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Intratympanic Treatment of Intractable Unilateral Ménière Disease: Gentamicin or Dexamethasone? A Randomized Controlled Trial

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Abstract

Objective. To determine the efficacy and safety of low-dose intratympanic gentamicin (ITG) compared with intratympanic dexamethasone (ITD) in patients with intractable unilateral Ménière disease (MD).

Study Design. Open prospective randomized controlled study.

Setting. Tertiary referral center.

Subjects and Methods. Sixty patients affected by definite unilateral MD were enrolled between January 1, 2007, and June 30, 2008. Thirty-two patients were treated with a buffered gentamicin solution injected in the middle ear (maximum of 2 injections); 28 patients were treated with ITD (4 mg/mL, 3 injections at intervals of 1 every 3 days). Mean outcome measurements consisted of control of vertigo attacks, pure tone average (PTA), speech discrimination score, functional disability score, and statistical analysis using repeated measures analysis of variance.

Results. In the ITG group at 2-year follow-up, complete control of vertigo (class A) was achieved in 26 patients (81%) and substantial control of vertigo (class B) in 4 patients (12.5%). In the ITD group, class A was achieved in 12 (43%), and class B in 5 (18%) patients. In the gentamicin group, 4 patients showed a reduction in PTA of $\geq$10 dB. In the ITD group, PTA was unchanged or slightly improved in 16 patients (belonging to class A-B) and worse in 12.

Conclusions. Low-dose ITG achieved better outcome than ITD in the control of vertigo attacks in patients suffering from unilateral MD, with a very low incidence of hearing deterioration. ITD offers poorer vertigo control rate, and hearing preservation is achieved only in cases with no vertigo recurrences.

Keywords

intratympanic, Ménière disease, dexamethasone, gentamicin, vertigo, hearing loss

The typical symptoms of Ménière disease (MD; fluctuating hearing loss, tinnitus, aural pressure, and episodic vertigo) can be managed using a medical therapy that allows controlling the disease in as many as two-thirds of the patients.[1] When the medical treatment is not able to reduce the recurrent spells of vertigo, an ablative approach is recommended. The advent of less invasive procedures, such as intratympanic therapies, has deeply changed the approach of refractory MD in the past 3 decades. Intratympanic gentamicin (ITG) became popular from the 1990s onward, and its local delivery to the inner ear is now considered an effective treatment for the vestibular symptoms.[2,3] For many years, multiple daily doses of gentamicin were used during a predetermined period until a sign of ototoxicity developed.[4-6] On the other hand, a low-dose protocol[7-9] can be used, administrating just 1 or 2 injections with a similar effectiveness for vertigo control and with a lower risk for major side effects (mainly hearing loss and a prolonged period of imbalance after treatment) as compared with high-dose protocol.[10]

The control of vertigo attacks with a minimized risk of hearing loss and post-treatment disequilibrium could be achieved using intratympanic (IT) steroids. The use of steroids for the treatment of MD is primarily based on the theory of an immune-mediated origin of the disease.[11] The

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beneficial effects of IT steroids could be due to the anti-inflammatory effects of both methylprednisolone (MPS) and dexamethasone (DXM). Pharmacokinetic studies have shown that steroids applied to the round window will result in significantly higher drug levels in the inner ear fluids when compared with systemic delivery,[12] obviously associated with the advantage of the absence of many undesirable side effects or contraindications.

In addition to anti-inflammatory effects, steroids can affect ion and fluid homeostasis of the inner ear by induction of mineralcorticoid receptor-mediated genes[13,14] and by control of the aquaporin channels.[15] Finally, cochlear blood flow (CBF) may be positively affected by topical application of steroids.[16,17]

Several articles on IT steroids for MD have been published showing positive[18-22] or negative results.[23-27] However, these studies are not easily comparable because they differ from each other in terms of study design, type and dose of the steroid used, protocol, and time of follow-up.

The purpose of our study is to compare the efficacy of intratympanic dexamethasone vs low-dose intratympanic gentamicin in the control of vertigo attacks and to evaluate the effects on hearing in patients suffering from unilateral definite intractable MD.

