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What is This?
Intratympanic Gentamicin for Ménière’s Disease: Short- and Long-term Follow-up of Two Regimens of Treatment

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Abstract

Objectives. (1) To compare the results of the 2 regimens of treatment at 2-year follow-up and (2) to evaluate the need and the efficacy of retreatment after the recurrence of vertigo attacks in a longer period of follow-up (using the Kaplan-Meier method of analysis).

Study Design. Retrospective chart review.

Setting. Tertiary referral center.

Subjects and Methods. We analyzed 77 patients treated with intratympanic gentamicin (ITG). Thirty-five patients were treated with high-dose (HD) ITG (in total 6 injections, twice a day, repeated every 3 days) and 42 with low-dose (LD) ITG (1-2 injections). The results of treatment were evaluated in terms of functional level scale, control of vertigo, and hearing impairment.

Results. At 2-year follow-up, a similar percentage of vertigo control was obtained in the 2 groups; the incidence of hearing loss and posttreatment disequilibrium was significantly higher in patients treated with HD-ITG. The long-term follow-up showed a control of vertigo attacks with a single round of treatment in 71.4% of patients treated with HD-ITG and in 55% of those treated with LD-ITG. With repeated rounds, an effective control of vertigo could be achieved in 88.5% using a HD-ITG protocol and 97.7% using a LD-ITG protocol.

Conclusions. LD-ITG allows obtaining good results in term of vertigo attacks associated with a limited occurrence of side effects. The long-term follow-up showed that LD-ITG needed repeated rounds more frequently than the HD-protocol. HD-ITG ran less risk of needing repeated rounds, but retreatment was ineffective in 40% of the cases requiring surgical therapy.

Keywords

vertigo, Ménière’s disease, gentamicin, intratympanic, dizziness
the cohort of patients included in the study.\textsuperscript{13,14} For these reasons the Kaplan-Meier analysis provides an excellent method for assessing the success or failure of ITG when recurrent symptomatology needs new injections.

We initially used a relatively high-dose ITG protocol, starting from 2000 and progressively switching to a low-dose therapy after 2003. The objectives of our study were to: (1) compare the results of the 2 regimens of treatment at 2-year follow-up, according to the AAO-HNS guidelines, and (2) evaluate the need and the efficacy of retreatment after the recurrence of vertigo attacks in a longer (more than 4 years) period of follow-up (using the Kaplan-Meier method of analysis).

**Materials and Methods**

A retrospective chart review was conducted in the Otoneurological Unit of the Pisa University Hospital between January 2000 and January 2008. Approval of the study was granted by the local ethics committee, Comitato Etico dell’Azienda Ospedaliera–Università di Pisa. All patients were affected with unilateral definite MD on the basis of AAO-HNS criteria\textsuperscript{12}; all the subjects had previously been treated with medical therapy (diuretics, betahistine, and low salt diet) for at least 6 months before they were admitted to ITG treatment. No patient had previously been treated with surgical conservative procedures (ie, endolymphatic sac decompression) or intratympanic steroid injections. After a detailed explanation of the possible risks and benefits of the procedure, a written consent was obtained.

The 2 procedures of ITG injections followed the standardized protocol: patients treated with high-dose (HD) ITG were administered 6 injections of gentamicin (2 mL of gentamicin sulfate, 40 mg/mL, buffered with 1 mL of sodium bicarbonate to obtain a 6.4-pH solution with 27.6 mg/mL concentration) twice daily, repeated every 3 days.

The low-dose (LD) protocol\textsuperscript{4} consisted of 1 injection of buffered gentamicin: patients were evaluated after 7, 14, and 21 days after the injection to assess treatment outcome; it was considered to be effective if 1 or more bedside tests indicated a reduction of vestibular function. Otherwise a second injection was planned 20 days after the first injection.

The HD protocol was used from the year 2000, but the number of these procedures was reduced progressively with the introduction of LD-ITG treatment from 2003 onwards (Figure 1).

Before the treatment all 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. The results of treatment were expressed in terms of Functional Level Score (FLS) and control of vertigo, calculated according to the 1995 AAO-HNS guidelines (class A-F). Hearing impairment was evaluated according to 0.5, 1, 2, and 3 kHz frequency average (pure tone audiometry, PTA) and speech discrimination score (SDS). All these measures were obtained immediately before the treatment and were repeated after 1 month, 1 year, and then every year.

