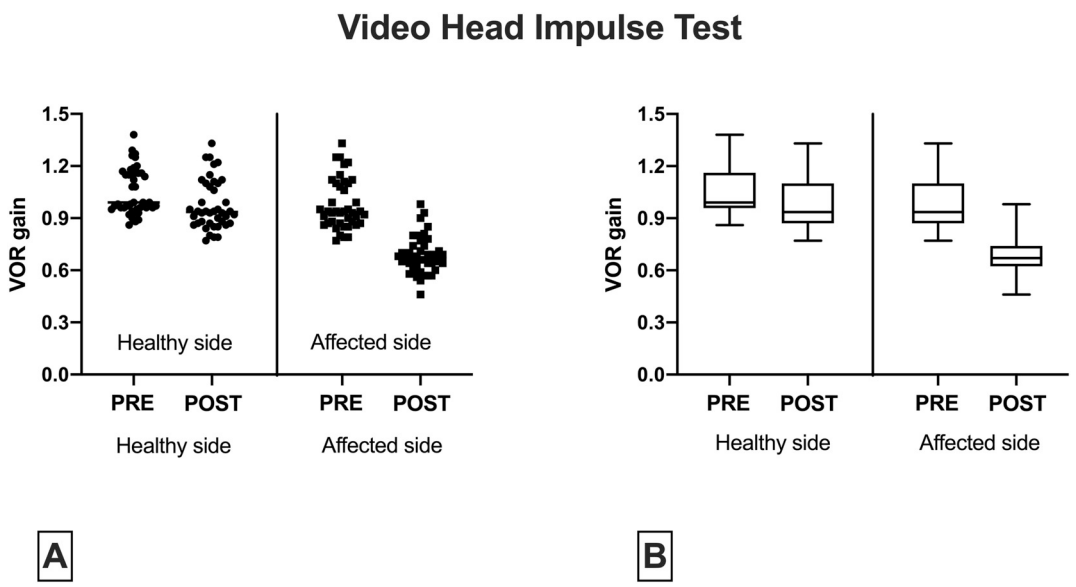

Fig. 2. Video Head Impulse Test (vHIT) results before and after treatment (A, B). In the healthy side, VOR gain did not change after treatment ($p = 0.0504$). In the affected side, VOR gain significantly decreased after treatment ($p < 0.0001$).

(2.4%) and 3 received 5 injections (7.1%). Average IT injection per patient was 2.4 (range 1–5). Six patients (14.3%) required > 5 IT gentamicin injections and were considered as treatment failure. During a period of 6 months before treatment, patients had an average of 4.4 vertigo attacks/month (range: 2–7); during the six months after treatment the average number of attacks/month decreased to 0.52 (range: 0–5); the difference was statistically significant ($p < 0.0001$; $t = 13.91$). Thirty-four patients (70.8%) reached Class A vertigo control; 37 patients (77%) reached Class A + Class B; 5 patients (10.4%) Class C + Class D and no patients were in Class E and F.

vHIT results before and after treatment are shown in Fig. 2. In the healthy side, VOR gain was 1.056 +/− 0.06119 before treatment and 0.9948 +/− 0.03081 after treatment. The difference was not statistically significant ($p = 0.0504$, $t = 1.986$). In the affected side, VOR gain was 0.9750 +/− 0.2893 before treatment and 0.6857 +/− 0.02742 after treatment. The difference was statistically significant ($p < 0.0001$; $t = 10.55$).

Average PTA thresholds before and after treatment are detailed in Fig. 3. Before treatment, average PTA in the affected ear was 52.5 dB HL at 500 Hz, 53.7 dB HL at 1000 Hz, 54.8 dB HL at 2000 Hz and 58.3 dB HL at 3000 Hz. After treatment, average PTA in the affected ear was 48.8 dB HL at 500 Hz, 49.8 dB HL at 1000 Hz, 51.4 dB HL at 2000 Hz and 56.1 dB HL at 3000 Hz. No significant differences were found between PTA threshold before and after treatment ($p = 0.1573$, $t = 1.616$).

Mean DHI score before treatment was 56.8 +/− 13.3; the score decreased to 42.4 +/− 11.2 after treatment. Mean THI score before treatment was 29.3 +/− 12.5; the score decreased to 24.7 +/− 13.8 after treatment. Changes for both questionnaires were not statistically significant ($p > 0.05$) (Fig. 4).

No local or general adverse events were reported in all patients included in the study during and after gentamicin IT administration.

4. Discussion

The treatment aim of MD is typically the control of vertigo symptoms by a variety of conservative procedures (e.g., low salt diet, diuretics, betahistine) [3,7,10,11]. When conservative and medical measures fail, IT injections of corticosteroids or aminoglycosides are performed [16,18,20] although some authors have recently proposed an IT injection of a mixture of gentamicin and dexamethasone as a more effective treatment for vertigo control compared to IT dexamethasone