Materials and Methods

An open prospective, 2-year follow-up study was carried out in the Ear Nose and Throat Section of the Neuroscience Department of the Pisa University Hospital between January 2007 and April 2011. The study was conducted for patients affected with unilateral definite MD on the basis of the criteria of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS)[28]; subjects had also undergone medical therapy (diuretics, betahistine, and low-salt diet) for at least 6 months.

After a detailed explanation of the possible risk and benefits of the procedure, a written consent was obtained. Approval of the study was granted by the local ethics committee, Comitato Etico dell'Azienda Ospedaliera-Universitaria Pisana.

Patients underwent a complete otoneurological examination, caloric testing, audiogram, and impedance audiometry. A search for spontaneous nystagmus, head shaking test, and head impulse test were performed to identify any clinical sign of canal paresis. Hearing impairment was evaluated according to 0.5, 1, 2, and 3 kHz frequency average (pure tone audiometry, PTA) and speech discrimination score (SDS). A change of 10 dB or more in PTA or a change of 15% in SDS was considered clinically significant. The Functional Level Score (FLS) and the class as defined by the 1995 AAO-HNS guidelines[28] were also obtained. Vertigo control was calculated according to the 1995 AAO-HNS guidelines (class A-F).[28]

All these measures were obtained immediately before the treatment and were repeated after 1 month, 1 year, and 2 years following the procedure. For random assignment of the participants, a computer-generated list of random numbers was used[29] (**Figure 1**). Patients were randomized and divided into 2 groups: 32 patients were treated with IT gentamicin and 28 patients were treated with intratympanic dexamethasone (ITD).

Treatment Protocol

Two mL of gentamicin sulfate (40 mg/mL) was buffered with 1 mL of sodium bicarbonate to obtain a 6.4-pH solution with 27.6-mg/mL concentration. Under the otomicroscope, patients were placed in supine position with the head turned 45° toward the unaffected ear. Local anesthesia was obtained by filling the external ear canal with lidocaine. Using a 22-gauge spinal needle and 1-mL syringe, the solution was injected through the midposterior aspect of the eardrum to fill the middle ear. Patients were asked not to swallow or talk to prevent solution drainage from the eustachian tube, and they remained in the supine position with the affected ear facing up for 15 minutes—after which they were discharged. Patients were followed for 2 weeks to assess treatment outcome: it was considered to be effective if 1 or more bedside tests indicated a reduction of vestibular function. If the patient had not developed signs of vestibular hypofunction or a significant reduction of the caloric response on the treated ear, a second injection was planned after 20 days from the first injection.

For the DXM (4 mg/mL) perfusion we used the same procedure, but the injection was repeated 3 times at intervals of 1 every 3 days. Side effects of both types of protocols were also recorded.

Statistical Analysis

Student *t* test for unpaired and paired data was employed to evaluate significant differences between groups and at each follow-up compared with baseline values. Kolmogorov-Smirnov test was used to assess Gaussian distribution of variables: Mann-Whitney *U* and Wilcoxon nonparametric tests were used when the variable distribution was not normally distributed. Pearson χ^2 test was used to compare patients' proportion between different classes.

A mixed between-within subjects analysis of variance was conducted to evaluate the effect of therapies on PTA and SDS during the times of follow-up. Statistical significance was assumed for P values $< .05$. Data are presented as mean $\pm$ SD (standard deviation).

Results

Sixty patients with unilateral definite MD were included in the study. Thirty-two patients (21 females and 11 males) were treated with ITG and 28 (18 females and 10 males) with ITD. The mean age was 54.2 years (SD, 12.9 years) in the gentamicin group and 53.7 years (SD, 12.9 years) in the ITD group. The average of MD course was 17.4 months (SD, 7.1 months) and 17.2 months (SD, 7.2 months) since the first symptoms appeared for the gentamicin and dexamethasone groups respectively. Of the ITG group, 19 patients received 1 injection and 13 received 2 injections.