Posttreatment disequilibrium was evaluated as follows: normal (the patient is able to stand on tandem Romberg for 3 seconds with eyes open), mild (the patient is unable to stand on tandem Romberg for at least 3 seconds with eyes open), moderate (unable to stand on Romberg for at least 3 seconds with eyes open), and severe (the patient is unable to stand up without help).

Repeated rounds of HD- or LD-ITG were given if the patients experienced recurrent vertigo spells (2 or more episodes lasting more than 20 minutes in the 6 months following treatment). The duration of follow-up ranged from 48 months to 12 years (medium average 108.7 months for the HD group and 87.2 months for the LD group).

**Statistical Analysis**

The Kolmogorov-Smirnov (K-S) test was used to assess normality of data. Statistical tests were used to compare changes between baseline and follow-up visits and to evaluate differences between groups and included paired/unpaired \(t\) test and ANOVA for difference in mean values, Mann-Whitney U and Wilcoxon nonparametric tests for skewed variables, chi-square test for difference in counts and frequency. FLS and PTA had a skewed distribution by K-S test \((P < .001)\); therefore, nonparametric tests were employed to analyze their values.

The Kaplan-Meier “time-to-event” method was used to quantify and to generate longitudinal curves regarding:

1. The number of patients who needed additional rounds of ITG treatment.
2. The number of patients requiring a surgically destructive procedure to control vertigo.

For each patient, the starting time was taken at the end of the first ITG treatment, while the time of event was either the date of visit where the patient underwent an additional round of ITG treatment (for patients who needed a further round of ITG treatment) or the date of additional surgery. The number of these procedures was reduced progressively with the introduction of LD-ITG treatment from 2003 onwards (Figure 1).
treatment cycle), the date of visit where the patient underwent surgical treatment, or the last available visit (for patients who did not need further treatment). Statistical significance between curves belonging to different groups (high vs low ITG dose) was assessed using the Breslow test. A P value of less than .05 was considered statistically significant. Data are presented as mean ± standard deviation (SD). Analyses were performed using SPSS (version 21, IBM Corp, Armonk, New York).

Results

By the time the study was closed (January 2013), we were able to analyze the clinical data of 77 patients: 35 (21 females, 14 males, mean age 50.4, SD 10.4 years) treated with HD-ITG and 42 (24 females, 18 males, mean age 48.5, SD 9.6 years) with LD-ITG. We excluded from the data analysis 1 patient belonging to the LD group who was classified as a failure (defined as requiring a surgical destructive surgical procedure) after 1-year follow-up and who was scheduled for vestibular neurectomy. Regarding the LD group, 24 patients received 1 injection and 18 received 2 injections, as their initial ITG treatment.

The average of MD course was 16.3 months (SD 4.14 months) and 15.8 (SD 4.10) from the moment of appearance of symptoms for the high-dose and low-dose groups, respectively.

Of the HD group, at 2-year follow-up, complete control of vertigo (class A) was achieved in 28 patients (80%) and substantial control (class B) in 5 (14%). In the LD group, 30 patients (71%) obtained complete control of vertigo and 8 patients (19%) good control (class B). At 2-year follow-up, the FLS showed an improvement to level 1 or 2 in 22 (54%) and 8 (19%) patients of the HD group, respectively. In the LD group level 1 was achieved in 26 (74%) patients and level 2 was achieved in 11 (31%) patients. The results showed no statistically significant differences between the 2 groups (P = .67).

The mean PTA pretreatment was 56.7 (SD 12.9) and 54.0 (SD 11.6) for the HD and LD groups, respectively; at 2-year follow-up the mean PTA value was 72.3 (SD 14.1) for the patients treated with HD-ITG; in the LD-ITG group the PTA was 59.9 (SD 11.4). The results showed a statistically significant decrease of PTA between the two methods: the P values were, respectively, .001, .001, and <.001 at 1 month, 1 year, and 2 years (Figure 3).

The pretreatment SDS mean value was 65.7 (SD 12.7) and 67.3 (SD 16.4) for the HD and LD group, respectively; at 2-year follow-up, the values changed to 55.4 (HD group) and 62 (LD group). The deterioration of SDS values was lower in the LD group but not statistically significant in every period of follow-up (Figure 4).

After 2 years, in accordance with the AAO-HNS criteria, hearing was worse in 13 (37%) patients treated with high-dose ITG. In the low-dose group, hearing showed a clinically significant deterioration in 5 (12%) patients.