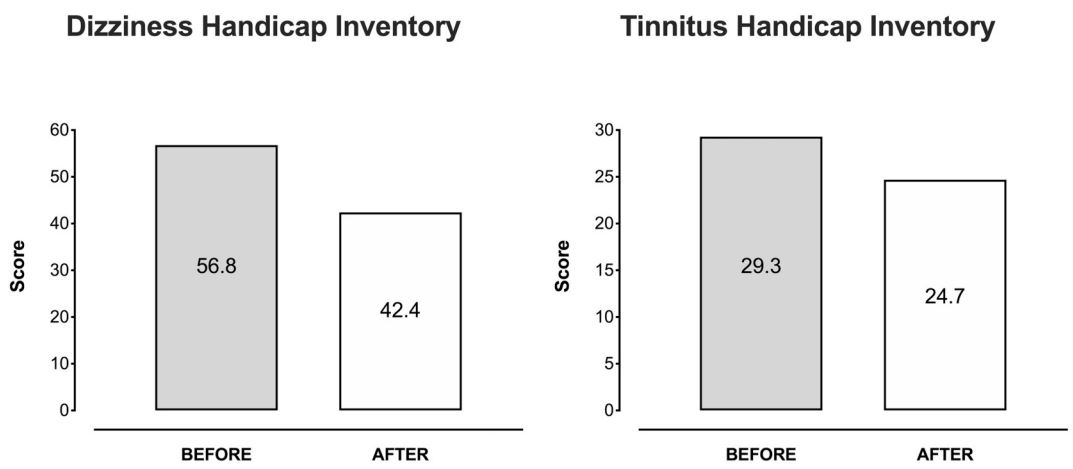

Fig. 4. Scores of the Dizziness Handicap Inventory (DHI) and of the Tinnitus Handicap Inventory questionnaires before and after treatment.

alone [35].

IT gentamicin injection is a minimally invasive technique for the treatment of severe unilateral MD firstly proposed in 1977 by Lange et al. [36]. Despite IT steroids can maintain the vestibular function, IT gentamicin is an ablative procedure that has been shown to obtain high rates of vertigo control with minimal risk of hearing deterioration and healthy-side vestibular hypofunction [17,18].

Gentamicin can be administered using different doses and protocols. Some authors favor the use of one-time low-dose gentamicin in which the drug is injected once, while further treatments are only performed in cases of recurrent vertigo attacks. Others prefer high-dose gentamicin, titration or continuous administration in which the drug is injected until vestibular weakness is reached [22–30].

Our results showed an elevate efficacy and safety of low-dose gentamicin administered following a method based on patient's clinical symptomatology. In the present study, we administered low-dose IT gentamicin one to five times depending on vertigo attacks; we obtained a significant vertigo control in the majority of patients, with hearing improvement or preservation in all cases, no significant vestibular hypofunction in the healthy side and no adverse events. Gentamicin administration was repeated only if vertigo attacks recur (clinical symptomatology-based method) respecting in all cases a 2-week interval between injections; such administration method was previously recommended in a Cochrane review by Pullens and van Benthem [19], that suggested that it is preferable to use low-dosage administration with longer intervals between treatments to minimize ototoxicity.

Our results are partly in accordance with other studies available in the literature. Cohen-Kerem et al. [37] reported that vertigo control does not depend by the gentamicin treatment regimen (fixed vs titration), although they recommended to use IT injection titration technique and low dose to reduce hearing impairment. This differs from results of a meta-analysis by Chia et al. [38] in which titration of gentamicin until the point of onset of ablative symptoms is the recommended method with significantly complete (81.7%) and effective (96.3%) vertigo control compared with the low-dose method (66.7% and 86%, respectively). Lange et al. [39] reported a complete vertigo control in 95% of their patients using repeated low dose (12 mg) IT gentamicin administration (three injections over a 15-day period); however, the authors reported hearing deterioration in 9% of their cases. Boleas-Aguirre et al. used the same dose of gentamicin with a significant vertigo control and a 0% hearing deterioration. Moller et al. [40] used a fixed-dose protocol with daily administrations for 3 to 11 days, observing a nearly total (93.3%) vertigo control and hearing deterioration in 33% of cases. Atlas and Parnes [41,42] used a titration protocol in 83 patients reporting a satisfactory vertigo control (90%) and hearing deterioration (10-dB) at 24 months in 17% of their patients. Bodmer et al. [43] noted hearing deterioration in 25% of their cases. Casani et al. reported a 12.5% of hearing loss despite very high vertigo control (Class A + B) in 93.5% of patients at 2-year follow up [44].

In the present study we have also evaluated VOR gain for lateral semicircular canal before and after gentamicin treatment in the healthy and affected sides. A slight – although not significant - decrease was noted in the healthy side; this is in accordance with Büki and Junger [45] and can be explained by the push–pull cooperation between the horizontal semicircular canal pair as described by Weber about vestibular deafferentation [46]. In the affected side we found a significant decrease of VOR gain after treatment; this is consistent with what reported by other authors [47–49] that found a decrease of VOR gain in the affected ear in patients treated with IT gentamicin, suggesting to use this measure to evaluate further injections of IT gentamicin in patients with unilateral MD [50].

5. Conclusion

IT gentamicin administration has been proven as a valid treatment in patients with unilateral MD in which conservative treatments fail; however, its safety on the hearing function is still debated. There is no current consensus on clinical guidelines for the use of gentamicin in terms of dose and duration although evidence suggests preferring low-dose protocols to minimize hearing deterioration.

In our study, we observed that low-dose IT gentamicin (10 mg) administered from one to 5 tives based on clinical symptomatology can produce a satisfactory control of vertigo attacks after treatment with limited risk of hearing deterioration; such protocol had an effect mainly on the vestibular function as demonstrated by the significant reduction in VOR gain in the affected side in the absence of clinical cochlear damage.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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