Thirty-one patients belonging to the ITG group were considered in the data analysis at 2-year follow-up; only

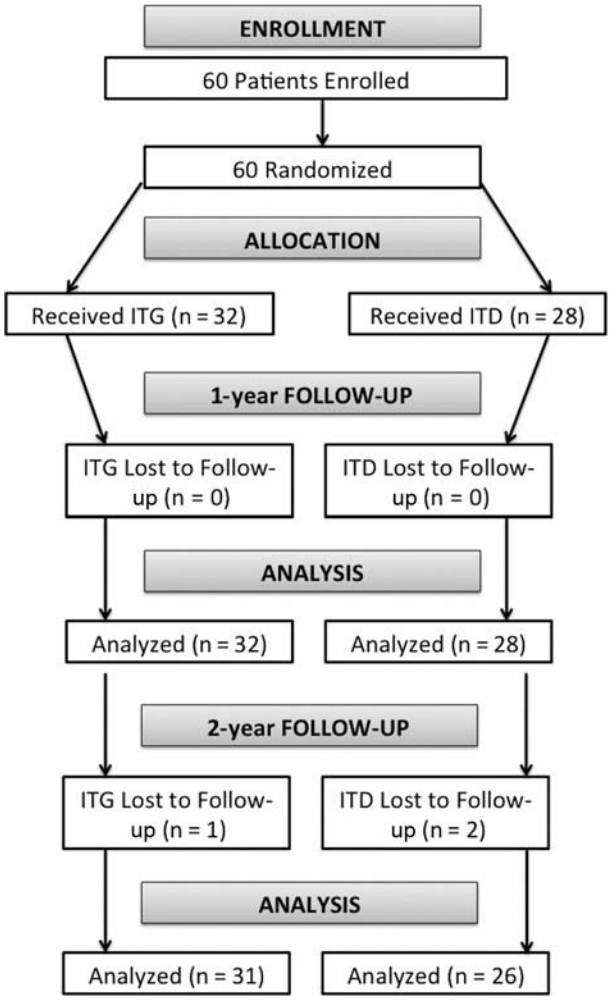

Figure 1. Flow diagram demonstrating patient enrollment and progress in the randomized controlled trial. ITG indicates intratympanic gentamicin; ITD, intratympanic dexamethasone.

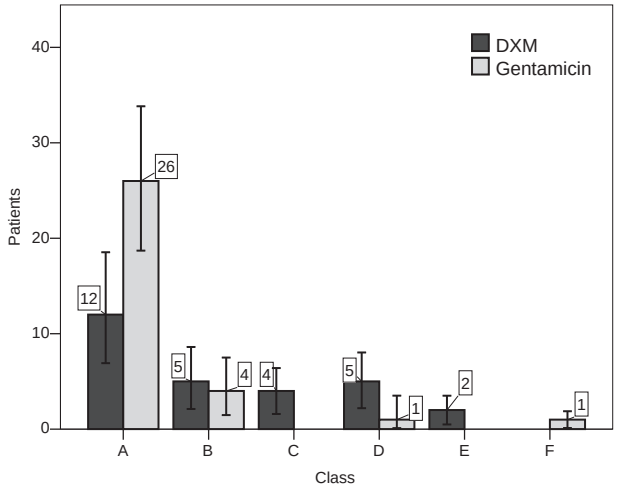

Figure 2. Number of patients belonging to vertigo classes after 2 years of treatment with intratympanic gentamicin and intratympanic dexamethasone. Error bars represent the 95% confidence interval.

1 patient (C.S.) was classified as a failure after the 1-year follow-up, and he was scheduled for vestibular neurectomy.

Regarding the patients of the ITD group, if no vertigo attacks were reported, no further therapy was recommended. Otherwise, further treatment with ITD was scheduled. Consequently, 4 patients (14.28%) received 1 re-treatment, and 5 (17.85%) patients received 2 re-treatments. Two patients of the ITD group did not complete the 2-year follow-up; they were classified as failure (no control of the spells) and were administered ablative treatment with gentamicin.

Vertigo

Of the ITG group, at the 2-year follow-up, complete vertigo control (class A) was achieved in 26 patients (81.3%) and substantial control (class B) in 4 (12.5%) patients. One patient reported limited control (class D). As mentioned above, 1 patient had no control of vertigo spells, and the 2-year follow-up was not completed (**Figure 2**).

In the ITD group, 12 patients (42.9%) obtained complete control of vertigo (class A) and 5 (17.9%) good control (class B); 9 patients (32.2%), despite 1 or 2 series of re-treatments with ITD, were classified as class C-D. Two subjects (7%) reported failure (class E-F) and were scheduled for ITG treatment (**Figure 1**). A significant difference ($P < .01$) between the ITG and ITD groups was observed.