Twenty-two (63%) patients treated with high-dose ITG reported imbalance occurring after the treatment: in 16 (45.7%) cases it was mild/moderate and lasted no more than 10 days, while in 6 (17.1%) patients the imbalance was severe and lasted for more than 1 month, requiring a cycle of vestibular rehabilitation. Only 10 (24.4%) patients belonging to the low-dose group complained of mild post-treatment disequilibrium that disappeared within 10 days in all cases. Regarding the posttreatment imbalance, statistical analysis showed a significant difference between the 2 groups (P < .001).
The long-term follow-up showed that 18 patients of the LD group, after a period free from acute symptomatology ranging from 16 to 52 months (mean 34.4 months), experienced recurrence of vertigo attacks that were refractory to medical treatment. Ten patients treated with HD-ITG showed a recurrence of vertigo attack after a symptom-free period ranging from 18 to 70 months (mean 46.8). All these patients underwent additional rounds of retreatment with the same protocol previously used. After a follow-up period of at least 4 years, all the patients (except 1) treated with additional rounds of LD-ITG were symptom free, while 4 of the 10 patients treated with repeated high-dose ITG were considered “failures,” as they needed to be surgically treated with vestibular neurectomy because of the persistence of vertigo spells (in 2 cases associated with Tumarkin’s falls) (Figure 5).

Discussion

Over the years a trend toward the use of a reduced amount of administered gentamicin and a larger interval between the injections has been introduced. We followed this tendency in order to minimize the risk of hearing deterioration and persistent dizziness after ITG. The present study retrospectively compares the hearing outcome and vertigo control in patients affected with unilateral definite MD receiving HD-ITG with that of patients receiving LD-ITG.

Using the AAO-HNS criteria, at 2-year follow-up, we recorded a similar percentage of vertigo control (class A-B) in the 2 groups: 94% of the high-dose group showed a complete (80%) or substantial (14%) control of vertigo compared with 90% registered in the low-dose group (71% complete and 19% substantial). On the other hand, the incidence of side effects, mainly hearing loss and posttreatment imbalance, is remarkably different in these techniques, being significantly higher in patients treated with the HD-ITG. A high percentage (37%) of MD patients treated with HD-ITG showed a significant worsening of their hearing in comparison with low-dose receivers. These results are concordant with those reported in the more recent meta-analysis, confirming that a smaller dose of gentamicin delivered to the inner ear allows to obtain good results in term of vertigo control associated with a significant reduction of the risk of hearing loss.2,3,11 Similar considerations can be made if we take into account the number of patients suffering from severe posttreatment disequilibrium: no cases were registered in the low-dose group while 6 patients of the high-dose group reported a long-lasting degree of imbalance that interfered with daily activities and required specific treatment.

According to the AAO-HNS criteria, the majority of studies on this topic used the arbitrary limit of 2-year follow-up to evaluate the efficacy of any treatment performed to cure MD. Nevertheless, clinical experience says that recurrences after ITG are very common and unpredictable, making the aforementioned method of analysis unsuitable when the treatment modalities do not have a definite “end of therapy.” For this reason some recent reports about ITG therapy of MD experienced the advantages of the Kaplan-Meier survival curve in monitoring patients with
different lengths of follow-up.\textsuperscript{13-15} Using this method, MD patients can be followed for an extended period of time, and some reports have documented the recurrence of vertigo attacks after a period of more than 2 years after ITG treatment.\textsuperscript{14,16-18}

Our study showed that long-term control of vertigo attacks in MD with a single round of treatment could be obtained in 71.4\% of patients treated with HD-ITG and in 55.0\% of those treated with LD-ITG. With repeated rounds an effective control of vertigo could be achieved in 97.7\% of the patients treated with LD-ITG, while only 88.5\% reached this goal using repeated rounds of HD-ITG. In other terms, the retreatment gave better results in the LD group than in the HD group. Only 1 patient was shifted to surgical procedure compared to the 4 subjects belonging to the HD group. These results offer an opportunity to make some interesting considerations. First, despite the lower percentage of patients with no vertigo recurrences using a single round of ITG, at long-term follow-up the LD protocol allows to obtain good results in terms of vertigo attacks and with a limited occurrence of worsening of the hearing and of posttreatment imbalance. Second, in the group of patients treated with HD-ITG, the length of the symptom-free interval was greater, but when retreatting with the same protocol, we observed a relatively higher number of patients with no vertigo control, and consequently 4 patients were shifted to surgical ablative procedures.