At 1-year follow-up, 13 (40.6%) of the patients treated with ITG showed an improvement to level one of FLS; the same level was obtained in 11 patients from the ITD, without any statistically significant difference between the 2 groups ($P > .05$). Conversely, at 2-year follow-up, there was a statistically significant difference between the 2 groups ($P < .05$): indeed, level 1 was achieved in 22 patients (71%) and level 2 in 8 patients (25.8%) treated with ITG, while 12 (46.1%) and 5 (19.2%) patients treated with ITD reached level 1 and level 2, respectively.

Hearing Outcome

The mean PTA pretreatment was 58.7 (SD, 13.3) and 56.5 (SD, 13.4) for the ITG and ITD groups, respectively; after 1 month, the PTA values changed on average to 61.3 (SD, 14.6) and to 53.7 (SD, 15.6); at 1 year, the PTA was 62.3 (SD, 15.3; ITG group) and 54.6 (SD, 16; ITD group). At 2-year follow-up, mean PTA value was 64.5 (SD, 15.5) for the patients treated with ITG; and in the ITD group, the PTA was 56 (SD, 17.3). Overall, no statistically significant changes between groups were observed ($P > .05$; **Figure 3**).

Patients belonging to the ITG group showed a significant decrease of SDS after 1 month ($P < .05$). The initial SDS mean value was 67.0 (19.0); after 1 month, it was 63.1 (20.0); then, it was 61.1 (21.1) and 60.3 (22.6) at 1-year and 2-year follow-up, respectively. The pretreatment mean SDS value was 66.6 (16.4) in patients treated with ITD. The value changed to 67.5 (17.7), 67.1 (17.6), and 65.0 (18.7) at

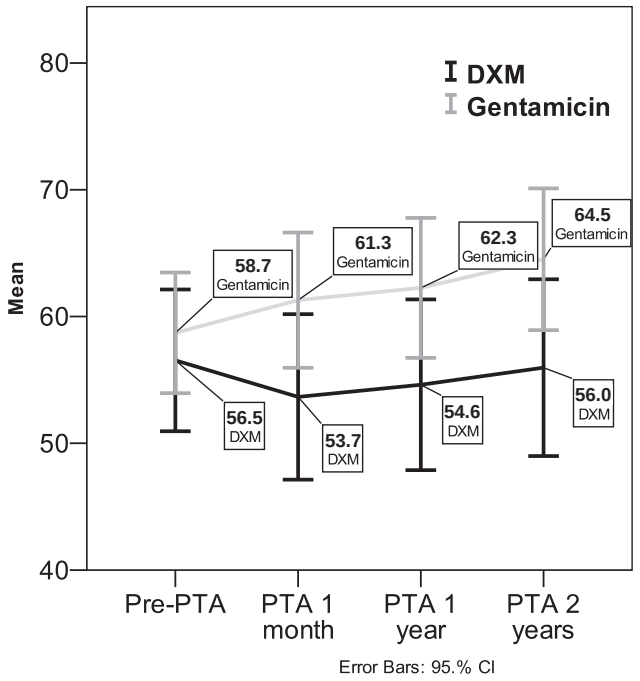

Figure 3. PTA values before intratympanic gentamicin and intratympanic dexamethasone therapies and at each follow-up. Error bars represent the 95% confidence interval of mean values.

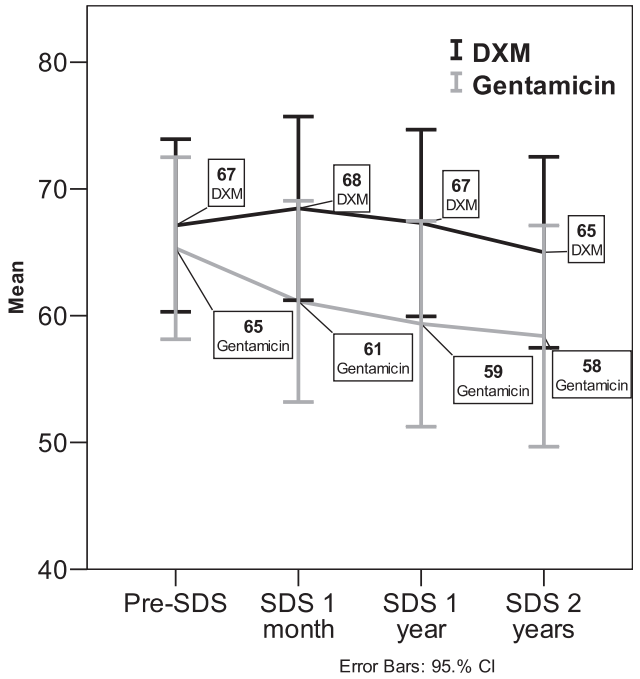

Figure 4. SDS values before intratympanic gentamicin and intratympanic dexamethasone therapies and at each follow-up. Error bars represent the 95% confidence interval of mean values.

the 1-month, 1-year, and 2-year follow-up, respectively. In the ITD group, no significant variations of SDS were observed during each follow-up ($P > .05$; **Figure 4**).

After 2 years, in accordance with the 1995 AAO–HNS criteria, hearing was worse in 4 patients (12.5%) and unchanged in the remaining 28 patients treated with ITG. In the ITD group, hearing showed no clinically significant deterioration in 13 (46.42%) patients, while an improvement was recorded in 3 (10.71%). These 16 subjects were classified as class A-B regarding their vertigo control rate. The remaining 10 patients (excluding the 2 cases classified as failure) showed a worsening of their PTA level of >10 dB.

Discussion

The present study compares hearing outcome and vertigo control in patients affected with intractable unilateral definite MD receiving ITG with those receiving ITD. The risk of hearing deterioration and persistent dizziness from ITG remains a significant concern, particularly with the use of high-dose protocols. For this reason, the IT treatments for MD have to be focused on maximizing the vertigo control while minimizing the adverse effects. There are 2 minimally invasive protocols fulfilling these criteria: low-dose IT gentamicin, and IT steroids.

Our results highlight the higher efficacy of low-dose ITG in the control of vertigo attacks in MD when compared with ITD. At 2-year follow-up, the number of patients with a complete or substantial control (class A-B) of vertigo after 1 or 2 series of ITG therapy was superior to 90% with a statistically significant difference when compared with the results obtained in the patients treated with ITD (61% in class A-B). These results are similar to those following multiple daily dosing or titration technique, despite the smaller dose of gentamicin delivered to the inner ear.

Regarding the hearing outcome, no statistically significant differences were verified between the 2 groups in terms of mean PTA and SDS values. On the whole, the mean PTA and SDS values are slightly better for the patients treated with ITD. PTA mean values were -0.9 at 1 year and -0.5 at 2 years in the ITD group, while +1.6 at 1 year and +6.6 at 2 years for patients treated with ITG. A slight improvement (+2.8 dB for PTA and 1.4% for SDS) of these 2 parameters was recorded at 1-month follow-up in the ITD group. On the other hand, a gradual deterioration of the mean SDS values was observed in the ITG group in the first year of follow-up, with no variation at 2 years. If we consider the hearing outcome in terms of variations of PTA and SDS for any single treated patient (according to AAO-HNS criteria), increased hearing loss in the ITG group was reported in 4 patients (12.5%). In 1 case, hearing deterioration could be considered the consequence of the progression of the disease, as the patient suffered from repeated vertigo attacks. Regarding the ITD group, at 2-year follow-up we reported unchanged PTA levels in 13 (46%) patients and an improvement of >10 dB in 3 (10.7%) patients, all belonging to class A or B. The remaining 10 patients (excluding the 2 cases of failure, class F) showed a worsening of their hearing certainly related to the progression of the disease.