Our experience seems to confirm the validity of the recently proposed “on demand” administration of LD-ITG. The previously used method of HD-ITG appeared to be more effective for obtaining control of vertigo quickly, but we have to take the higher rates of hearing loss and disequilibrium into account. In this group, the long-term follow-up showed a longer symptom-free period but mainly demonstrated that retreatment is unable to obtain vertigo control in 40\% of the patients.

What type of ITG treatment should be proposed to a patient suffering from unilateral refractory MD? The HD-ITG seemed to lead to a better rate of long-term vertigo control, despite its being associated with an increased risk of side effects. LD-ITG showed the advantage of a very small percentage of side effects but gave less chance of reducing the number of vertigo attack with only one round of treatment.

The effects of these 2 types of treatments are very different: the aim of HD-ITG is to induce severe damage to vestibular hair cells.\textsuperscript{19} Experimental studies have demonstrated that ITG can enter hair cells through the stereociliary transduction channel; then the drug remains linked to the specific binding protein located in the apical cytoplasm of the type I hair cells.\textsuperscript{20} Only by increasing the gentamicin dose can the drug saturate these binding proteins, spreading all through the cytoplasm and leading to proteolytic cell death.\textsuperscript{21} Furthermore, it is well demonstrated both in experimental and clinical studies that the time-course of hair cell dysfunction and subsequent degeneration is closely correlated with the temporal uptake of gentamicin.\textsuperscript{19,21} The drug is retained in hair cells for at least 3 weeks after a single intratympanic injection: this interval between repeated ITG injections should prevent severe damage to vestibular and cochlear cells. The low-dose protocol is linked to these experimental suggestions, probably inducing a partial and/or temporary damage to inner ear cells.

A surprising result encountered in our experience is the poor outcome of retreatment in 4 of the 10 patients previously injected with HD-ITG who were affected by recurrent vertigo attacks. Actually, in these latter subjects we noticed a very poor posttreatment symptomatology in terms of imbalance and dizziness. The individual response to ITG is unpredictable, depending on many variables (permeability of round and oval window, different diffusion of the drug in the inner ear fluids, different mechanisms of hair cell damage). The poor response to ITG could be explained by a reduced permeability of the middle ear windows or because of a kind of “resistance” to the damage induced by the drug on the inner ear cells (perhaps increase of the cytoplasmic gentamicin binding proteins?).

This study has several limitations: considering the retrospective nature of this study, we cannot strongly affirm the superiority of the HD or LD protocol. Second, there is a relevant difference in the follow-up time between the 2 groups: the HD-ITG patients have a longer follow-up period, during which also the natural history of the MD may have an important influence. Furthermore, the development of new methods (eg, Video-HIT) allowed us to study our patients in a more effective way: this situation could affect the evaluation of the effects on vestibular function. Finally, the sample size is not large enough to support a strong external validity of our study, especially with regard to the efficacy of retreatment after long-term recurrences of vertigo.

Conclusion
Bearing in mind the limits of this study, we can nevertheless state that LD-ITG represents a good method of treatment of unilateral refractory MD, combining a low rate of side effects with an excellent capacity to provide vertigo control. However, using the Kaplan-Meier method, the long-term follow-up showed that LD-ITG needed repeated rounds of injections more frequently than the high-dose protocol. All this indicates that LD-ITG should be proposed as an “on demand” protocol; patients should be informed about the possibility of repeated rounds of treatment until complete vertigo control has been achieved. On the other hand, patients treated with HD-ITG run less risk of needing repeated rounds, but the efficacy of the retreatment seems to be not so high, requiring in almost 40\% of cases the need for more aggressive ablative therapy.

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Author Contributions
Augusto P. Casani, study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript,
study supervision, revision, data collection, statistical analysis; Niccolò Cerchiai, acquisition of data, drafting of the manuscript, technical and material support, study supervision; Elena Navari, acquisition of data, manuscript drafting, administrative support, revision; Iacopo Dallan, study concept and design, critical revision of the manuscript for important intellectual conflict; Paolo Piaggi, study design, manuscript drafting and revision, data collection, statistical analysis; Stefano Sellari-Franceschini, study concept and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual conflict.

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References