Itoh and Sakata first described IT steroids for MD in 1991.[18] Since that time, various articles have described the use of IT steroids in MD (**Table I**). A double-blind randomized

Table 1. Intratympanic Steroids for Ménière Disease: Clinical Trials

Author(s)	Study Design	Type and Dosage of Steroid	No. of Injections (protocol)	Follow-up	Outcome Criteria	Vertigo Control	Hearing Loss
Garduno-Anaya,[20] 2005	Prospective randomized double-blind	DXM 4 mg/mL	1 for 5 d	2 y	AAO-HNS,[28] 1995	82% complete or substantial vs 57% placebo	9% ↑ 9% ↓
Silverstein,[23] 1998	Prospective randomized double-blind	DXM 8 mg/mL	3 for 3 d	>13 wk	AAO-HNS,[28] 1995	No difference, DXM vs placebo	NA
Sennaroglu,[6] 2001	Prospective case series	DXM 1 mg/mL	5 drops every 2 d for 3 mo, through VT	18 mo	AAO-HNS,[28] 1995	72% with DXM 75% with ITG 52% with ESD	16% ↑ (DXM) 38% ↓ (DXM)
Itoh,[18] 1991	Prospective	DXM 2 mg/mL	4-5 every 1-2 wk	NA	AAO-HNS,[28] 1985	80% with DXM 81% lidocaine	"poor"
Barrs,[24] 2001	Retrospective	DXM 4 mg/mL	2/d, then 1/wk, for 3 wk	3, 6, 12 mo	AAO-HNS,[28] 1995	52% at 3 mo 43% at 6 mo	NA
Barrs,[25] 2004	Retrospective	DXM 10 mg/mL	2/wk for 3 wk (5 in total)	2 y	Complete control vertigo	24% at 2 y 47% with multiple dosing regimen	NA
Hirvonen,[26] 2000	Case series	DXM 16 mg/mL	3/wk	1 y	NA	76% "sufficient" control	"poor"
Shea,[19] 1996	Case series	DXM 16 mg/mL	1 + steroid IV and oral	2 y	AAO-HNS,[28] 1995	96% at 1 y 76% at 2 y	68% at 1 y 35% at 2 y
Herraiz et al 2010[22]	Retrospective	MPS 40 mg/mL	1/wk for 3 wk	1/2 y	AAO-HNS,[28] 1995	81% at 1 y 78% at 2 y	48% ↑ at 1 y 33% ↑ at 2 y
Boleas-Aguirre,[21] 2008	Retrospective	DXM 16 mg/mL	On demand	2 y	"Survival" Kaplan-Meyer curve	91% no ablative treatment 70% class A	NA
Dodson,[27] 2004	Retrospective	DXM/MPS	1-5	1 y	Vertigo Control PTA/SDS	18%	13.6%↑
Selivanova,[37] 2005	Prospective no controlled	DXM 8 mg/mL	1		PTA levels	NA	71% ↑
Hillman,[36] 2003	Retrospective	DXM 16 mg/mL	1/wk for 3 wk	Up to 20 mo	AAO-HNS,[28] 1995	NA	40% ↑ 4% ↓

Abbreviations: AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; DXM, dexamethasone; ESD, endolymphatic sac decompression; ITG, intratympanic gentamicin; IV, intravenous; MPS, methylprednisolone; NA, not available; PTA, pure tone average; SDS, speech discrimination score; VT, ventilation tube; ↑, improvement; ↓, worsening.

crossover trial using ITD (8 mg/mL) showed no benefit over placebo.[23] On the contrary, another randomized placebo-controlled trial showed complete control of vertigo spells in 82% of patients treated with ITD compared with 57% of those receiving placebo.[20] Good control of the vertigo spells was reported after topical DXM applications.[6] This latter article is the only report comparing ITG and ITD: starting from their results the authors proposed an algorithm in which the absence of response to medical therapy of MD leads to starting with ITD, reserving ITG for patients with profound sensorineural hearing loss.[6]

A retrospective study demonstrated a complete resolution of vertigo in 52% of the patients at 3-month follow-up: the percentage changed to 43% after 6 months[24] and to 24% after 2 years.[25] Boleas-Aguirre at al[21] reported 91% ''acceptable'' vertigo control using DXM 12 mg/mL. Most of the patients (63%) needed more than 1 series of treatment. The authors proposed a kind of ''ITD titration protocol,'' supposing that ITD provides temporary relief of symptoms and needs to be repeated with the aim of achieving a quicker spontaneous remission of MD.[21] The most recent prospective study regarding the use of IT steroids for MD used MPS, reporting reduction of vertigo in more than 90% of the patients.[22]

Our results are in contrast with the favorable outcomes of these latter reports: the number of the patients classified as A-B was less than 70% and these results could be an effect of the natural history of the disease.[30-33] As in the majority of the clinical studies, we used DXM because of its greater tolerability compared with MPS and on the basis of its pharmacokinetic features. Although MPS has greater round window permeability and higher concentrations in endolymph after intratympanic injections,[34] absorption of DXM into the stria and surrounding tissues was more rapid than MPS.[35,36]

Our reported poorer response could be due to a lower dosage of DXM, but in our country 4 mg/mL is the only available concentration. We cannot exclude that a continuous drug application (via pump systems) or the use of sustained delivery system may provide better outcomes.

With regard to the hearing loss outcomes in patients treated with ITD, we observed good hearing preservation only in patients who reported good or substantial vertigo control. Previous reports [6,20,22,37,38] consider IT steroids as a valuable tool for stopping progressive hearing impairment in MD. Our results showed that hearing loss is strictly correlated to the progression of the disease, with no influence of ITD. Only 3 (10.7%) patients improved their PTA levels and 13 (46%) were unchanged at 2-year follow-up: all these patients belong either to class A or B. The remaining 12 patients with worsened hearing threshold reported a concomitant poor control of vertigo spells.

On the other hand, in the ITG group, the incidence of increased hearing loss is approximately 12%; and in the majority of cases, the magnitude of the hearing loss is small and has little impact on the quality of life of patients.

Regarding the side effects of the 2 types of treatment, we can argue that ITD represents a well-tolerated procedure with a very low morbidity. Mild pain and transient vertigo were reported in only a few cases after the injection, and no patient had residual tympanic membrane perforation.

Two recent meta-analyses[3,10] have carefully evaluated the results of many studies regarding IT gentamicin in MD, reporting results that demonstrated complete or substantial control of vertigo attacks in almost 90% of the patients. Comparing the various techniques, they found that the low-dose technique showed inferior vertigo control (87% vs 96% obtained with the titration method), associated with a relatively high incidence of hearing deterioration (24% vs 13.1% reported with the weekly dosing technique). Those results are in contrast with our experience: our protocol achieved a high rate of vertigo control associated with a low incidence of increased hearing loss (12.5%). Probably increasing the interval between the gentamicin injections to 3 weeks should minimize the risks of hearing deterioration, as confirmed in an animal study.[39] However, at low doses, gentamicin seems to affect primarily the secretory dark cells,[40] thus contributing to a reduction of endolymph overpressure in the inner ear with a lesser extent of hearing damage.

Our study has several limitations: first, it is not placebo-controlled; second, we did not adopt a double-blind trial. However, in accordance with Hu and Parnes,[41] we believe that the role of placebo should not be heavily stressed in MD. As previously stated, a complete or partial resolution of vertigo attacks could be achieved spontaneously after 7 to 10 years from diagnosis of MD.[29-32] Because of clinical, medico-legal, and administrative difficulties, we were not able to plan a double-blind trial, the results of which would have provided better levels of evidence. Finally, the sample size is too small to support a strong external validity of our study. Nevertheless, the difficulty of recruiting enough Ménière subjects for a 2-year prospective study with adherence to the 1995 AAO-HNS guidelines for reporting is well known.

Conclusion

Keeping in mind the limitations of this study, we could state that our results cannot serve as the basis for generalized treatment recommendations. We can emphasize, however, that intratympanic delivery of low-dose gentamicin could be considered a relatively safe and effective therapy in the treatment of intractable MD, providing superior vertigo control compared with ITD (93.5% vs 61%) and associated with a very low incidence of hearing impairment (12.5%).

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Author Contributions

Augusto Pietro Casani, study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, study supervision; **Paolo Piaggi**, study design, manuscript drafting and revision, data collection, statistical analysis; **Niccolò Cerchiai**, acquisition of data, drafting of the manuscript,

administrative support, technical and material support; **Veronica Seccia**, acquisition of data, manuscript drafting, revision; **Stefano Sellari Franceschini**, study concept and design, analysis and interpretation of data, study supervision; **Iacopo Dallan**, study concept and design, critical revision of the manuscript for important intellectual conflict.

Disclosures

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